AVERY'S NEONATOLOGY BOARD REVIEW

CERTIFICATION AND CLINICAL REFRESHER

PATRICIA R. CHESS

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2015v1.0

Avery's Neonatology Board Review

Certification and Clinical Refresher

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FIRST EDITION

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AVERY'S NEONATOLOGY BOARD REVIEW: CERTIFICATION AND CLINICAL REFRESHER, FIRST EDITION ISBN: 978-0-323-54932-5

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Library of Congress Control Number: 2019934902

Content Strategist: Sarah Barth
Content Development Specialist: Caroline Dorey-Stein
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Printed in China

Last digit is the print number: 9 8 7 6 5 4 3 2 1

Preface

When preparing for the Neonatal-Perinatal Board exam, it is helpful to utilize a variety of tools. This first edition of *Avery's Neonatology Board Review: Certification and Clinical Refresher*, partner to *Avery's Diseases of the Newborn*, has been created as an aide to neonatologists preparing for their subspecialty boards as well as for neonatologists interested in brushing up on their neonatal knowledge. Additional educational tools are available through the American Academy of Pediatrics, including *Neoreviews*, *Neoreviews-Plus*, and *NeoPREP*. The outline and content are based on the 2016 American Board of Pediatrics Content Outline for Neonatal-Perinatal Medicine. I would like to thank all of the authors and section editors for their contributions to this book.

Acknowledgments

I would like to thank my mentors, my patients and their families, and neonatology fellows past, present, and future, who were the inspiration for creating this book, as well as the authors and section editors, in particular Dr Dylag for providing critical review of the entire book. I would also like to thank my family, especially my husband Mitch, my rock and my wings, and our children, Rachel, Laura, Daniel, and Stephen, and grandchildren Jaimie and Evan, our greatest joy.

Notice

While this book has been thoughtfully written by experts in the field and edited carefully, the authors, editors, and publisher cannot ensure there are no errors or omissions and assume no liability from any injury or damage that may occur from content contained in this material.

Understanding of this field is constantly changing. It is important for physicians to review any material for current relevance in light of updated research and understanding.

Any drug indication or dosage needs to be reviewed by appropriate references including manufacturer's information before prescribing.

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Contents

1 *Maximizing Test Performance,* 1
VICKI ROTH

SECTION 1
Maternal-Fetal Medicine, 5
J. CHRISTOPHER GLANTZ and LISA M. GRAY

2 *Pregnancy,* 6
J. CHRISTOPHER GLANTZ and LISA M. GRAY

3 *Fetal Assessment and Treatment,* 17
J. CHRISTOPHER GLANTZ and LISA M. GRAY

4 *Labor and Delivery,* 21
J. CHRISTOPHER GLANTZ and LISA M. GRAY

SECTION 2
Asphyxia and Resuscitation, 25
MELISSA CARMEN

5 *Asphyxia,* 26
MELISSA CARMEN

SECTION 3
Cardiovascular, 31
KIMBERLY VERA

6 *Cardiac Development,* 32
KIMBERLY VERA

7 *Cardiovascular Physiology,* 38
KIMBERLY VERA

8 *Presentation of Congenital Heart Disease,* 41
KIMBERLY VERA

9 *Cardiopulmonary Dysfunction,* 55
KIMBERLY VERA

10 *Electrocardiography, Electrophysiology, and Dysrhythmias,* 59
KIMBERLY VERA

11 *Pharmacologic Therapy of Heart Disease,* 65
KIMBERLY VERA

SECTION 4
Respiratory, 67
ECHEZONA T. MADUEKWE, WILLIAM MANISCALCO, NARAYAN PRABHU IYER, DEEPAK KUMAR and PATRICIA R. CHESS

12 *Embryology and Physiology,* 68
ECHEZONA T. MADUEKWE

13 *Respiratory Distress Syndrome,* 80
WILLIAM MANISCALCO

14 *Aspiration, Pneumonia, and Persistent Pulmonary Hypertension,* 85
NARAYAN PRABHU IYER and DEEPAK KUMAR

15 *Pleural Disorders and Additional Causes of Respiratory Distress,* 89
NARAYAN PRABHU IYER and DEEPAK KUMAR

16 *Apnea of Prematurity and Neonatal Respiratory Depression,* 94
NARAYAN PRABHU IYER and DEEPAK KUMAR

17 *Assisted Ventilation, ECMO, and Pharmacologic Agents,* 98
PATRICIA R. CHESS

SECTION 5
Genetics and IEM, 105
LAURIE STEINER, JOTISHNA SHARMA and GEORGIANNE LEE ARNOLD

18 *Molecular Genetics,* 106
LAURIE STEINER

19 *Patterns of Congenital Disorders,* 111
JOTISHNA SHARMA

20 *Nongenetic Etiologies for Congenital Defects,* 119
GEORGIANNE LEE ARNOLD

21 *Evaluation of Infants With Congenital Anomalies,* 122
JOTISHNA SHARMA

22 *Inborn Errors of Metabolism,* 127
GEORGIANNE LEE ARNOLD

SECTION 6
Nutrition, 135
WILLIAM W. HAY JR and KENDRA HENDRICKSON

23 *Nutrition and Growth: The Fetus,* 136
WILLIAM W. HAY JR and KENDRA HENDRICKSON

24 *Minerals, Vitamins, and Trace Minerals,* 141
WILLIAM W. HAY JR and KENDRA HENDRICKSON

25 *Enteral Nutrition,* 145
WILLIAM W. HAY JR and KENDRA HENDRICKSON

26 *Parenteral Nutrition,* 151
WILLIAM W. HAY JR and KENDRA HENDRICKSON

SECTION 7
Renal/Fluids/Electrolytes, 155
ERIN RADEMACHER

27 *Water-Electrolyte Metabolism and Acid-Base Balance,* 156
ERIN RADEMACHER

28 *Abnormal Renal Development,* 168
ERIN RADEMACHER

SECTION 8
Endocrine, 175
DAVID R. WEBER and ALISON FALCK

29 *Normal and Abnormal Sexual Differentiation,* 176
DAVID R. WEBER

30 *Adrenal Disorders,* 181
DAVID R. WEBER

31 *Thyroid Disorders,* 185
DAVID R. WEBER

32 *Glucose Metabolism,* 189
DAVID R. WEBER

33 *Calcium, Phosphorus, and Magnesium Metabolism,* 193
DAVID R. WEBER

34 *Thermoregulation,* 199
ALISON FALCK and DAVID R. WEBER

SECTION 9
Immunology, 201
KRISTIN SCHEIBLE

35 *Development of the Immune System,* 202
KRISTIN SCHEIBLE

36 *Components of the Immune System,* 206
KRISTIN SCHEIBLE

37 *Abnormal Immune System Development,* 211
KRISTIN SCHEIBLE

SECTION 10
Infectious Diseases, 217
GEOFFREY A. WEINBERG

38 *Infections of Organ Systems,* 218
GEOFFREY A. WEINBERG

39 *Causative Agents of Infections,* 225
GEOFFREY A. WEINBERG

40 *Prevention of Infections and Immunization,* 238
GEOFFREY A. WEINBERG

SECTION 11
Gastroenterology, 243
REBECCA ABELL and MEGAN E. GABEL

41 *Normal and Abnormal Gastrointestinal Development,* 244
REBECCA ABELL and MEGAN E. GABEL

42 *Developmental Anomalies,* 247
REBECCA ABELL and MEGAN E. GABEL

43 *Acquired Disorders of the Gastrointestinal Tract,* 254
REBECCA ABELL and MEGAN E. GABEL

44 *Liver Disease, Abdominal Masses, and Ascites in the Newborn Infant,* 258
REBECCA ABELL and MEGAN E. GABEL

SECTION 12
Hyperbilirubinemia, 261
AARTI RAGHAVAN

45 *Bilirubin Biochemistry Metabolism and Measurement,* 262
AARTI RAGHAVAN

46 *Bilirubin Toxicity,* 264
AARTI RAGHAVAN

47 *Physiologic and Breast Milk Jaundice,* 267
AARTI RAGHAVAN

SECTION 13
Skin Disorders, 269
TOLA OYESANYA, JACQUELINE SELPH and BERNARD A. COHEN

48 *Skin Development and Function,* 270
TOLA OYESANYA, JACQUELINE SELPH, and BERNARD A. COHEN

49 *Neonatal Skin Lesions,* 272
TOLA OYESANYA, JACQUELINE SELPH and BERNARD COHEN

SECTION 14
Hematology/Oncology, 287
LAURIE STEINER and JEFFREY R. ANDOLINA

50 *Erythrocytes,* 288
LAURIE STEINER

51 *White Blood Cells,* 296
JEFFREY R. ANDOLINA

52 *Platelets and Coagulation,* 299
LAURIE STEINER

53 *Transfusion Therapy in Neonates,* 304
JEFFREY R. ANDOLINA

54 *Solid Tumors and Leukemias,* 307
JEFFREY R. ANDOLINA

SECTION 15
Neurology, 313
NIRANJANA NATARAJAN, LAURA PRICE, JENNIFER BURNSED, SONIA LOMELI BONIFACIO and RONNIE GUILLET

55 *Neurologic Evaluation,* 314
NIRANJANA NATARAJAN

56 *Development of the Nervous System,* 316
LAURA PRICE

57 *Neonatal Encephalopathy,* 319
JENNIFER BURNSED

58 *Intracranial Hemorrhage and Vascular Injury,* 322
SONIA LOMELI BONIFACIO

59 *Neonatal Neurology: Cranial and Neurologic Trauma,* 326
SONIA LOMELI BONIFACIO

60 *Neonatal Seizures,* 329
JENNIFER BURNSED

61 *Central Nervous System Infections,* 331
RONNIE GUILLET

62 *Neonatal Abstinence Syndromes,* 333
LAURA PRICE

63 *Neurology: Hypotonia and Other Aspects,* 335
NIRANJANA NATARAJAN

SECTION 16
Neurodevelopment, 339
ALLISON H. PAYNE

64 *Incidence of Neurodevelopmental Impairments,* 340
ALLISON H. PAYNE

65 *Causes and Effects of Environment on Neurodevelopmental Impairment,* 344
ALLISON H. PAYNE

66 *Clinical Features of Neurodevelopmental Impairment,* 347
ALLISON H. PAYNE

SECTION 17
Eye, Ear, Nose, and Throat, 351
MATTHEW GEARINGER, BENJAMIN HAMMOND, LYNDY J. WILCOX and CATHERINE K. HART

67 *Eye Development, Retinopathy of Prematurity,* 352
MATTHEW GEARINGER and BENJAMIN HAMMOND

68 *Ear Development and Anomalies,* 357
LYNDY J. WILCOX and CATHERINE K. HART

69 *Nose, Mouth, and Throat Development and Anomalies,* 360
LYNDY J. WILCOX and CATHERINE K. HART

SECTION 18
Diagnostic Imaging, 365
MITCHELL CHESS

70 *Neurologic Imaging,* 366
MITCHELL CHESS

71 *Chest Imaging,* 375
MITCHELL CHESS

72 *Abdominal Imaging,* 382
MITCHELL CHESS

73 *Miscellaneous,* 387
MITCHELL CHESS

SECTION 19
Pharmacology, 393
TRACEY L. MCCOLLUM

74 *Drug Disposition and Pharmacokinetics,* 394
TRACEY L. MCCOLLUM

75 *Clinical Toxicology,* 400
TRACEY L. MCCOLLUM

76 *Indications, Mechanisms, and Adverse Reactions for Common Drugs,* 403
TRACEY L. MCCOLLUM

SECTION 20
Ethics and Health Services Delivery, 407
MARLYSE HAWARD and ANNIE JANVIER

77 *Organization of Perinatal Care,* 408
MARLYSE HAWARD and ANNIE JANVIER

78 *Ethical and Legal Issues in Neonatology,* 411
MARLYSE HAWARD and ANNIE JANVIER

SECTION 21
Core Knowledge and Scholarly Activities, 417
CARL T. D'ANGIO and EMER FINAN

79 *Biostatistics in Research,* 418
CARL T. D'ANGIO

80 *Epidemiology and Clinical Research Design,* 425
CARL T. D'ANGIO

81 *Applying Research to Clinical Practice,* 431
CARL T. D'ANGIO

82 *Principles of Teaching and Learning,* 436
RITA DADIZ and EMER FINAN

83 *Ethics in Research,* 440
CARL T. D'ANGIO

Answers Section, 444
Index, 469

Avery's Neonatology Board Review

Certification and Clinical Refresher

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1 Maximizing Test Performance

VICKI ROTH

Before Beginning Your Review

- Completing a self-assessment
  - Prior to the date you intend to begin your studies, take stock of your initial preparedness. Using the content outline for this exam, create a quick chart rating your fund of knowledge and experience with each topic.
  - As you know, the topics on this exam tap into a range of learning approaches (e.g., visual and quantitative learning, simultaneous vs. sequential reasoning, memorization vs. conceptual thinking, etc.). So, in addition to rating your readiness by topic, a good self-assessment also includes a brief evaluation of your preferences, strengths, and weaknesses as a learner. (More on this issue later.)

TIP: If you will not be attending an in-person review course that includes a self-assessment, use a portion of the items in your question bank to create your own pretest.

- Building a study map
  - A study map ensures that all topics are addressed well and that appropriate review strategies are employed for each one. A study map also makes life easier, as the decisions about what to study in a given week are front loaded.
  - A well-constructed study map begins with time finding. Short bursts of study time can appear spontaneously during the day; when they do, be prepared to use them (see "Deciding where to study" below But more extensive periods of review time are needed, too, and finding them usually requires some detective work.
  - In addition to the start date for your study and your anticipated exam date, an effective map also includes the following elements:
    - Specific dates for the review of each topic
    - Dates for catch-up study sessions
      - Catch-up hours are earmarked for study but have no assigned topic until close to the study-session dates.
        - Catch-up hours make room for study when other work or life commitments have interfered with your map. They also provide opportunities for additional study of topics that prove to be more challenging than expected.
        - Candidates often significantly underestimate the number of catch-up study hours needed, so it is advisable to include many such sessions in the study map right from the beginning.
    - Dates for loop-back sessions
      - Loop-backs are brief and lightweight study periods designed to reconnect with material that you examined in more detail 1–2 weeks earlier. The goal of these study periods is to improve the student's ability to retrieve information across time and to reduce anxiety about retaining information that has already been studied.
  - Creating a map with the features described here requires about 1.5–2 hours.

TIP: Given the density and volume of material to review, it is easy to build ambitious study maps that are impossible to maintain. A good plan is one that takes into account the practical requirements of your other responsibilities (i.e., make a map that is livable).

TIP: If you have a disability that qualifies for testing accommodations under the Americans with Disabilities Amendments Act and you intend to seek an accommodation, your map should include the time needed to complete the request process.

- Assembling your study kit
  - Just as we are more likely to go to the fitness center for a workout if we pack a gym bag the night before, we make better use of our study time if we collect and organize a set of review material in advance.
  - To prevent a scattered approach to study, it often works best to think of your study materials in three layers:
    - The first is your set of central resources, like this text, that can provide the overall foundation for your review.
    - The second layer might include several resources, perhaps ones you already own, that you turn to for short, detailed study of specific subtopics that need more attention. These first two layers should provide most of the resources needed for your study.
    - The third layer of materials is only for limited occasions when you encounter a persistently difficult subtopic that needs to be looked at from another angle. It is likely you already possess much of what is needed for this third layer as well.
  - For your study kit, also collect other materials including a notebook or portfolio, paper flashcards and/or a flashcard application, markers, etc. In addition, if you will not have easy access to a white board during your study sessions, consider purchasing a large sketchpad.
- Deciding where to study
  - When you find yourself with a few moments prior to a meeting or while waiting in a queue, make use of this time by having quick-review materials close at hand (e.g., review notes on your phone or a deck of flashcards

in your pocket). In these cases, deciding where to study is not a priority; rather, the goal is to benefit from these slivers of time when and wherever they appear. A fair bit of learning is additive, meaning that we take on about a flashcard's worth of information at a time. So, use these short study interludes during your day, even if your location is not ideal.
- However, planning for longer sessions should include decisions about study locations. It may be simpler to study in a single accessible location, but this can be a suboptimal approach for board review. As we study, elements of our environment, such as the type of lighting or the color of the walls, can become embedded with the target information. Later on, when those environmental cues are no longer present, retrieval can then be more difficult than anticipated. Changing study locations from time-to-time helps build the geographic independence that allows you to remember concepts and details, regardless of where you are.

TIP: Sometimes the only plausible place to work on your board review is in your own home. When this is the case, set up a place to study that is dedicated solely for this purpose.
TIP: As you will not have control over the environmental conditions of your actual test location, consider working at times in a location that includes a slightly uncomfortable feature. For example, study for a few sessions in a chilly room, if air conditioning annoys you; in a room with fluorescent bulbs, if that type of lighting is irksome; and so on. This practice will help you plan ahead (e.g., by dressing in layers) or at least will build your capacity to cope with any irritating conditions in the testing room.

The Review Itself

- For each group of concepts and facts, make sure that your study approaches include all three stages of the learning cycle: input, quizzing, and testing steps.
  - The *input step* employs reading, listening, and watching study materials, such as texts and review guides, podcasts, lectures, and videos.
    - While you are engaged with these input activities, you are likely to be jotting something down. It may feel as if writing and drawing should cement your learning, but the making of study tools such as flashcards, charts, diagrams, and concept maps—while all good options—largely still fits within this first step of the learning cycle. It is true that creating a study tool requires selectivity about what you write down and the use of your own words or images, but just creating study tools is typically not enough. It is likely that your retention of the materials written in these study tools will be less than expected.
  - So, within each session, stop periodically to examine your retention of the material you have taken in during the input step. The essential feature of this *quizzing step* is asking yourself questions and then immediately checking the accuracy of your responses. Easy ways to complete this step include reviewing any flashcards you have just created and generating questions from the rows and columns of the charts you have made.
    - During this stage of the learning cycle, special attention should be paid to the power of drawing. A great deal of the material you need to review is visual and sequential in nature, so quickly made illustrations, flowcharts, and concept maps are effective ways to rehearse this material.
    - Do not spend time making artistically sophisticated illustrations and charts, however. The goal is to sketch out your ideas quickly from memory and then check your work.
  - During the *testing step*, set up conditions that simulate some elements of the actual exam. While completing practice questions, add time limits and refrain from stopping in-between questions to check your answers. More information about this step can be found in the "Practice question review" section, later.

TIP: Given the amount of material you have to review, it can seem more productive to complete extensive swaths of input activities before turning to the quizzing or testing steps of the learning cycle. Resist the impulse to just remain in the input stage by remembering how productivity is calculated. Getting the optimal amount of output for the amount of input you invest is your goal; this typically requires frequent toggling between the three stages of the learning cycle.
TIP: At intervals, add a self-check about the learning cycle to your study map. As time goes on, it is easy for the balance among these steps to become skewed. A common issue, for instance, is to lapse into an approach dominated by one of the stages of the learning cycle (e.g., just reading or just doing practice questions). While it is not necessary to allocate an exact one-third of study time to each of the stages, it works best if some attention is paid to all three for each set of concepts and facts.

- Pacing yourself
  - As mentioned, brief units of study time can be valuable, but some longer study sessions are also essential for adequate preparation. However, at times it can be difficult to maintain full engagement with your review materials during these more extensive sessions. Appropriate pacing helps to offset exhaustion and distraction.
  - A recommended rhythm for longer sessions includes studying in about 50-minute periods followed by 10-minute breaks. To help you stay on track, use a timer on your phone for both the learning and the break portions of your study.
  - The nature of the mini-breaks has more influence than you might initially think. "Negative" breaks can lead to reduced concentration in the next cycle, while "positive" ones work in your favor.
  - Negative breaks are those that introduce other agendas, even those that are entertaining. So, avoid using the 10-minute breaks to check messages, make calls, watch videos, surf the Internet, watch television, and the like. Nobody concludes such breaks feeling energized and ready to take on the next learning challenge. (It may be that your work and family obligations require you to take messages, but the time devoted to these duties should not be counted as mini-breaks.)
  - Positive mini-breaks are those that allow you to recenter for a few minutes. A light snack, a few minutes of

stretching, a quick walk around the block, listening to a favorite song—all of these can help you get ready for the next 50 minutes of study, and they neatly fit within the recommended 10-minute time frame.

TIP: Because you are so pressed for time in general, you may have developed an approach to work that propels you through long sessions without stopping. If so, keep in mind that this work habit leads to diminishing returns during board review sessions. Let yourself take those short breaks so your learning can become consolidated.

TIP: The 50:10-minute study cycle dovetails well with the steps of the learning cycle described earlier. For instance, you might designate the first 50 minutes for input practice by reading a text, taking a short break next, and then going on to a 50-minute period of quizzing yourself about the material you just read. Another helpful pattern is to devote your first session of the day to timed questions about the material studied earlier that week. Subsequent 50-minute sessions can include the input, quizzing, and testing pattern with new material.

Reviewing Practice Questions

This section details how to make the best use of the testing stage of the learning cycle. To efficiently process a group of timed questions that you have already completed, try labeling each of your answers as follows:

A. *A correct answer that was easy for you to get right.* Some review of the explanatory material provided for the wrong answers can be helpful, but keep this part of your review light so you can devote sufficient time to the following answer categories.

B. *A correct answer that required more effort for to achieve.* To clarify, this category is for questions that made you hesitate because you had difficulty recalling the required information. You may have been able to narrow down the answers to two choices, and, in this case, you selected the correct one.

The most efficient way to make use of such items for further review is to answer this question:

What would I have known if I had been able to answer this question easily?

This question helps you zero in on the precise information or steps in reasoning that you need to practice.

C. A correct answer that you selected for the wrong reason or through a lucky guess. Treat these like wrong answers as per D, E, and F below.

D. *An item you got wrong because you never knew the needed information.* For these questions, sometimes the explanations provided in the answer key are enough to master the subject at hand. However, some of the time, you need to read additional material. In these cases, it is smart to assign a value to the concept to be reviewed, and then set a timer accordingly. For instance, you may have missed a question that reveals a gap in your knowledge base that would take about 10 minutes to remediate, while another topic might require 20 minutes of work. Timing these extra reviews helps you return to your original task promptly. (If you uncover the need for extensive review of a topic, it is often a good idea to move this larger unit of study to one of the upcoming catch-up periods that you have scheduled on your study map.)

E. *An item that you got wrong because you partially knew the needed information.* This category is the flipside of (B), that is, you may have been able to make some headway toward the answer, but you were unable to pinpoint the correct choice. Again, the strategy here is to look for those small elements of information that would allow you to answer a question on this topic correctly in the future.

F. *An item that you got wrong because of a misconception about the topic.* This category differs from (D) and (E) above in that the learner believes something to be true, when in fact it is not. For instance, many young students believe that plants increase in mass by taking it up from the soil; while others think that seasonal changes in temperature result from an increase or decrease in Earth's proximity to the sun. While you undoubtedly understand carbon fixation and the tilt of Earth's axis, we all have errors in our overall base of knowledge. However diligent we may be, our own misconceptions can be difficult to spot. A clue that a misconception might be in play can be found when we answer items incorrectly, but the correct answers do not make sense, even after careful review. An efficient way to remedy misconceptions is to work collaboratively with a study partner. More on this next.

More Advice

- Studying with a colleague.
  - While finding time to review board material with a colleague can be an issue, the payoff can be significant. In addition to rooting out misconceptions, these sessions can provide the chance for needed repetition and a motivational boost.
  - It is optimal during these sessions for the person who knows the least about a given subtopic to explain what he or she can, and then to allow the other to make additions and corrections.
  - Use Skype or other videoconferencing applications when in-person sessions are not practical.
- Visiting the testing center
  - If this will be your first time taking an exam at the testing center where you are registered, plan a visit to this location. This will allow you to gauge more accurately the time needed to get there, to check out parking options, and to appraise the location where the test will be taking place.
- Attending to diet, sleep, and exercise
  - Also essential is finding time for a reasonable level of self-care. Because reviewing for this exam adds to your workday, it is easy to let nutrition, rest, and exercise fall by the wayside. However, both the review process and the exam itself require stamina, so looking after your well-being is part of good preparation.
  - Self-care does not need to be perfect to be good. If you are not able to fit in an entire workout routine, for example, then a brisk walk can still be beneficial. Similarly, while long sessions of home cooking might not fit into your day, making better choices at the hospital cafeteria is probably doable.

- The goal of the day before the test date is to set up conditions that optimize knowledge retrieval during the exam. So, do not use this day trying to force in one last set of facts or asking yourself to answer another set of practice questions. Instead, to the extent your work and family duties allow, make this a day for light activity and rest.

- Thinking positively
  - As sports psychologists know, the way we visualize our future performance has an impact on how we ultimately do. So as the exam gets closer, try these positive images:
    - recalling a prior time when you did well on a challenging exam;
    - imagining a question on your upcoming board exam that you do not answer with full confidence, shaking it off, and continuing onto the next item;
    - picturing success with a complicated question;
    - visualizing yourself dispelling nervousness by using short relaxation strategies;
    - imagining yourself answering the last question on the exam knowing that you had acquitted yourself well overall;
    - picturing yourself walking out of the testing center knowing that this was a successful day.

SECTION 1

Maternal-Fetal Medicine

J. CHRISTOPHER GLANTZ and LISA M. GRAY

2 Pregnancy

J. CHRISTOPHER GLANTZ and LISA M. GRAY

Maternal Adaptation to Pregnancy

- Hemodynamic
  - Plasma volume increases 50% while red blood cell (RBC) mass expands 20%; physiologic anemia of pregnancy
  - Heart size increases 10% (hypertrophy and increased diastolic filling)
  - Stroke volume and heart rate increase; 50% increase in cardiac output
  - When supine and ≥20 weeks, uterine compression of the vena cava lowers venous return and cardiac output, causing hypotension
  - Uterine blood flow increases 10-fold to ≈1 L/min
  - Systemic vascular resistance declines (progesterone, prostaglandin, angiotensin resistance, and shunting through low-resistance placenta)
  - Diastolic blood pressure (BP) declines 10 mm Hg by 20 weeks, then gradually increases back to baseline
- Renal
  - Renal blood flow and glomerular filtration rate increase by 50%
  - Serum urea nitrogen and creatinine levels decrease by 40%
  - Glucose load exceeds loop reabsorption, causing glycosuria
  - Dilation of renal calyces and ureters; "physiologic" hydronephrosis is common (right > left due to uterine dextrorotation)
  - Glycosuria plus urine stasis increase the risk of pyelonephritis
- Respiratory
  - Minimal change in respiratory rate but increase in tidal volume causes increased minute ventilation (no change in FEV_1 (Forced Expiratory Volume (in one second) or forced vital capacity)
  - Hyperventilation raises Po_2 (Partial pressure of oxygen) and lowers Pco_2 (partial pressure of carbon dioxide); improves maternal-fetal gradients
  - Compensatory increased renal bicarbonate excretion maintains pH and avoids respiratory alkalosis
  - Decreased functional reserve capacity increases susceptibility to hypoxia
- Hematologic
  - Increased thrombogenesis + decreased thrombolysis = hypercoagulable
  - Venous thromboembolism (VTE) risk increased five-fold
  - White blood cell (WBC) count increases; mild thrombocytopenia common
- Endocrine
  - Placental hormones alter maternal metabolism; increased fatty acid metabolism + insulin resistance = more glucose available to fetus
  - Steroid hormone synthesis increases
  - Estrogen induces production of thyroid-binding globulin; increased total thyroid hormone levels, but free levels are unchanged
- Gastrointestinal
  - Gastrointestinal motility is slowed; increases nutrient-water absorption
  - Nausea, vomiting, and constipation are common
- Changes in laboratory values
  - Increased: steroid hormones, prolactin, total T_4, WBC, alkaline phosphatase (from placental production), lipids, coagulation factors, PO_2
  - Decreased: hematocrit (Hct), platelets, creatinine, blood urea nitrogen (BUN), glucose, sodium, calcium (total but not ionized), bicarbonate, Pco_2
  - No change: free thyroxine (T_4), transaminases, bilirubin, prothrombin time (PT), partial thromboplastin time (PTT), bleeding time

THE PLACENTA

- Morphology and development
  - Trophoblast derived from extraembryonic cells in blastocyst
    - Cytotrophoblast: cells extend into decidua to anchor villi and invade maternal spiral arteries, dilating them to improve flow
    - Syncytiotrophoblast: a "shell" of fused cytotrophoblasts
  - Progressive placental growth increases cross-sectional vascular area and lowers placental vascular resistance
  - Hemochorial architecture
    - Maternal blood in direct contact with fetal chorion (not fetal blood)
    - Villi containing fetal blood vessels project into intervillous spaces
- Respiratory gas exchange
  - Efficient transfer of respiratory gases by simple diffusion along gradients
  - Fetal hemoglobin has higher affinity for O_2 than maternal hemoglobin; preferentially offloads O_2 to the fetus
  - Transfer is flow-dependent; gas exchange is limited by maternal uterine vascular disease, hypotension, hypovolemia, infection, placental infarction, abruption, or hypoplasia.

- Placental transport: substances cross via different mechanisms based on size, lipid solubility, protein binding, and presence of transporters
  - Simple diffusion: respiratory gases, small nonpolar molecules
  - Facilitated diffusion: glucose, some glucocorticoids
  - Channels: water and some ions
  - Active transport: sodium, potassium, amino acids, proteins
  - Receptor-mediated endocytosis: low-density lipoproteins (LDLs) and iron
- Metabolism and endocrine function
  - Fetus has limited gluconeogenesis; most glucose is maternally derived
  - Human placental lactogen and placental growth hormone stimulate maternal lipolysis and gluconeogenesis, increasing glucose levels for fetal use
- Abnormal placentation
  - Poor trophoblast invasion is associated with fetal loss and preeclampsia
  - Excessive or abnormal trophoblast invasion causes placenta accreta/percreta

MULTIFETAL GESTATIONS

- Zygosity (number of ova fertilized):
  - Monozygous = one ovum; multizygous = more than one ovum (most common)
- Chorionicity (number of placentas) and amnionicity (number of sacs) are determined by zygosity and/or time of conceptus split.
  - Multizygous: each fetus has its own placenta and sac
  - Monozygous with splitting in:
    - 1–3 days: each fetus has its own placenta and amniotic sac
    - 3–8 days: shared placenta (monochorionic) but two amniotic sacs
    - 8–13 days: shared placenta and sac (monoamniotic)
    - >13 days: conjoined twins
- Multifetal gestations are associated with adverse infant outcomes.
  - Anomalies, aneuploidy, stillbirth, preterm delivery (PTD), fetal (intrauterine) growth restriction (IUGR), preterm premature rupture of membranes (PPROM), perinatal death, intraventricular hemorrhage (IVH), and periventricular leukomalacia

ASSISTED REPRODUCTIVE TECHNOLOGY (ASSISTANCE WHEN INFERTILE)

- Ovulation induction
  - Medications used to improve ovulation when egg quality is normal
  - Use of clomiphene citrate or letrozole has 8%–10% twinning risk
  - Use of injectable gonadotropins has increased risk of high-order multiples
- Intrauterine insemination (partner or donor)
  - Bypasses cervix in cases of abnormal sperm count
  - Not independently associated with increased risk of multifetal gestation
  - Unrelated donor used if male factor infertility or to avoid inherited disease
- In vitro fertilization (IVF)
  - Process
    - Injectable gonadotropins stimulate multiple ovarian follicles
    - Eggs are harvested via ultrasound-guided transvaginal aspiration
    - Eggs and sperm are mixed in vitro
    - Conceptus is incubated and then transferred into the uterus
  - May use unrelated egg donor to address premature ovarian failure or poor egg quality, or to avoid inherited disease
  - IVF is an independent risk factor for
    - Multifetal gestation risk related to number of embryos transferred
    - Aneuploidy, fetal anomalies, hypertensive disorders of pregnancy, IUGR, PTD, abnormal placentation, cesarean delivery

Prenatal Care

PRECONCEPTION CARE

- Maternal health optimization before pregnancy improves perinatal outcomes
  - Control chronic medical conditions: discontinue teratogenic medications
  - Screen for relative contraindications to pregnancy (e.g., severe renal insufficiency, certain cardiac conditions)
- Reproductive planning
  - Avoid short interpregnancy interval (delivery to next conception <18 months)
  - Contraception until health is optimized
- Testing and immunization
  - Sexually transmitted infection (STI) screening and treatment
  - Update needed immunizations
  - Expanded genetic carrier screening for high-risk groups (e.g., Ashkenazi Jews, French Canadian, Mediterranean, Southeast Asian)
- Substance use and teratogens
  - Counsel on smoking cessation
  - Avoid teratogens and illicit substance use (refer for treatment)
- Nutrition and dietary supplementation
  - Reduce excess body weight: healthy diet (refer for nutrition consultation), regular exercise, bariatric surgery (if appropriate)
  - 400 μg folic acid started 1-month preconception decreases rate of open neural tube defects (ONTDs); 4 mg daily for women with prior defect
  - Assess diet and consider supplementation to achieve recommended daily doses of calcium, vitamin D, iron, and other vitamins and minerals as needed

INITIAL PRENATAL VISIT

- Establish prenatal care in first trimester
- Complete history and risk assessment
  - Medical, obstetrics and gynecology (OB/GYN), family, genetic, and social history
  - Medication use, substance use and abuse, domestic violence
- Determination of gestational age (GA), estimated due date (EDD)
  - Menstrual history, uterine size, and ultrasound (if discrepant findings)
  - Accurate GA vital, especially if possible PTD, IUGR, or postdates
- Physical examination; routine prenatal laboratory tests
  - Complete blood count (CBC)
  - Blood typing and antibody screening
  - STI screening: serology for rubella, syphilis, hepatitis B surface antigen, human immunodeficiency virus (HIV); chlamydia and gonorrhea testing
  - Urinalysis and culture
- Possible additional laboratory tests
  - Cystic fibrosis carrier testing, hemoglobin electrophoresis (if at risk for hemoglobinopathy), hepatitis C, urine drug screening

SUBSEQUENT PRENATAL VISITS

- Monthly until 28 weeks, then every other week to 36 weeks, then weekly
  - Weight, BP, urine protein and glucose levels, fundal height, fetal heart rate (FHR)
  - Assess for signs and symptoms of labor, hypertensive disorders, or abnormal fetal growth.

OTHER ROUTINE ASSESSMENTS AND INTERVENTIONS

- Aneuploidy screening
  - Low-risk patients: first-trimester screen at 11–13 weeks or second-trimester (quad screen) at 14–22 weeks
  - High-risk patients (maternal age ≥35 years, prior aneuploidy, abnormal serum screening, ultrasound): cell-free DNA analysis at ≥10 weeks
  - Diagnostic testing: chorionic villus sampling (CVS) at 10–13 weeks, amniocentesis at ≥15 weeks
- Maternal serum alpha fetoprotein (AFP) screening at 14–22 weeks
- Fetal anatomy ultrasound at 18–20 weeks
- Gestational diabetes (GDM) screening at 24–28 weeks
- Repeat antibody screen at 28 weeks if Rh-negative; Rh immune globulin administration
- Immunizations
  - Hepatitis B: all susceptible women
  - Hepatitis A: if hepatitis B or C positive (+)
  - Influenza: all women in every pregnancy
  - Tdap: all women after 27 weeks in every pregnancy
  - Pneumococcal or meningococcal: HIV+, sickle cell disease, or asplenia
- Group B streptococcus (GBS) culture at 35–37 weeks

Pregnancy Complications

MATERNAL HEALTH CONDITIONS

- Obesity: prevalence in women of reproductive age is ≈30%; ≈60% when overweight and obese categories are combined
  - Confers increased maternal risk proportional to body mass index
  - Maternal effects: hypertension, GDM, cesarean delivery (intraoperative and postoperative complications), venous thromboembolism (VTE)
  - Fetal effects: miscarriage, stillbirth, birth defects (particularly neural tube and cardiac), macrosomia
  - Management
    - Weight loss (or bariatric surgery) prior to conception
    - Early screening for gestational diabetes (GDM)
    - Fetal surveillance to monitor growth (fundal heights are unreliable)
- Diabetes mellitus (DM)
  - Complicates ≈6%–10% of pregnancies (90% GDM)
  - Pregestational DM
    - May have comorbid renal, cardiovascular, and neurologic disease that worsen perinatal outcome
    - Risk of complications proportional to degree of glycemic control and comorbid conditions
  - Gestational DM
    - Lower risk of complications than pregestational DM
    - Early screening diagnoses likely represent previously undiagnosed type 2 DM (although still characterized as gestational)
  - Maternal effects of DM
    - Hypertension, delivery lacerations, hemorrhage, cesarean delivery
  - Fetal effects of DM
    - Pregestational DM only: miscarriage, stillbirth, and birth defects (especially heart and ONTD)
    - Any DM: fetal growth disorders (usually macrosomia), cardiomyopathy, birth injury, neonatal metabolic abnormalities, respiratory distress syndrome (RDS)
  - Management
    - Nutritional counseling to attempt dietary control
    - Achieve glycemic control: blood glucose (BG) checks—qid
      - Fasting BG < 95 mg/dL
      - 1-hour postprandial BG < 140 mg/dL
      - Metformin, glyburide, or insulin if diet fails
    - Fetal evaluation
      - Targeted anatomic ultrasound; echocardiography for pregestational diabetics
      - Fetal surveillance (ultrasound to monitor growth and antepartum testing to monitor fetal oxygenation; note that this will be referred to as "fetal surveillance" from now on)
      - Delivery timing determined by degree of glycemic control
        - Gestational with good control: 40 weeks
        - Pregestational with good control: 39 weeks
        - Poor control: typically 37–38 weeks
      - Cesarean if estimated fetal weight (EFW) >4500 g; twice the risk of shoulder dystocia compared with the same EFW without DM

- Hypertensive disease
  - Complicates ≈10% of pregnancies
  - Chronic hypertension (CHTN)
    - Hypertension preceding conception or noted before 20 weeks
    - At risk for superimposed preeclampsia
    - Comorbid renal disease or diabetes worsens outcomes
    - Management
      - Baseline laboratory evaluation of renal and liver function
      - BP monitoring; antihypertensive management (if required)
      - Fetal surveillance; delivery at term (38–39 weeks)
  - Gestational hypertension
    - Asymptomatic high BP first noted after 20 weeks of pregnancy
    - May progress to preeclampsia, so close follow up is required
    - Management: same as CHTN, but deliver slightly earlier (37-38 weeks)
  - Preeclampsia syndromes
    - Preeclampsia: hypertension associated with proteinuria (>300 mg/day), laboratory abnormalities, or symptoms at >20 weeks of pregnancy
    - Eclampsia: new-onset seizures in a woman with preeclampsia
    - HELLP syndrome: severe subtype of preeclampsia with abnormal laboratory profile
      - Hemolysis: elevated lactate dehydrogenase (LDH) level, low Hct, abnormal smear
      - Elevated liver enzyme levels: transaminases ≥ 2× normal
      - Low platelets: thrombocytopenia (<100K)
    - Signs and symptoms usually resolve rapidly in postpartum period but some diagnoses are not made until after delivery.
    - Gestational age and severity of disease dictate management; severity often inversely proportional to gestational age at onset.
    - Severe features defined by the presence of any of the following:
      - Persistent systolic BP ≥160 or diastolic BP ≥110 mm Hg
      - Persistent symptoms: headache, visual disturbances, upper abdominal pain, dyspnea (pulmonary edema)
      - Laboratory abnormalities: those seen with HELLP, or serum creatinine ≥1.1 mg/dL (or doubling from baseline)
    - Management
      - Maternal hospitalization; close outpatient observation can be considered for mild disease
      - Steroids for fetal maturity (if appropriate)
      - Serial BP, laboratory testing, and fetal monitoring
      - Antihypertensive management (if required)
      - Intrapartum magnesium sulfate for maternal seizure prophylaxis and/or for fetal neuroprotection (<32 weeks)
    - Delivery timing
      - Immediate if: eclampsia, pulmonary edema, refractory hypertension, abruption, fetal demise, non reassuring fetal status, or if any severe features at ≥ 34 weeks.
      - Expectant management is appropriate when < 37 weeks and no severe features, or in some cases < 34 weeks if severe features are present but stable and hypertension is controlled,
      - In those cases, give steroids for lung maturation and attempt to delay delivery ≥ 48 hrs if otherwise stable.
  - Antihypertensive therapy
    - For severe-range hypertension to prevent maternal stroke
      - First line: IV labetalol or hydralazine; PO nifedipine
      - Other beta or calcium channel blockers may be used, but their safety is less clear.
      - Methyldopa: historically used due to fetal safety profile but less effective than first-line agents
      - Diuretics: counteract normal expansion of blood volume; not usually started during pregnancy
      - Angiotensin-converting enzyme inhibitors (ACEIs), angiotensin receptor blockers (ARBs): contraindicated in pregnancy due to decreased fetal renal perfusion and skull ossification
    - Antihypertensives are of unproven benefit for milder hypertension, and thus are not typically recommended.
  - Maternal effects: stroke, seizures, renal dysfunction, hemorrhage, death
  - Fetal effects: IUGR, PTD, placental abruption, hypoxia, perinatal death
- Cardiac disease
  - Complicates 1%–4% of pregnancies
  - Congenital heart disease (CHD) is more common than acquired disease
  - A leading cause of maternal mortality: preconception consultation to
    - Optimize prepregnancy maternal medical or surgical therapy
    - Provide contraception until maternal health is optimized
    - Discuss pregnancy contraindications (high maternal mortality)
      - New York Heart Association (NYHA) Class III or IV symptoms, severe mitral or aortic stenosis, aortic root dilation > 4.5 cm, severe pulmonary hypertension, ejection fraction ≤ 30%, prior peripartum cardiomyopathy with persistent dysfunction, or symptomatic coronary artery disease
  - Most conditions are managed similarly to those in the nonpregnant state, but
    - Higher risk of decompensation (increased cardiovascular demands)
    - Some medical therapy contraindicated (e.g., ACEIs, ARBs)
    - Surgical interventions may carry unacceptable fetal risks
      - Fetal loss risk with maternal cardiopulmonary bypass
    - Maternal effects: cardiac arrhythmias, functional decompensation (may be permanent), heart failure, VTE, death
    - Fetal effects: IUGR, PTD, death, CHD (up to 15% if maternal CHD)
  - Management
    - Serial assessment of maternal cardiac function (with echocardiography [echo])

- Multidisciplinary maternal care
- Fetal echocardiography (if maternal CHD) and fetal surveillance
- Delivery planning
  - Timing of delivery determined by maternal cardiac status
  - Vaginal delivery preferred for most diseases; may be assisted delivery if patient cannot undergo Valsalva
  - Epidural recommended to decrease catecholamine release

- Pulmonary disease
  - Risks are related to degree of maternal hypoxia and ability to tolerate physiologic changes in pregnancy
  - Maternal effects: worsening hypoxia, respiratory failure, death
  - Fetal effects: IUGR and PTD
  - General management
    - Multidisciplinary maternal care
    - Supplemental O_2 to keep O_2 saturation >95%
    - Fetal surveillance
    - Preterm delivery if refractory respiratory insufficiency
      - Vaginal delivery with epidural preferred
  - Asthma
    - No alterations in care from nonpregnant state
    - Most pregnancies have good outcome
    - Increased risk of PPROM and PTD if steroid dependent
  - Cystic fibrosis (CF)
    - High risk of serious complications: maternal malnutrition, need for mechanical ventilation, infection, diabetes (gestational effects + pancreatic insufficiency), PTD; 1% maternal mortality
  - Respiratory infections
    - Increased risks due to relative immune suppression
      - High attack rates and hospitalization rates; worse outcomes
    - Pneumonia
      - 25% of cases require hospitalization
      - 2% intubation; 2% maternal mortality
      - Care is similar to nonpregnant patients
    - Influenza
      - 10× rate of hospitalization and intensive care unit (ICU) admission
      - Universal immunization is recommended
      - Prompt antiviral treatment of pregnant women decreases ICU and hospital admission, mechanical ventilation, and death
- Renal disease
  - Risk of complications is proportional to degree of renal insufficiency
  - Maternal effects: hypertensive disorders and declining renal function
  - Fetal effects: PTD (usually indicated), IUGR, perinatal mortality
  - Concurrent hypertension or diabetes worsens perinatal outcomes
  - Serum creatinine level >2.5 mg/dL is a relative contraindication to pregnancy; high probability of end-stage renal disease with low live birth rate
  - Dialysis confers high risk of fetal loss; ≈100% risk of PTD and IUGR
  - Renal transplant recipients can have successful pregnancies if >1-year posttransplantation, no signs of rejection, and minimal residual insufficiency
  - Management: laboratory and fetal surveillance
    - Term or near-term delivery if stable (although PTD is commonly indicated)
- Hematologic disease
  - Anemia (hemoglobin [Hgb] <11 g/dL)
    - Iron deficiency is the most common cause; universal supplementation decreases maternal anemia and iron deficiency at term
    - Fetal effects: usually good perinatal outcome; adverse effects (e.g., IUGR, PTD, perinatal death) only in severe cases
  - Hemoglobinopathies
    - Severity of disease depends on gene carriage
    - Fetal risks include inheritance, miscarriage, IUGR, or stillbirth
    - Sickle cell disease (SCD)
      - Sickle cell trait has favorable pregnancy outcome, but 25% risk of SCD in offspring if both partners have trait
      - Maternal effects: pain crisis (75%), infection, acute chest syndrome, blood transfusion, VTE, death (1%)
      - Management
        - Genetic counseling, maternal vaccination, high-dose folic acid supplementation (4 mg daily)
        - Laboratory and fetal surveillance: most can deliver at term
      - Alpha-thalassemia
        - Pregnancy outcome and degree of anemia depend on number of normal alpha genes (four = normal, zero = lethal)
        - Most affected pregnancies occur in silent carriers or those with mild anemia (two or three functional alpha genes); most have a favorable pregnancy outcome
        - Management: laboratory screening and genetic counseling; *cis* mutations (Southeast Asians) confer risk of lethal anemia
- Thromboembolic risk: personal and family history and thrombophilia test results determine the need for antepartum or postpartum anticoagulation
  - Heparins do not cross the placenta, thus lack direct fetal effects
  - Warfarin crosses the placenta and confers 6% risk of embryopathy
  - No obstetric safety data for other anticoagulant medications
  - Mechanical heart valves pose high risk of thrombosis
    - Heparin is less effective than warfarin in this context; warfarin's maternal benefits may outweigh fetal risks
- Immunologic disease
  - Lupus
    - Outcomes depend on periconception disease status and presence of comorbid conditions; best outcomes are with quiescent disease more than 6 months before conception
    - Maternal effects: hypertension, renal insufficiency, VTE

- Fetal effects
  - Miscarriage, stillbirth, IUGR, PTD
  - Fetal marrow suppression (if on immunosuppressants)
  - Congenital heart block (anti-Ro, anti-La antibodies)
  - Transient neonatal lupus syndrome (maternal antibodies)
- Management
  - Most treatments are compatible with use in pregnancy; improved outcomes with hydroxychloroquine
  - Laboratory and fetal surveillance: term delivery if stable
- Antiphospholipid antibody syndrome
  - Increased risk of VTE: prophylaxis with heparins, low-dose aspirin
  - Fetal effects: IUGR and stillbirth
- Idiopathic thrombocytopenia purpura (antiplatelet antibodies)
  - Antibodies cross placenta; may cause neonatal thrombocytopenia
  - Maternal platelet counts do not correlate well with neonatal counts
  - Spontaneous vaginal delivery is acceptable; operative vaginal delivery is relatively contraindicated

- Malignancy
  - Gestational age at diagnosis may alter management and prognosis.
    - Tumor growth is generally not affected by pregnancy.
  - Pregnancy termination
    - Consider with first-trimester diagnosis if needed to expedite definitive maternal therapy
    - Is advised for lethal fetal conditions (e.g., moles)
  - Most chemotherapy agents can be used after first trimester
    - Main exception is folate inhibitors (methotrexate)
    - Maternal benefits of prompt treatment usually outweigh fetal risks of therapy
    - Surgery is usually acceptable, but radiation is contraindicated
  - Fetal effects: IUGR, PTD (to pursue more aggressive maternal therapy), and hematologic suppression (delivery should be timed several weeks after last chemotherapy course to minimize risk)
    - Fetal metastases (rare, most common with melanoma)
- Phenylketonuria
  - Fetal effects: fetal inheritance, low birth weight, cardiac defects, microcephaly, cognitive impairment
  - Management
    - Genetic counseling
    - Maternal dietary management: best if phenylalanine level <6 mg/dL before and during pregnancy (diet unpleasant; compliance is poor)
    - Fetal evaluation: targeted anatomy survey and echocardiography
    - Term delivery
- Neurologic disease
  - Epilepsy
    - 90% of women have a healthy pregnancy
    - Planned conception and optimization of antiepileptic drugs (AEDs) result in fewer seizures and fetal anomalies
    - If seizure-free for 6–12 months and the neurologist agrees, consider stopping AEDs several months before conception
    - If possible, discontinue potentially teratogenic AEDs
      - Phenytoin—skull, facial, brain anomalies; IUGR
      - Valproic acid—neural tube, facial, cardiac defects; hypospadias; poor cognition
      - Topiramate—facial clefts
      - Carbamazepine—facial clefts
  - Management: serum AED monitoring, high-dose folic acid (although benefit uncertain with AEDs), targeted anatomy survey (consider echocardiography), term labor and delivery. Goal is lowest effective dose of monotherapy
- Spinal cord injury
  - Fertility is not compromised
  - Maternal effects: urinary tract infections, pressure ulcers, altered mobility, VTE, autonomic dysreflexia
  - Fetal effects: unattended birth (maternal nonawareness of labor)
  - Management
    - Serial urine cultures; antibiotic suppression for recurrent urinary tract infections (UTIs)
    - Serial cervical examinations and maternal education on symptoms of labor (e.g., abdominal tension, lower extremity cramping and spasticity, dyspnea)
    - Delivery planning
      - Minimize autonomic dysreflexia: early epidural, Foley catheter, frequent vital sign monitoring
      - Assisted vaginal delivery if unable to push
- Multiple sclerosis
  - Remission in pregnancy is typical; postpartum flares are common.
  - Treatment with disease-modifying drugs:
    - Reassuring but limited fetal safety information
    - Decreases risk of postpartum flare
    - Some providers discontinue during pregnancy because outcomes are generally favorable without treatment
  - Fetal effects: IUGR
- Myasthenia gravis
  - Management generally is similar to nonpregnant state
  - Usually stable during pregnancy; perinatal outcome good; flares most common in first trimester
  - Transient neonatal myasthenia: 10%–20% risk from passage of antiacetylcholine receptor antibodies; may persist for 3 months
  - Some commonly used medications may precipitate myasthenic crisis and should be avoided: antibiotics (aminoglycosides, vancomycin, clindamycin), beta blockers, magnesium sulfate
- Infectious disease
  - HIV: universal prenatal testing is recommended
    - Main obstetric risk is perinatal transmission
      - Proportional to maternal viral load
      - Greatest risk with initial seroconversion
    - Reduction in perinatal transmission
      - Antiviral treatment reduces risk from 25% to <2% (antepartum, intrapartum, neonatal prophylaxis)

- Most antiretrovirals are acceptable for use
- Avoid fetal exposure to maternal blood (invasive testing, rupture of membranes, fetal scalp electrode placement)
- Vaginal delivery is appropriate unless viral load >1000, in which case cesarean delivery is scheduled at 38 weeks

- Hepatitis B
  - Universal prenatal testing is recommended
  - Main obstetric risk is perinatal transmission
    - Proportional to maternal viral load and e-antigen positivity
    - Reduction in perinatal transmission
      - Universal neonatal vaccination and hepatitis B immunoglobulin (HBIG) prophylaxis markedly reduces risk
      - Antivirals are acceptable for use in pregnancy; treatment recommended for log viral load ≥5
      - Avoid fetal exposure to maternal blood
      - No benefit to cesarean delivery
- Hepatitis C
  - Screen high-risk patients (history of drug abuse, prior blood transfusion, seropositive partner)
  - Main obstetric risk is perinatal transmission
    - Avoid fetal exposure to maternal blood
    - No benefit to cesarean delivery
- Herpes: if positive history, begin acyclovir at 36 weeks to minimize shedding at birth. Cesarean if active lesion while in labor
- Acute pyelonephritis
  - Maternal effects: sepsis, acute respiratory distress syndrome (ARDS), respiratory failure
  - Fetal effects: PTD or fetal death
  - Prompt antibiotic treatment improves outcomes

- Psychiatric illness
  - Pregnancy risks of untreated disease: poor engagement with prenatal care, suicide, poor maternal weight gain, IUGR, neonatal neurodevelopmental impairment
  - Adequate mental health care improves maternal self-care, function, compliance with prenatal care, and lowers the risk of self-harm
  - Risks of untreated disease generally outweigh risks of medication
    - Selective serotonin reuptake inhibitors (SSRIs)
      - Commonly used with relative safety
      - Sertraline is preferred first-line agent
      - Paroxetine has inconsistent association with fetal cardiac defects; consider echocardiography if used
      - Neonatal effects: abstinence syndrome
    - Antipsychotics: increased risk of diabetes
    - Benzodiazepines: small increase in facial clefts; neonatal hypotonia and abstinence syndrome
    - Mood stabilizers: lithium has been associated with Ebstein anomaly (newer data dispute this risk); consider fetal echo
- Trauma
  - Falls, motor vehicle accidents, domestic violence, penetrating trauma
  - Perinatal risks: uterine rupture/trauma, placental abruption, fetal hypoxia, fetal injury, PTD, perinatal death
  - Maternal stabilization is first priority, then:
    - Establish gestational age; ultrasound/fetal survey; monitor FHR
    - Expedited delivery for fetal indications if the mother is stable or perimortem
- Nonobstetric surgery
  - Surgery indicated for essential maternal indications should be performed.
    - Fetal risks of untreated maternal disease outweigh those of surgery.
  - If possible, nonurgent (but indicated) surgery should be deferred to second trimester because miscarriage and preterm contractions are less likely.
  - Elective surgery should be postponed until after delivery.
  - Increased risk of PTD after surgery during pregnancy; may be due to condition that necessitates surgery or to surgery itself
  - Anesthesia
    - No currently used general anesthetics are teratogenic
    - Physiologic changes in pregnancy raise risks of general anesthesia (remains relatively safe if no concurrent cardiorespiratory disease)
      - Airway changes can complicate intubation
      - Increased susceptibility to hypoxia
      - Delayed gastric emptying with increased risk of aspiration
    - Regional anesthesia may be appropriate and minimizes maternal risks and fetal drug exposure
  - Intraoperative optimization
    - Avoid hypotension: avoid supine positioning (use left lateral tilt); anticipate and aggressively treat hemorrhage
    - Avoid hypoxia: preoxygenate before anesthesia induction and maintain normal ventilation
    - FHR monitoring during surgery is controversial; may depend on the procedure, gestational age, and feasibility

FETAL CONDITIONS

- Aneuploidy
  - Diagnosed by karyotype or microarray via amniocentesis, CVS, or umbilical cord blood sampling (cell-free DNA is a screen, not definitive)
  - High rate of structural anomalies and fetal loss
  - Multidisciplinary care is recommended for ongoing gestations
- Anomalies
  - Fetal anomalies may be isolated or multiple as part of a syndrome
  - Prognosis is highly variable; depends on type and number of anomalies
  - Certain anomalies may dictate delivery timing or management
    - Cesarean delivery is recommended for
      - Bulky external defects (hydrocephalus, large omphalocele)
      - Defects at risk of rupture (myelomeningocele—although outcome data on planned cesarean delivery are conflicting)
      - Defects with risk of hemorrhage (sacrococcygeal teratoma)

- Defects that require immediate postnatal intervention (e.g., congenital heart disease with intact atrial septum)
- EXIT (ex utero intrapartum treatment) procedure for conditions associated with severe airway obstruction (e.g., large epignathus or severe micrognathia)
  - Fetal head delivered during cesarean done under deep general anesthesia, placental circulation maintained, airway placed, delivery completed
- Vaginal delivery following spontaneous labor appropriate for most other anomalous fetuses (including gastroschisis)

- Alloimmunization
  - Red blood cell alloimmunization, isoimmunization
    - Maternal sensitization to RBC antigens from fetal-maternal hemorrhage or maternal blood transfusion
    - Maternal antibodies cross the placenta and cause immune-mediated destruction of fetal RBCs
    - Severe fetal anemia may lead to hydrops or death
    - Fetus is at risk if positive maternal antibody screen titer >1:8 or prior affected fetus and father is positive for RBC antigen; paternal antigen testing can stratify risk
    - Management: serial antibody titers and serial ultrasound screening for fetal anemia (if at risk)
      - Fetal transfusion for severe fetal anemia by fetal middle cerebral artery Doppler confirmed by percutaneous umbilical blood sampling (PUBS)
  - Fetal or neonatal alloimmune thrombocytopenia
    - Maternal sensitization to fetal platelet antigens
    - Maternal antibodies cross the placenta and cause immune-mediated destruction of fetal platelets; confers high risk of IVH
    - Diagnosis (suspected if prior affected neonate or current finding of prenatal intracranial hemorrhage)
      - Parental platelet antigen typing with evidence of maternal-paternal mismatch; maternal antiplatelet antibodies
    - Management: prenatal maternal intravenous immunoglobulin (IVIG) and steroids; avoid vaginal delivery if fetal cord platelet count < 100,000/μL.
- Fetal hydrops
  - Immune hydrops
    - Fetal cardiac failure secondary to severe anemia from maternal RBC alloimmunization
    - Incidence decreased with use of Rh immune globulin; other RBC antigens now relatively more common
  - Nonimmune hydrops
    - Fetal cardiac failure from other causes
    - Broad differential diagnosis
      - Cardiac: heart defects or arrhythmias; high-output failure
      - Aneuploidy and genetic syndromes
      - Structural anomalies: skeletal, thoracic, urinary tract
      - Other: anemia, infection, metabolic defects
    - Evaluation includes ultrasound, amniocentesis for genetic and microbiologic analyses, and maternal antibody screen and Kleihauer Betke
    - Some cases are treatable (e.g., fetal anemia or arrhythmias), but most are not
    - Prognosis is poor and depends on gestational age, degree of hydrops, and presumptive cause
- Fetal growth restriction
  - Defined as sonographic EFW <10th percentile (but most fetuses <10th percentile are constitutionally small and not growth restricted)
  - Pathologic causes of small for gestational age fetus
    - Uteroplacental insufficiency (most common)
      - Lagging abdominal circumference may be an early sign
      - Confirmed by oligohydramnios and/or abnormal Doppler
    - Structural anomalies, aneuploidy, and genetic syndromes
      - Amniocentesis recommended for karyotype and microarray
    - Fetal infection: suspected with concurrent calcifications, microcephaly, ventriculomegaly, brain abnormalities
      - Diagnosed by amniotic fluid culture or polymerase chain reaction (PCR) assay
    - Management
      - Twice-weekly nonstress tests (NSTs)
      - Weekly ultrasound for amniotic fluid volume and Doppler
      - Serial assessment of fetal growth (every 2–3 weeks)
      - Early delivery may be indicated for nonreassuring testing, Doppler findings, or lack of interval growth
- Macrosomia
  - Variably defined as EFW >4000 g or >4500 g
  - Increases the risk of cephalopelvic disproportion and shoulder dystocia
    - Cesarean delivery considered for EFW >4500 g (diabetic) or EFW >5000 g (nondiabetic) because shoulder dystocia risk is >50%
  - Management is hampered by inaccuracy of sonographic EFW estimates leading to cesarean deliveries that in retrospect were unnecessary.
- Fetal infections
  - Transplacental: rubella, cytomegalovirus (CMV), herpes simplex virus (HSV; generally primary), parvovirus, toxoplasmosis, listeria, syphilis
  - Intrapartum: HIV, varicella, hepatitis B and C, group B Streptococcus (GBS), HSV
  - Maternal symptoms often mild or absent but there may be sonographic signs of fetal infection (most often IUGR, calcifications, or hydrops)
  - Diagnosis and treatment
    - Maternal serology (may be difficult to determine time of exposure)
    - Amniotic fluid culture or PCR (specific for fetal infection but may lack sensitivity if done early; repeat testing may be required)
    - Antibiotic treatment is available for some maternal and fetal infections (e.g., toxoplasmosis, syphilis)
    - Intrauterine transfusion may be indicated (and lifesaving) with severe fetal anemia due to parvovirus
    - Universal GBS screening and intrapartum antibiotic prophylaxis of GBS-positive women decrease early-onset GBS sepsis

- Complications of twins
  - Conjoined twins: rare (≈1% of monozygotic twins)
    - Prognosis is poor; depends on number and nature of shared organs
  - Dichorionic twins
    - Most common type of twinning (≈two-thirds of all twins)
    - Maternal risks: gestational DM, preeclampsia, anemia, acute fatty liver, cesarean delivery, postpartum hemorrhage
    - Fetal risks: miscarriage, stillbirth, structural and genetic anomalies, growth disturbances, PTD, malpresentation, PROM, umbilical cord prolapse, abruption after delivery of first twin
    - Delivery generally at 38 weeks, with route depending on presentation (trial of labor is acceptable if presenting twin is cephalic, irrespective of twin B presentation)
  - Monochorionic twins
    - Approximately one-third of all twin pregnancies
    - Risks include those of dichorionic twins, with additional risks:
      - Twin-twin transfusion syndrome (TTTS): vascular anastomoses result in unbalanced blood flow between twins
        - Donor twin: anemia, IUGR, and oligohydramnios ("stuck twin" if severe)
        - Recipient: polycythemia, large EFW, polyhydramnios
        - Affects 15% of monochorionic twin pregnancies
        - Less frequent when monoamniotic
      - Staged I–V based on sonographic features
        - Consider laser therapy if above stage I
        - High risk of perinatal loss if untreated severe TTTS
    - Twin anemia-polycythemia sequence (TAPS)
      - Form of TTTS resulting in disparate fetal hematocrits without amniotic fluid discrepancies
      - Caused by fewer or smaller caliber anastomoses
    - Twin reversed arterial perfusion (TRAP)
      - One normally developed twin and one acardiac twin
      - "Pump" twin's heart is responsible for circulation through both fetuses; at risk for high-output failure
      - Treated with selective umbilical cord occlusion of the acardiac twin
    - Monoamniotic twins
      - High risk of cord entanglement and fetal demise
      - Close fetal surveillance starting at viability
      - Cesarean delivery at 32–34 weeks
    - Co-twin death
      - Dichorionic: Slight increase in risk of death for surviving twin
      - Monochorionic: ≈20% risk of death or neurodevelopmental injury in surviving twin from acute hypotension/exsanguination into low-resistance dead co-twin
      - Expectant management (close sonographic and FHR monitoring with delivery by 36 weeks) following co-twin death
        - Expedited delivery is unlikely to improve outcome

OBSTETRIC COMPLICATIONS

- Placenta previa
  - Placenta covering the internal cervical os
  - Risk factors: prior cesarean delivery or uterine surgery, prior placenta previa, multifetal gestation, multiparity, smoking
  - Diagnosis
    - Transvaginal ultrasound in second trimester
    - Repeat ultrasound at 32–35 weeks to rule out persistence
    - Most previas resolve by term
      - Uterus grows, and the placental edge draws away from os
  - Maternal-fetal complications
    - Hemorrhage (two-thirds have antepartum bleeding), placenta accreta, PTD, hysterectomy, maternal or fetal death
  - Management
    - Pelvic rest; cesarean at 36–38 weeks (depending on stability)
- Low-lying placenta (within 2 cm of but not covering os)
  - Hemorrhage risk increased with proximity to os
  - Cesarean delivery considered if <1 cm from os
- Vasa previa
  - Rare complication of velamentous cord: fetal vessels traverse cervical os
    - Fetal exsanguination can occur when membranes rupture
  - Diagnosed by transvaginal ultrasound
  - Management
    - Consider antepartum admission for fetal surveillance and proximity to obstetric and neonatal ICU (NICU) services
    - Cesarean delivery at 34–36 weeks
- Placenta accreta, increta, and percreta (abnormal trophoblast invasion)
  - Risk factors: prior cesarean delivery; uterine surgery (risk proportional to number of surgeries), or placenta accreta; placenta previa; submucous fibroid; age ≥35 years; smoking
  - Diagnosis by ultrasound in second or third trimester
    - Multiple placenta lacunae ("moth-eaten" appearance)
    - Increased vascularity at bladder interface
    - Lack of normal retroplacental hypoechoic zone
  - Classification
    - Accreta: villi adherent to (but do not invade) myometrium
    - Increta: villi invade myometrium
    - Percreta: villi extend to uterine serosa or into adjacent structures
  - Maternal-fetal complications: hemorrhage, disseminated intravascular coagulation (DIC), PTD, IUGR, hysterectomy, maternal or fetal death
  - Management
    - Planned 34- to 36-week cesarean delivery via fundal incision to avoid placenta; placenta left in situ, and hysterectomy done
    - Preparation for potential massive blood product transfusion and/or bowel-bladder resection

- Placental abruption
  - Partial or complete detachment of the placenta from the uterine wall prior to delivery of the fetus; may be chronic or acute
  - Signs and symptoms: abdominal pain, vaginal bleeding (but may be concealed), uterine hypertonus or tachysystole, FHR abnormalities
  - Risk factors (but most cases occur without risk factors): smoking, hypertension, trauma, cocaine use, polyhydramnios, twins, rupture of membranes (ROM)
  - Maternal risks: hemorrhage, coagulopathy, cesarean delivery, hysterectomy, and death
  - Fetal risks: PTD, asphyxia, perinatal death
  - Management depends on gestational age and degree of hemorrhage
    - When preterm, expectant management considered as long as bleeding not excessive, vital signs stable, fetal status reassuring
    - Inpatient hospitalization until bleeding resolves
    - Steroids for fetal maturity
    - Close maternal and fetal surveillance
    - Delivery at 36–37 weeks
- Antepartum and intrapartum hemorrhage
  - Differential diagnosis of vaginal bleeding
    - First trimester: miscarriage (up to 60% are due to aneuploidy)
    - Second and third trimesters: PTL (Preterm labor), placenta or vasa previa, abruption, PROM
  - Maternal risks: coagulopathy, hypovolemia, shock, death
  - Fetal risks: PTD, IUGR, nonreassuring fetal status, perinatal death
- PPROM
  - Risk factors: smoking, antepartum hemorrhage, polyhydramnios, multifetal gestations, trauma, invasive procedures
  - Maternal risks: infection, sepsis, abruption, cesarean delivery
  - Fetal risks: PTD, fetal infection, sepsis, IUGR, umbilical cord prolapse, perinatal death
  - Management
    - Hospitalization (close outpatient observation can be considered in select patients); most patients deliver within 7 days of PPROM
    - Steroids, GBS prophylaxis, latency antibiotics (increase time from PPROM to delivery), and serial maternal-fetal assessment
    - Optimal timing of delivery is unknown; delivery usually initiated at ≥34 weeks
- Preterm labor
  - 50% of patients admitted with threatened PTL ultimately deliver at term
  - Risk factors
    - Maternal: uterine anomalies, trauma, infection, maternal illness, low socioeconomic status, African-American ethnicity
    - Obstetric: multifetal gestations, PPROM, antepartum hemorrhage/abruption, cervical insufficiency
    - Fetal: anomalies, genetic syndromes, IUGR
  - Maternal risks vary by underlying cause
  - Fetal risks: PTD, infection, sepsis, malpresentation, umbilical cord prolapse, perinatal death
  - Management
    - Hospitalization, GBS prophylaxis, steroids
    - Tocolysis for 48 hours to complete steroid course; long-term tocolysis not beneficial

SERIAL MATERNAL-FETAL ASSESSMENT

- Oligohydramnios
  - Variably defined as an amniotic fluid index (AFI or four-quadrant technique) <5 cm or single deepest vertical pocket (SDP) <2 cm
  - SDP technique results in equivalent perinatal outcome but fewer inductions and cesarean deliveries
  - Differential diagnosis: rupture of membranes, fetal urinary tract anomalies, uteroplacental insufficiency
  - Management depends on underlying cause; rupture of membranes and uteroplacental insufficiency may prompt indicated PTD
- Polyhydramnios
  - Variably defined as AFI ≥24 cm or SDP ≥8 cm
  - Differential diagnosis
    - Idiopathic (most common), DM, aneuploidy, TTTS, fetal hydrops, fetal neuromuscular disorder (impaired fetal swallowing), structural anomalies that obstruct fetal swallowing (e.g., GI obstruction, facial clefts, restrictive skin defects)
  - Maternal risks: hemorrhage, dyspnea, cesarean delivery
  - Fetal risks: malpresentation, PTD, cord prolapse, placental abruption
  - Management depends on cause
    - Amnioreduction for maternal symptoms
    - Most cases can deliver at term
- Postterm pregnancy: pregnancy progressing into the 42nd gestational week
  - Uncommon because earlier spontaneous or induced delivery is likely
    - Increasing evidence that labor induction after 39 weeks avoids fetal risks of ongoing pregnancy without increased maternal risk
  - Fetal effects: dysmaturity, hypoxia, meconium, macrosomia, stillbirth
  - Management:
    - Fetal surveillance with NST and AFI assessment after 40 weeks; delivery preferable before 42 weeks

DRUG AND ENVIRONMENTAL EXPOSURES

- Teratogenic effects are related to agent, dose, duration, and time of exposure
  - Before 6 weeks: "all or none" effect (embryo death vs. no effect)
  - Between 6–9 weeks: organogenesis may be affected
  - After 9 weeks: may impair organ development and maturation
- Medication exposures
  - Commonly used in obstetric management
    - Calcium channel blockers (e.g., nifedipine)—no adverse effects

- Beta blockers (e.g., labetalol)—IUGR
- Beta agonists (e.g., terbutaline)—tachycardia, neonatal hypoglycemia
- Nonsteroidal antiinflammatory drugs (e.g., indomethacin, ibuprofen)
  - Short courses in second trimester are well tolerated
  - Use at >32 weeks can cause premature ductus constriction.
  - Prolonged use—fetal renal injury
- Magnesium sulfate—poor neonatal tone and respiratory effort
- Steroids
  - Fluorinated steroids (e.g., betamethasone, dexamethasone) readily cross the placenta; nonfluorinated steroids (e.g., prednisone, methylprednisolone) are largely inactivated
  - Beneficial effects for fetal maturity—increased surfactant production; decreased risk of IVH, necrotizing enterocolitis, and perinatal death
  - Adverse fetal effects with chronic or repeated use—facial clefts, decreased growth and head size, adrenal suppression

- Radiation exposures
  - Teratogenic effects unlikely if 5–10 mGy (this is more than most diagnostic tests)
  - High-dose exposure: "all or none" effect in early first trimester, but later exposure associated with IUGR, smaller head size, cognitive impairment
  - Therapeutic procedures
    - Radiation therapy is contraindicated in pregnancy.
    - Radioactive iodine (to treat maternal Graves disease)
      - ≤12 weeks—generally no observed fetal effects
      - >12 weeks—concentrated in fetal thyroid: hypothyroidism
- Drugs of abuse
  - Tobacco: (≈10% during pregnancy in the United States)—associated with PPROM, abnormal placentation, IUGR, PTD, and sudden infant death syndrome
  - Marijuana: (≈6%–8% during pregnancy in the United States)—associated with low birth weight, neurocognitive impairment, and sudden infant death syndrome
  - Alcohol: fetal alcohol syndrome (FAS)—associated with IUGR, microcephaly, facial dysmorphism (short palpebral fissures, thin upper lip, smooth philtrum)
    - Common cause of neurocognitive impairment
    - Dose-response effect but no known threshold for a safe intake
  - Cocaine and amphetamines: associated with increased risk of miscarriage, hypertension, placental abruption, PTL, PPROM, maternal cardiac arrest
    - Fetal and neonatal effects: ischemic malformations (cocaine), PTD, IUGR, perinatal death, neonatal withdrawal symptoms, neurocognitive impairment
  - Heroin, opioids: associated with increased risk of infectious sequelae of IV drug use (e.g., hepatitis, HIV, bacteremia, endocarditis, other STIs), miscarriage, IUGR, placental abruption, PTD, stillbirth
    - Neonatal abstinence syndrome affects 60%–70% of exposed neonates
    - Breastfeeding decreases duration and severity and is advised if no illicit use
  - Complications are lower with opioid agonist therapy (methadone or buprenorphine); lower rate of relapse than detoxification
- Environmental exposures
  - Lead: sources of exposure include drinking water, flaking house paint, workplace exposure, jewelry, cosmetics, dishes from outside the United States, herbal supplements
    - Fetal effects: miscarriage, IUGR, PTD, cognitive impairment
  - Mercury: exposure from large fish, dental amalgams, thermometers, cosmetics and ceramics from outside the United States, and industrial waste
    - Fetal effects: cognitive impairment or Minamata disease

Suggested Readings

American Academy of Pediatrics and American College of Obstetricians and Gynecologists. *Guidelines for Perinatal Care*. 8th ed. Washington, D.C.: American College of Obstetricians and Gynecologists; 2017.

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Questions

1. Which of the following is true regarding maternal adaptation to pregnancy and the impact on chronic disease?
   a. Serial echocardiography should be done in mothers with cardiac disease because pregnancy-induced cardiovascular changes may worsen cardiac dysfunction.
   b. Peak flow monitoring cannot be used for asthma management because peak expiratory flow and FEV_1 are altered by pregnancy.
   c. Increased doses of antihypertensives are required in pregnancy because of the increase in systemic vascular resistance.
   d. Pregestational diabetics require less insulin during pregnancy because of lower renal clearance of insulin.
   e. Free T_4 levels cannot be used to monitor thyroid disease because these values are increased in pregnancy.

2. An Ashkenazi Jewish couple with a child affected by Tay-Sachs disease presents for preconception counseling. Their child's genetic analysis has identified a causative mutation that is detected on routine screening panels. Neither partner has had prior genetic testing. The wife has chronic hypertension treated with lisinopril. All the following are recommended except:
   a. Folic acid supplementation prior to conception
   b. Discontinuance of lisinopril and labetalol started before conception
   c. Expanded carrier screening for Eastern and Central European Jewish descent
   d. An interpregnancy interval of less than 18 months
   e. Gamete donation from a known Tay-Sachs negative donor to conceive the next pregnancy

3. A 30-year-old G3P1011 woman presents at 12 weeks with known Kell sensitization (red blood cell alloimmunization). She had an uncomplicated pregnancy 4 years ago and a 24-week fetal demise that occurred last year. She had a motor vehicle accident 5 years ago that required multiple blood transfusions. She is wondering if Kell sensitization caused the fetal demise. How would you answer her question?
   a. It definitely caused the fetal demise.
   b. It cannot cause fetal demise unless there was bleeding in the pregnancy.
   c. It did not cause the fetal demise because her first pregnancy was uncomplicated.
   d. It may have caused the demise; paternal antigen testing is required to determine if other pregnancies are at risk.

4. Which of the following is not routinely recommended in the management of pregestational diabetes in pregnancy?
   a. Nutrition consult to review dietary and lifestyle modifications
   b. Fetal echocardiography at 20 weeks due to increased risk of congenital heart defects
   c. Frequent blood glucose checks and oral hypoglycemics or insulin as needed
   d. Cesarean delivery if the EFW > 4500 g, given the high risk of shoulder dystocia
   e. All patients should be delivered at 37 weeks due to an increased risk of stillbirth,

5. A 27-year-old G1P0 at 29 weeks is admitted with new severe range hypertension. Antihypertensives and a steroid course are ordered. Laboratory evaluation shows 1400 mg/day proteinuria, creatinine of 1.0 mg/dL, AST of 106 mg/dL, platelet count of 95,000/μL, and hematocrit of 28%. Other laboratory tests are normal. A reactive NST was obtained. Fetal growth is normal. The patient has no symptoms. What is the diagnosis, and what is the most appropriate next step in management?
   a. Gestational hypertension; discharge from the hospital with close outpatient follow-up
   b. Preeclampsia without severe features; expectant management until 37 weeks
   c. HELLP syndrome; delivery after completion of steroid course
   d. Preeclampsia with severe features; delivery after confirmation of fetal lung maturity
   e. Preeclampsia with severe features; expectant management until 34 weeks of gestation of controlled hypertension, stable laboratory results, and reassuring fetal status

6. A patient has a normal fetal anatomy survey at 18 weeks. She decides to have maternal serum quad testing for aneuploidy screening, which shows an elevated risk of trisomy 21. Which of the following is true?
   a. The anatomy survey must have overlooked features of trisomy 21 because the false-positive rate of the quad screen is low.
   b. The quad screen must be a false-positive because no sonographic features of trisomy 21 were detected.
   c. Diagnostic testing for trisomy 21 should be offered.
   d. The fetus has trisomy 21.

3 Fetal Assessment and Treatment

J. CHRISTOPHER GLANTZ and LISA M. GRAY

Invasive Fetal Testing

- Common indications for genetic testing (amniocentesis or chorionic villus sampling [CVS])
  - Advanced maternal age (≥35 years at delivery), abnormal genetic screening, fetal anomalies, maternal or previous fetal aneuploidy, history of metabolic disease or hemoglobinopathy
- Chorionic villus sampling
  - Performed at 11–13 weeks; not always successful
  - Samples placental villi; 1% chance of confined placental mosaicism (aneuploid cells make up part of the placenta but are not found in the fetus)
  - 0.5%–1% risk of pregnancy loss
- Amniocentesis
  - Performed at ≥15 weeks
  - Allows genetic testing and/or assessment for fetal infection
  - Carries 1/200–1000 risk of pregnancy loss
- Fetal blood sampling (cordocentesis)
  - Performed at ≥18 weeks (limited by size and accessibility of fetal vessels)
  - Allows genetic testing, assessment of blood type, hematocrit, platelet count, fetal transfusion
  - Carries 1% risk of fetal loss

Genetic Testing

- Carrier screening: testing to identify carriers of autosomal recessive conditions. Couples who are both carriers have a 25% risk of having an affected child.
  - Carrier frequencies vary by race and ethnicity.
  - Cystic fibrosis: maternal blood is sent for targeted gene mutation analysis.
    - Highest incidence in caucasians
    - Universal screening is offered to mother; paternal testing offered if mother is a carrier
  - Tay-Sachs: maternal blood is sent for targeted gene mutation analysis
    - Highest incidence in Ashkenazi Jews
    - Maternal screening is offered in this population; paternal testing is offered if mother is a carrier
    - Expanded carrier screening panels are available for Ashkenazi Jews
  - Sickle cell disease and thalassemia
    - Sickle cell and β-thalassemia trait are identified by hemoglobin electrophoresis
    - The α-thalassemia trait can be identified by mild anemia with low mean corpuscular volume (MCV) on maternal complete blood count (CBC); hemoglobin electrophoresis and genetic testing may be necessary to confirm the finding
    - Targeted screening is recommended in at-risk ethnic groups (African-American, Mediterranean, Southeast Asian)
- Screening
  - Fetal aneuploidy
    - First trimester screening—ultrasound for nuchal translucency measurement + maternal blood for human chorionic gonadotropin (hCG) and pregnancy-associated plasma protein A (PAPP-A)
      - Performed at 11–13 weeks; set 5% screen-positive rate
      - 75%–80% sensitivity for trisomy 21 (lower for T18)
    - Second-trimester (quad) screening—maternal blood test for serum hCG, alpha-fetoprotein (AFP), estriol, and inhibin
      - Performed at 14–22 weeks; set 5% screen-positive rate
      - 75% sensitivity for trisomy 21 (lower for T18)
    - Cell-free DNA screening—free DNA in maternal blood is analyzed for chromosomal imbalances
      - Performed at ≥10 weeks
      - 99% sensitivity for trisomy 21
      - >90% sensitivity for trisomy 13 and 18, monosomy X
      - Not validated in low-risk populations
      - Too expensive to be the preferred aneuploidy screen
  - Maternal serum AFP (MSAFP)—maternal blood test that screens for open fetal defects (e.g., neural tube, ventral wall)
    - Performed at 14–22 weeks
    - High MSAFP indicates increased risk for open fetal defects; 95% sensitivity (ultrasound also sensitive for these defects)
    - Also associated with placental dysfunction, fetal growth restriction, multiple gestation, fetal demise, and underestimated gestational age
  - Group B Streptococcus (GBS)
    - 20% of pregnant women carry GBS in the vagina; it can be transmitted to the fetus at birth
    - Without intrapartum treatment, 1% of colonized neonates develop early-onset GBS sepsis
    - Maternal risk factors for neonatal GBS sepsis include PTL, preterm premature rupture of membranes (PPROM), intrapartum fever, previous GBS sepsis in a newborn, and GBS cystitis

- Universal screening protocol (rectovaginal culture at 35–37 weeks) with routine intrapartum prophylaxis has reduced the incidence of neonatal sepsis
- Rubella
  - Congenital infection can cause fetal anomalies or death
  - Universal screening is performed to identify at-risk women; postpartum vaccination is offered
- Hepatitis B
  - Vertical transmission is possible; infection is endemic in many parts of the world.
  - Universal screening (with hepatitis B surface antigen testing) is performed to identify the following:
    - Infected women for fetal risk assessment and possible antiviral treatment
    - At-risk women to offer antepartum vaccination
- Human immunodeficiency virus (HIV)
  - Vertical transmission is possible; infection is endemic in some parts of the world
  - Diagnosed by a combination of antigen/antibody testing; viral load can be assessed using the polymerase chain reaction (PCR) assay
  - Universal screening is recommended to identify infected women to offer antiviral treatment for maternal health preservation and prevention of neonatal transmission

- Diagnostic testing
  - Karyotype detects large duplications, deletions, and aneuploidy; 99.9% accuracy
    - Requires culture of amniocytes or villi so is subject to culture failure
  - Microarray: can detect microduplications and microdeletions
    - Can be performed on nonviable tissue
    - May detect variants of uncertain clinical significance that require comprehensive genetic counseling

Ultrasound Screening

- Gestational age determination
  - Due date determination by last menstrual period (LMP) may be imprecise (variation in menstrual cycle length and uncertain day of conception)
  - Sonographic fetal measurements can estimate gestational age
    - First trimester (most accurate)—fetal crown-rump length is used
      - Estimated due date (EDD) is changed if ultrasound (US) dating differs by >5–7 days from LMP dating.
    - Second and third trimester: composite biometry (combination of head, abdominal, and femur measurements) used
      - Second trimester US accuracy: ±10–14 days
      - Third trimester US accuracy: ±2–3 weeks
- Anomaly detection
  - Rationale: prenatal anomaly detection may do the following:
    - Inform parental decisions about abortion and avoidance of maternal morbidity from delivery procedures, and to clarify care goals.
    - Optimize fetal and neonatal care.
    - Transfer to higher level of care as indicated, engage needed specialists, permit fetal testing and interventions, allow postnatal planning.
  - Ability to detect anomalies depends on
    - Nature of the anomaly
      - High detection—spina bifida, abdominal wall defects
      - Low detection—small ASD/VSD, cleft palate without cleft lip
    - Number of fetuses: limited resolution in multifetal gestations
    - Maternal body habitus: limited resolution with obesity
    - Gestational age at examination
      - First trimester—limited by small fetal size
      - Second trimester—optimal age for anomaly detection
      - Third trimester—limited by fetal ossification, crowding
    - Experience of the ultrasound laboratory
  - RADIUS study (large randomized trial of routine prenatal ultrasound) did not show improved perinatal outcomes.
    - Detection rates varied by sites; rates of abortion varied.
- Aneuploidy detection
  - Rationale: fetal aneuploidy often has visible anomalies or markers
  - Fetuses with structural anomalies have increased risk of aneuploidy (varies by the anomaly)
  - First-trimester detection: nuchal translucency (NT) screening
    - Nuchal edema is associated with aneuploidy (risk proportional to NT measurement) and congenital heart disease
    - Risk is modified by concurrent maternal serum analyte testing
    - If NT > 3.0 mm
      - >10% risk of aneuploidy
      - Justifies diagnostic testing or cell-free DNA screening
      - Increased risk of fetal heart defects (need echo)
  - Second-trimester detection
    - Genetic sonogram looks for anomalies and sonographic markers (normal variants that are associated with fetal aneuploidy)
      - Absent nasal bone, nuchal fold ≥ 6 mm, echogenic bowel
      - Minor markers: choroid plexus cysts, echogenic intracardiac focus, short femurs/humeri, pyelectasis
      - Sonographic detection rates—60% for trisomy 21, up to 90% for trisomy 13 and 18
- Anemia surveillance
  - Anemia lowers blood viscosity; velocity of blood flow is inversely proportional to blood viscosity
  - Middle cerebral artery (MCA) peak systolic velocity (PSV) is measured with Doppler and converted to multiples of the median (MoM)
    - Weekly MCA-PSV surveillance with isoimmunization and high antibody titer
    - MCA-PSV > 1.5 MoM associated with moderate to severe fetal anemia; consider intrauterine transfusion
- Growth assessment
  - Fetal growth can be monitored with serial US
  - Fetal biometric measurements (head circumference, biparietal diameter, abdominal circumference, femur length) are used to determine estimated fetal weight (EFW)

- Accuracy of fetal weight estimates: ±10%–15%
- Reassess at ≥14-day intervals (results unreliable if done more frequently)

Evaluation of Fetal Status

- Fetal movement surveillance
  - Rationale: the fetus requires oxygen for physical activity; increased risk of stillbirth when decreased fetal movement
  - Mother counts fetal movements: ≥10 within 2 hours, normal
    - Decreased fetal movement should prompt antenatal testing
  - Poor discriminator of adverse outcomes
    - Most periods of decreased fetal movement are due to fetal sleep, normal variation, lack of maternal perception
    - Fetus may already be dead when lack of movement noted
- Nonstress test (NST)
  - Rationale: normal oxygenation is required for the heart to respond to autonomic nervous system signals (detectable by fetal heart rate (FHR) monitoring)
  - Consists of ≥20 minutes of FHR and uterine activity monitoring
  - Reactive NST is defined by
    - Normal FHR baseline: 110–160 beats/min (bpm)
    - Moderate FHR variability: variation of 5–25 bpm around baseline
    - Presence of two or more accelerations in FHR: 10 bpm (<32 weeks) or 15 bpm (≥32 weeks) above the baseline
    - Absence of late decelerations
  - Widely used for initial fetal assessment of fetal status; loss of reactivity is an early indicator of hypoxemia
  - A reactive NST predicts a high likelihood of survival for the following week.
    - Less predictive in conditions in which acute decompensation may occur (e.g., diabetes, intrauterine growth restriction [IUGR])
  - Nonreactive NSTs often are false-positive but should prompt further evaluation (usually biophysical profile); 85% of these will be normal.
- Biophysical profile (BPP)
  - Rationale: fetus requires oxygen for physical activity; amniotic fluid volume indirectly related to placental function
  - Based on ultrasound parameters (30 minutes of observation) plus NST
  - Five parameters evaluated: 2 points if present and 0 points if absent
    - Fetal heart rate reactivity on NST
    - Fetal breathing: at least 30 seconds of fetal breathing movements
    - Fetal tone: one episode or more of fetal extension, with return to flexion
    - Gross fetal movement: three or more discrete body movements (e.g., rolling)
    - Amniotic fluid volume: deepest vertical pocket ≥2 cm
  - Parameters have differing sensitivity to fetal hypoxemia
    - NST > breathing > body movements > tone
    - Oligohydramnios is a marker of chronic hypoxemia caused by redistribution of flow and decreased renal perfusion
  - BPP parameters can be influenced by factors other than hypoxemia, such as the following:
    - Prematurity, drugs, sleep cycles, ruptured membranes (oligohydramnios), certain birth defects
  - Management is based on score and gestational age
    - 8–10/10: no asphyxia present, no need for further intervention
    - 6/10: equivocal test, fetal asphyxia cannot be excluded
      - At term: repeat BPP in 8 hours—deliver if persistent.
      - Preterm: repeat BPP in 8 to 24 hours—if persistent, consider delivery based on gestational age
    - 4/10: fetal hypoxemia likely, close monitoring or delivery
    - 0–2/10: fetal hypoxemia highly likely, delivery indicated
- Contraction stress test (CST)
  - Rationale: contractions squeeze arteries perfusing the placenta, reducing O_2 transfer; with poor placental reserve, fetal hypoxemia elicits late FHR decelerations.
  - FHR monitoring is performed during induced or spontaneous contractions: repetitive late decelerations indicate uteroplacental insufficiency.
  - CST is not affected by gestational age, sleep cycles, or medications, but cannot be done when labor is contraindicated (e.g., placenta previa).
  - More time and labor-intensive than BPP; thus, infrequently performed.
  - Negative CST (i.e., no late decelerations) has a similar predictive value for good fetal outcome as does a normal BPP score.
- Ultrasound Doppler velocimetry
  - Used to evaluate fetal anemia and placental function
  - Umbilical artery Doppler
    - Placenta normally has low vascular resistance; dysfunction increases resistance, decreasing passive diastolic flow more than systolic.
    - Ratio of systolic-to-diastolic flow (S/D ratio) is elevated with uteroplacental insufficiency; progressive placental resistance causes absent or reversed end diastolic flow (worsening prognosis).
    - Umbilical artery Doppler in suspected IUGR lowers perinatal mortality and cesarean and induction rates.
  - MCA Doppler
    - Fetal anemia causes MCA peak systolic velocity to increase due to decreased blood viscosity.
    - So-called brain-sparing adaptation to hypoxemia by increasing cerebral flow through lower MCA resistance (lowers pulsatility index).
- Fetal lung maturity testing
  - Rarely done because unindicated early delivery is avoided and testing is unnecessary if delivery is clearly indicated
  - Multiple amniotic fluid testing methods—lecithin-to-sphingomyelin ratio, phosphatidyl glycerol, lamellar body counts, and others

- All have similar accuracy: positive result highly predictive of maturity, but negative result a poor predictor of lung immaturity

Fetal Therapy

- Fetal transfusion
  - Indication: severe fetal anemia or thrombocytopenia
  - Lifesaving procedure but 1% fetal mortality from umbilical cord puncture, may result in emergent cesarean delivery
  - Procedure
    - Ultrasound guidance to insert needle into umbilical vein
    - Blood sent for CBC; if severe anemia or thrombocytopenia, transfusion volume calculated and infused and CBC rechecked
    - May need to repeat within several weeks
- Treatment of twin-twin transfusion syndrome (TTTS)
  - Amnioreduction (mild or late TTTS)
    - Up to several liters of amniotic fluid may be aspirated
    - Reduced fluid volume and pressure may improve intertwin flow
    - If no improvement, refer for laser therapy
  - Laser therapy (up to 26 weeks)
    - Endoscopic laser to photocoagulate unbalanced vascular anastomoses and normalize intertwin blood flow
    - Improved survival for moderate to severe TTTS
    - However, some placentae and anastomoses are inaccessible
  - Risks: PPROM, infection, preterm delivery (PTD), fetal death, intertwin membrane rupture (managed as monoamniotic gestation)
  - Delivery at 34–35 weeks for successfully treated cases
  - Selective reduction
    - Selective feticide by endoscopic occlusion of one twin's cord
    - Considered when laser therapy is not feasible or when anticipated outcome for one fetus is particularly poor
    - Carries similar risks to laser therapy
- Fetal surgery
  - Some fetal anomalies (e.g., myelomeningocele, sacrococcygeal teratoma) are amenable to surgical amelioration prior to birth.
  - Extremely invasive, with maternal surgical risks (including need for cesarean delivery in all future pregnancies) and high risk of PTD.
  - Candidates evaluated on case by case basis at a fetal therapy referral center.

Suggested Readings

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Questions

1. A patient at 32 weeks is having fetal growth surveillance for renal disease. The EFW is at the seventh percentile, with a normal amniotic fluid volume. The umbilical artery S/D ratio is elevated. Twice-weekly NSTs and weekly assessments of amniotic fluid volume are started for surveillance. Which of the following findings require delivery?
   a. Fetal EFW < 10th percentile on the next growth assessment
   b. There is interval development of oligohydramnios
   c. Umbilical artery velocimetry shows reversed end-diastolic flow
   d. Intermittent variable decelerations are noted on reactive NST

2. A woman with diabetes is having a biophysical profile assessment at 34 weeks. Fetal NST shows more than two accelerations in the fetal heart rate, which is 10 beats/min above the baseline. Fetal breathing was seen. The single deepest vertical pocket (SDP) of amniotic fluid exceeds 2 cm. Many fetal body movements are seen, including at least one kick, with return to flexion. What is the BPP score, and what additional testing do you recommend?
   a. 6; no further testing required at this time
   b. 6; continuous electronic fetal monitoring
   c. 8; no further testing required at this time
   d. 8; consider a repeat biophysical profile within 24 hours
   e. 10; no further testing required at this time

4 Labor and Delivery

J. CHRISTOPHER GLANTZ and LISA M. GRAY

Normal Labor and Delivery

- Labor is the physiologic process of coordinated uterine contractions that lead to delivery of the fetus and placenta.
  - First stage: onset of contractions to full cervical dilation
  - Second stage: delivery of the fetus (pushing)
  - Third stage: delivery of placenta
- Most women will enter spontaneous labor between 38 and 42 weeks.
- The precise mechanism controlling onset of labor is unknown.
- Uterine blood flow decreases during contractions due to myometrial compression on branch uterine arteries.
  - Placental perfusion is intermittently lowered, limiting gas exchange
  - Uncompromised fetuses tolerate these perfusion changes but, with low placental reserve, the fetus may become progressively hypoxemic
- Intrapartum fetal heart rate (FHR) monitoring
  - Used in all pregnancies to limit fetal morbidity and mortality
  - Low-risk pregnancies: intermittent auscultation is acceptable
  - High-risk pregnancies: continuous electronic FHR monitoring
    - External (Doppler-based; may not trace well) or internal (fetal scalp electrode; more accurate but invasive)
  - Features of FHR tracing used to assess fetal status:
    - FHR baseline: 110–160 beats/min (bpm)
      - Tachycardia—seen with infection, fetal anemia, acidosis, arrhythmia, or prolonged fetal activity
      - Bradycardia—associated with drug effects, fetal arrhythmia, maternal hypotension/hypothermia, acidosis
    - Variability: variation in FHR from measured baseline
      - Absent—if prolonged, may indicate severe acidosis
      - Minimal—0–5 bpm; most often fetal sleep cycle but possible acidosis if persistent
      - Moderate—6–25 bpm; reliably excludes acidosis
      - Marked—>25 bpm; possible early hypoxemia
    - Accelerations: elevations in FHR with fetal movement
    - Decelerations:
      - Early—shallow FHR depressions that begin with onset of contraction, nadir at contraction peak (mirror image to contraction); caused by head compression and considered benign
      - Variable—abrupt depressions in FHR that are variable in shape, duration, and association with contractions; caused by cord compression; may cause hypoxia if prolonged or recurrent
      - Late—shallow FHR depressions that begin after contraction starts, nadir after contraction peak; caused by uteroplacental insufficiency; indicative of at least transient hypoxemia
    - Category I tracings indicate normal fetal acid-base status and require no intervention.
      - Normal baseline and moderate variability with or without accelerations or early decelerations
    - Category III tracings are markedly abnormal; require evaluation and usually expedited delivery.
      - Bradycardia, sinusoidal, or absent variability plus repetitive variable or late decelerations
    - Category II tracings (most common) are those with any pattern that is not category I or III; require evaluation and possible intrauterine resuscitation (e.g., O_2, position change, hydration). If a category II tracing persists or worsens, delivery may be indicated.
- Labor analgesia
  - Narcotics: transient and variable labor pain relief; can cause neonatal respiratory depression
  - Epidural: long-acting and highly effective analgesia for labor or cesarean; minimal fetal effects if no maternal hypotension; small amounts of epidural or intrathecal narcotic rarely cause depression
  - Spinal: provides 2–3 hours of surgical-level analgesia; may cause more profound maternal hypotension than epidural
  - General anesthesia: provides continuous and effective analgesia for surgical delivery; requires intubation; can cause neonatal respiratory depression
- Routine delivery procedures:
  - Active management of placental delivery (e.g., uterotonics, gentle cord traction, uterine massage) decreases the risk of postpartum hemorrhage.
  - Delayed umbilical cord clamping increases neonatal iron stores.
    - Preterm infants: less need for transfusion, less necrotizing enterocolitis and intraventricular hemorrhage (IVH) but increased neonatal jaundice
    - Term infants: improved iron stores at 4 months but increased risk of neonatal jaundice

Labor and Delivery Complications

- Dystocia
  - Prolonged or protracted labor; arrest of dilation or descent
  - Oxytocin augmentation if suboptimal contraction pattern or intensity and if no evidence of cephalopelvic disproportion
  - May require instrumental or cesarean delivery
- Meconium-stained amniotic fluid
  - Common, affecting 10%–20% of pregnancies

- Usually benign, but also associated with fetal hypoxemia, pulmonary hypertension, meconium aspiration syndrome; warrants closer FHR monitoring and consideration of pediatric evaluation at delivery
- Postdelivery DeLee suctioning of meconium is no longer recommended

- Maternal hypotension
  - Causes: maternal hemorrhage, dehydration, supine position (with aortocaval compression), epidural-related sympathetic blockade
    - Less common: uterine rupture, sepsis, hepatic-splenic rupture
  - Management: treat underlying cause and maintain uterine perfusion
    - Position change, IV fluid bolus, ephedrine for refractory postepidural hypotension; manage hemorrhage
- Chorioamnionitis
  - Clinical diagnosis with maternal fever, maternal-fetal tachycardia, uterine tenderness, elevated white blood cell count (WBC), and foul-smelling or purulent amniotic fluid
  - Considered with any intrapartum fever (epidural analgesia and prostaglandin administration also are associated with fever)
  - Risk factors: prolonged labor or ruptured membranes, internal monitor placement, frequent digital cervical examinations
  - Maternal effects: sepsis, dysfunctional labor, endomyometritis, abscess
  - Fetal effects: sepsis, hypoxia, organ injury, death
  - Treatment: antibiotics, effect delivery (regardless of gestational age)
- Management of nonreassuring intrapartum FHR tracings
  - Tachycardia: identify and treat the cause of tachycardia (maternal fever, infection, hypovolemia, fetal anemia)
  - Variable decelerations: position change, vaginal examination (rule out cord prolapse), amnioinfusion if persistent and low amniotic fluid volume
  - Late decelerations or absent variability: improve uteroplacental blood flow—IV fluid bolus, maternal supplemental O_2, position change; prompt delivery if unresolved late decels
  - Bradycardia: identify and treat cause of bradycardia (e.g., maternal drugs, heart block, acidosis); prompt delivery if unresolved acute episode
  - Normal FHR monitoring predicts a nonacidotic, nonasphyxiated fetus, but abnormal monitoring is a poor predicator of fetal compromise
    - Little or no evidence of hypoxia in most babies born by cesarean for abnormal FHR tracings
    - Umbilical cord blood gases usually normal or just respiratory acidosis
- Prolonged second stage
  - Defined as a second stage lasting >2 hours without epidural or >3 hours with epidural
  - Can be expectantly managed if reassuring maternal and fetal status
  - Management
    - Operative vaginal delivery—use of forceps or vacuum extractor
      - Maternal risks: lacerations, hemorrhage, need for emergent cesarean delivery if unsuccessful
      - Fetal risks: shoulder dystocia, cephalohematoma or subgaleal hemorrhage, IVH, fractures, or nerve injury
      - Contraindications: incomplete dilation, high station, nonvertex presentation, uncertain fetal position, fetal bleeding or bone mineralization disorder
    - Cesarean delivery: cesarean in the second stage is associated with increased maternal-fetal complications (more difficult fetal extraction, hemorrhage)
- Breech vaginal delivery
  - Increased risk of fetal injury and neurodevelopmental impairment
  - Risk profile may be acceptable in certain candidates
    - Multiparous patient with normal estimated fetal weight (EFW)
    - Second twin when concordant fetal growth and cephalic first twin
    - Nonviable fetus
    - Excess maternal risk with cesarean delivery
  - Fetal risks: head entrapment, fractures, asphyxia, perinatal death
- Shoulder dystocia
  - Obstetric emergency when the fetal shoulder is impacted behind the maternal pubic symphysis
  - Risk factors: macrosomia, maternal diabetes, operative vaginal delivery, precipitous delivery, prior shoulder dystocia
  - Management
    - Stop maternal pushing and call for assistance
    - McRoberts position—flex maternal hips to widen pelvic outlet
    - Suprapubic pressure to change shoulder angle
    - Posterior arm delivery—reduces fetal bisacromial diameter
    - Rotational maneuvers—rotate the fetus by applying pressure to fetal shoulders to alleviate impaction
    - Intentional clavicular fracture—collapse shoulder medially
    - Cephalic replacement (Zavanelli maneuver) —push fetus back into the uterus and perform emergent cesarean delivery
  - Maternal-fetal complications
    - Maternal hemorrhage and pelvic floor lacerations
    - Fetal brachial plexus injury (most are transient), clavicular or humerus fracture, asphyxia, perinatal death
- Neonatal complications from cesarean delivery
  - Fetal hormonal changes during labor facilitate transition to extrauterine life
  - Cesarean delivery is associated with fetal lacerations and when scheduled, increased frequency of transient tachypnea and respiratory distress syndrome (RDS)

Breastfeeding

- Confers many maternal-fetal benefits
- Contraindicated with
  - HIV, active untreated tuberculosis, illicit drug use, heavy alcohol use, radioactive isotope therapy
  - Some medications required for maternal health maintenance (sedatives, anxiolytics, ACE inhibitors/ARB, cytotoxic drugs)

Suggested Readings

American Academy of Pediatrics and American College of Obstetricians and Gynecologists. *Guidelines for Perinatal Care*. 8th ed. Elk Grove, IL: AAP; Washington, D.C.: American College of Obstetricians and Gynecologists; 2017.

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Questions

1. For which of these clinical situations would you recommend a prompt, planned cesarean delivery?
   a. 30-year-old G3P2002 at 39 weeks; cesarean delivery × 1 (breech presentation)
   b. 20-year-old G1P0 at 39 weeks; fetal gastroschisis
   c. 24-year-old G2P1001 at 39 weeks; fetal hypoplastic left heart, unrestrictive atrial septum
   d. 23-year-old G1P0 at 36 weeks; fetal sacrococcygeal teratoma with signs of fetal hydrops
   e. 35-year-old G4P1112 with maternal dilated cardiomyopathy who has a left ventricular ejection fraction (LVEF) of 40%

2. A 31-year-old G4P3003 presents at 35 weeks with heavy vaginal bleeding and a known placenta previa. She previously received a steroid course for an episode of vaginal bleeding. She had two prior cesarean deliveries. An ultrasound at 18 weeks showed placental lacunae and abnormal bladder vascularity. Maternal vital signs are stable. Fetal NST is reactive. The most appropriate next step in management is:
   a. Prompt cesarean hysterectomy
   b. Repeat steroid course followed by cesarean hysterectomy
   c. Repeat steroid course followed by cesarean delivery
   d. Expectant management until term
   e. Expectant management until documentation of fetal lung maturity

SECTION 2

Asphyxia and Resuscitation

MELISSA CARMEN

5 Asphyxia

MELISSA CARMEN

Basic Information

- Causes are listed in Box 5.1.
- Pathophysiology:
  - Asphyxia results in a series of changes in the fetus and newborn, corresponding to changes in the pH of the blood.
  - Interruption in blood flow and oxygen supply will result in the fetus or newborn transitioning to anaerobic respiration, with a resultant buildup of lactic acid, leading to a decrease in the pH of the blood and an acidotic state.

Clinical Presentation

- Apnea:
  - Primary apnea: primary apnea can result from acidosis secondary to decreased fetal circulation; it is often recoverable with stimulation.
  - It may progress into a period of gasping and, without intervention, may develop into secondary apnea.
  - Secondary apnea results after a more prolonged period of decreased oxygenation and will lead to a decreased heart rate, as well as additional cardiovascular compromise if not corrected. Secondary apnea can only be corrected with improved ventilation, usually via positive-pressure ventilation (PPV) through a mask or endotracheal tube.
- Vascular redistribution:
  - The hypercapnia, hypoxemia, and acidosis that result from asphyxia will initially cause a redistribution of blood flow to the heart, brain, and adrenal glands.
  - Persistent hypercarbia, hypoxemia, and/or acidosis may lead to decreased systemic blood pressure and loss of autoregulation of the cerebral blood flow.
  - Prolonged periods of decreased systemic blood pressure and perfusion can result in end-organ damage in other systems as blood is shunted away from some organs to maintain cerebral perfusion.
  - Kidney—acute kidney injury with increased creatinine levels and abnormal urine production (e.g., polyuria, oliguria, and/or anuria)
  - GI tract—ischemic bowel injury; may increase the risk of necrotizing enterocolitis in at-risk infants.
  - Eventually, prolonged asphyxia results in decreased cerebral blood flow, which can lead to hypoxic-ischemic brain injury.
- Hypoxic-ischemic brain injury:
  - Cellular mechanism of injury (Fig. 5.1):
    - This occurs after a hypoxic or ischemic event resulting in asphyxia, shortly before or at the time of delivery.
    - Immediately after the insult, there is a depletion of high-energy phosphates (ATP), referred to as *primary energy failure.*
    - This results in immediate necrotic cell death, from which the brain metabolism may be able to recover. Necrosis occurs after cellular membrane breakdown (from lack of ATP) results in the leakage of cellular contents, resulting in inflammation and necrotic cell death.
    - However, if the injury is sufficiently severe, after a brief period of attempted recovery, the brain may enter a phase of secondary energy failure.
    - Secondary energy failure may occur hours to days after the initial insult (usually, 6–48 hours). Glutamate, an excitatory amino acid, accumulates in the extracellular space due to increased production, as well as decreased reuptake by damaged cells.
    - This results in an increased Ca^{2+} influx and activation of degradative enzymes, as well as reactive oxygen species, which lead to delayed, apoptotic cell death.
    - The goal of therapies, such as whole-body cooling, is to prevent the onset or lessen the impact of

Box 5.1 Causes of Perinatal Asphyxia

Maternal
Decreased uterine blood flow
Maternal hypotension
Regional anesthesia
Eclampsia
Abnormal uterine contractions

Placental
Infarcts
Premature separation (abruption)
Inflammatory changes

Fetal
Cord compression (nuchal, prolapsed) or entanglement (twins)
Breech presentation
Anemia
Hypovolemia (in utero blood loss)

Neonatal
Hypovolemia
Apnea related to drug-induced depression (narcotics, magnesium)
Congenital anomalies of the airway and lung
Prematurity

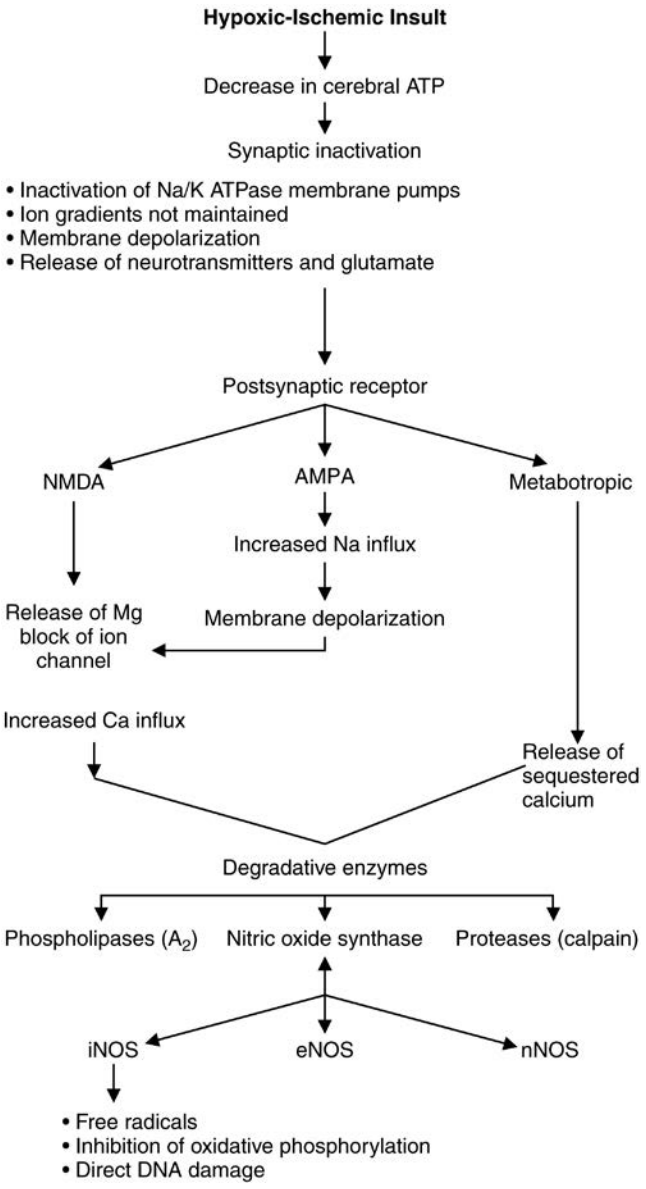

Fig. 5.1. Cellular mechanism of injury after hypoxic-ischemic insult. *AMPA,* alpha-amino-3-hydroxy-5-methyl-4-isoxazoleproprionic acid; *eNOS,* endothelial nitric oxide synthase; *iNOS, inducible nitric oxide synthase; nNOS, neuronal nitric oxide synthase; NMDA, N-methyl-D-aspartate.* (From Gleason C, Devaskar SU, eds. *Avery's Diseases of the Newborn*. 9th ed. St. Louis: Elsevier; 2012; Chapter 61.)

secondary energy failure by decreasing cellular metabolism in the brain:
  - Suppress cell death by decreasing proapoptotic proteins and increasing antiapoptotic proteins and neurotropic factors
  - Suppress inflammation by decreasing activated microglia and neutrophils, decreasing reactive oxygen species and proinflammatory cytokines
- Clinical features
  - Definition of hypoxic-ischemic encephalopathy (HIE) due to perinatal asphyxia, as given by the American Academy of Pediatrics (AAP) and American College of Obstetrics and Gynecology (ACOG):
  - Significant metabolic or mixed acidosis in an umbilical arterial sample:

Table 5.1 Apgar Scores

Parameter	Score		
Component assessed (points)	0	1	2
Heart rate (beats/min)	0	<100	>100
Respiratory effort	Apneic	Irregular, shallow, or gasping	Vigorous, crying, regular breathing
Color	Pale, cyanotic (central)	Pale or cyanotic extremities	Pink, well perfused
Muscle tone	Absent	Weak, passive tone	Active movement
Reflex irritability	Absent	Grimace	Active avoidance

  - Apgar score of <4 for longer than 5 minutes
  - Neonatal neurologic abnormalities
  - Multiple organ involvement
  - Umbilical venous blood—reflects supply from placenta (blood from placenta to fetus): average pH, 7.20–7.40; P_{O_2}, 30 mm Hg; P_{CO_2}, 40 mm Hg; base excess (BE) = −3
  - Umbilical artery blood – reflects condition of fetus (blood returning from fetus to placenta): average pH, 7.15–7.35; P_{O_2}, 16 mm Hg; P_{CO_2}, 55 mm Hg; BE = −3
  - pH <7.00 or BE > −12—high-risk fetal compromise
  - Apgar scores (Table 5.1)
  - Scores assigned at 1 and 5 minutes after birth. If the score remains less than 7 at 5 minutes, score should continue to be assigned every 5 minutes until 20 minutes of life.
  - Developed to provide a more consistent and objective way to describe the condition of an infant in the delivery room
  - Can be used to describe the infant's condition and response to delivery room interventions, but scores do not dictate the next step in resuscitation
  - Poor scores have been shown to be associated with increased mortality, but scores are not predictive of long-term neurologic outcomes.

Treatment

- Therapeutic cooling
  - Criteria for diagnosis of HIE that qualify neonates for therapeutic cooling may have slight variations from the AAP-ACOG definition; based on various studies of therapeutic head and whole-body cooling that have shown improved neurodevelopmental outcomes in infants with moderate to severe encephalopathy at birth.
  - Criteria include clinical and biochemical components
    - History of perinatal asphyxia event
    - Evidence of acute acidosis on umbilical artery gas
    - Apgar < 5 at 10 minutes or continued need for mechanical ventilation at 10 minutes after birth
  - Neurologic criteria
    - Seizure
    - Or evidence of moderate to severe encephalopathy on examination (must have at least three to six components in the moderate to severe category)

Resuscitation

Approximately 4%–10% of infants will require resuscitation at birth, necessitating PPV, with <1% requiring significant resuscitative measures, such as chest compressions or medications to increase the heart rate. All deliveries should be attended by at least one person trained in the initial steps of newborn resuscitation, with the ready availability of a provider trained in more advanced techniques, such as intubation and obtaining vascular access. Timely and effective resuscitation can greatly affect an infant's chance for a meaningful recovery after the perinatal asphyxia.

Management

AIRWAY AND VENTILATION

- Establishing a patent and secure airway that allows for adequate ventilation is crucial in the successful resuscitation of the neonate because most episodes of bradycardia will respond to improved ventilation.
- Most infants can be effectively ventilated with a bag and mask device and do not require the placement of an advanced airway, such as a laryngeal mask airway or endotracheal intubation.

INDICATIONS FOR POSITIVE-PRESSURE VENTILATION

- Apnea or gasping
- Heart rate (HR) < 100 beats/minute (bpm)
- Some infants who are spontaneously breathing but fail to maintain adequate ventilation may also benefit from PPV or from continuous positive airway pressure (CPAP) to help maintain functional residual capacity (FRC).

VENTILATION DEVICES AND PROCEDURES

- Flow-inflating bag
  - Requires a source of compressed air and secure seal of the mask on the face or endotracheal intubation
  - Can provide CPAP when mask applied to face and bag is not deflated
- Self-inflating bag
  - Can deliver positive-pressure breaths without compressed air source, but cannot provide CPAP
  - If attached to oxygen source, can delivery free-flow oxygen
- T-piece resuscitator
  - Requires a compressed air source
  - Can deliver consistent peak inspiratory pressure (PIP) and positive end-expiratory pressure (PEEP) by adjusting valves on the device to deliver desired pressures
  - Breaths delivered by intermittently occluding the cap on the T-piece attached to the mask
  - Can provide CPAP when mask applied to face and dial on T-piece cap is not occluded

Laryngeal Mask Airway

- A laryngeal mask airway (LMA) is a device that fits over the laryngeal inlet; it can be used to ventilate an infant without having to visualize the vocal cord and glottis directly for placement.
- It may be useful when attempts at endotracheal intubation are not successful or with abnormal airways that make placement of an endotracheal tube difficult (e.g., Pierre Robin sequence, macroglossia, cleft palate).

Endotracheal Intubation

- Should be considered when:
  - Mask ventilation is ineffective or is prolonged for more than a few minutes.
  - Chest compressions are being performed and a secure airway should already be established or be in the process of being established.
  - Congenital anomalies that have an increased risk of complications when air accumulates in the bowel due to positive pressure ventilation from a face mask (such as congenital diaphragmatic hernia); in this case intubation should be done immediately.
  - It is determined that the infant requires surfactant to establish improved oxygenation.
- After the infant is placed in the proper sniffing position, the laryngoscope should be placed with the tip in the vallecula so that the vocal cords and glottis can be visualized.
- An endotracheal tube is passed through the open cords.
- Avoid forcing the tube past closed vocal cords; complications of improper tube placement can include bleeding, damage to the vocal cords, esophageal intubation, and esophageal perforation.

Meconium

- Intubation for direct suctioning of meconium below the cords is no longer recommended by the Neonatal Resuscitation Program (NRP).

Oxygen

- Oxygen should be treated as a drug and used judiciously during resuscitation.
- Resuscitation of term infants should begin with 21% Fio_2 room air, with the level titrated up to maintain saturation in the target range noted by the NRP.
- There is no clear evidence about the best concentration to begin resuscitation of preterm infants, but some studies have shown that starting resuscitation with an oxygen concentration from 21%–40% may allow for effective resuscitation while limiting exposure to oxygen free radicals and reactive oxygen species.
- Preterm infants are especially at risk for cellular damage with prolonged exposure to high concentrations of oxygen, and efforts should be made to titrate oxygen levels as soon as possible during resuscitation.

ASSESSMENT OF EFFECTIVENESS

- Effective ventilation is the most important step in the resuscitation of the newborn.
- Every effort should be made to assess for and ensure effective ventilation before moving forward in the resuscitation algorithm to chest compression or resuscitation medications.
- Effective ventilation can be assessed by noting good chest rise and rising heart rate with each administered breath.
- If an endotracheal tube is in place, end-tidal CO_2 monitors may be useful to assess whether the tube is in the correct position and able to provide adequate ventilation.
- Improvement in heart rate and oxygenation are also indicators that the neonate is being adequately ventilated.
- Remember the mnemonic *MR SOPA* when provided ventilation through a mask device to troubleshoot for areas that may be impeding ventilation:
  - *M* – mask:
    - Check to make sure mask is the appropriate size for the patient and that it makes a secure seal around the mouth and nose.
  - *R* – reposition:
    - Reposition the infant's head and neck to ensure that the baby is in a proper sniffing position and the head is not too hyperextended or flexed, both of which may occlude the airway.
    - Neonates may benefit from a shoulder roll to aid in proper positioning.
  - *S* – suction:
    - A variety of fluids (e.g., blood, amniotic fluid, meconium) present at the time of delivery may obstruct an infant's airway.
    - Suction the nose before the mouth.
    - Routine suctioning of the stomach is not necessary unless PPV has been given for an extended period of time, and there is a need to decompress the stomach for air.
  - *O* – open:
    - Make sure that the infant's mouth is open by gently placing a finger in the mouth to open it, securing the mask and continuing attempts at ventilation.
  - *P* – pressure:
    - The infant may require various amounts of pressure to move the chest wall adequately.
    - Pressure should be increased until adequate chest rise is seen.
    - A preterm infant, especially one with surfactant deficiency, has decreased compliance in the lungs and may require increased pressure to open the alveoli adequately and properly ventilate.
    - It is important not to use excessive pressure because this can lead to barotrauma and/or pneumothorax.
  - *A* – alternative airway:
    - Mask ventilation is not always adequate to ventilate the lungs sufficiently.
    - If the above steps have been attempted, and there is still no improvement in ventilation and heart rate, the provider should move to placing a more secure airway, such as an LMA or endotracheal intubation.

Other Considerations

CARDIOVASCULAR CONSIDERATIONS

- The goal of neonatal resuscitation is to keep the infant's HR > 100 bpm.
- Adequate ventilation is the most effective intervention to return the HR to normal. However, there are cases where additional interventions, including chest compressions, fluid resuscitation, and/or vasoactive drugs, may be needed to allow for the return of spontaneous circulation.

Chest Compressions

- Chest compressions should be coordinated with ventilation breaths in a 3:1 (compression-to-breath) ratio.
- The goal is for 120 events in a 60-second period—that is, 90 compressions and 30 breaths.

Indications

- Indicated when HR remains less than 60 bpm after at least 30 seconds of PPV that inflates the lungs (effective ventilation).

Techniques

- Two-finger technique—the first and second fingers are placed perpendicular to the chest wall, on the sternum, just above the xyphoid process. Compress the chest one-third the anteroposterior (AP) diameter of the chest.
- Two-thumb encircling technique—place the thumbs on the sternum, just above the xyphoid process, and encircle the torso with remaining fingers. Compress the chest one-third the AP diameter of the chest.

Complications

- Rib fractures
- Impediment of ventilation if not properly coordinated with breaths

Volume Resuscitation

- The most common cause of hypovolemia at birth is due to fetal blood loss.
- This can be caused by placental abruption or laceration, fetal-maternal hemorrhage, cord avulsion, or prolapse.
- Signs of hypovolemia in the delivery room that may indicate the need for fluid resuscitation include pallor, decreased perfusion, and/or decreased pulses and acidemia.
- Fluid resuscitation should not be routinely used unless there is a known history of risk factors for hypovolemia.

- Administering fluid to a euvolemic infant whose cardiac function is diminished, either due to arrest or underlying cardiac disease, may actually worsen the infant's condition.
- Normal saline (0.9% NaCl solution) can be used at an initial dose of 10 mL/kg, usually over 5–10 minutes, but may be given faster.
- Packed red blood cells may also be needed if there is a history of significant fetal blood loss or suspicion of severe anemia.

Pharmacology and Drugs Used in Resuscitation

- Epinephrine in a 0.1-mg/mL concentration (1:10,000) is the only concentration that should be used in a neonatal resuscitation.
- The volume given during resuscitation is 0.1–0.3 mL/kg/dose IV or a 0.5–1 mL/kg/dose via endotracheal tube (ETT) (0.01–0.03 mg/kg/dose IV or 0.05–0.1 mg/kg/dose via ETT).
- IV dosing is the preferred route due to inconsistencies with administration and absorption via the ETT.
- Electrocardiographic monitoring should be considered when resuscitation is needed.

Suggested Readings

American Academy of Pediatrics and American Heart Association, Weiner GM, Zaichkin J, et al. *Textbook of Neonatal Resuscitation*. 7th ed. Elk Grove Village, IL: American Academy of Pediatrics; 2016.

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Shankaran S, Pappas A, Laptook AR, et al. Outcomes of safety and effectiveness in a multicenter randomized controlled trial of whole-body hypothermia for neonatal hypoxic-ischemic encephalopathy. *Pediatrics*. 2008;122(4):e791–e798.

Questions

1. You are called to the delivery of a 39-week infant, with no known maternal complications of pregnancy. Meconium was noted at the time of delivery. You arrive in the delivery room ~1 minute after birth and find the infant is on a warmer, apneic, and being vigorously stimulated by nursing staff. The HR is noted to be less than 100 bpm. Of the following, which is the most appropriate next step to improve the patient's heart rate?
   a. Continue vigorous stimulation of the patient
   b. Deep-suction the posterior pharynx
   c. Provide positive-pressure ventilation via bag-mask ventilation
   d. Intubate the patient
   e. Obtain umbilical access and administer intravenous epinephrine

2. Based on current evidence and practice guidelines, which of the following describes an infant who would most benefit from therapeutic whole-body cooling?
   a. 33-week infant born due to maternal preeclampsia, required intubation at birth, Apgar scores—1 at 1 minute, 3 at 5 minutes, 8 at 10 minutes
   b. 37-week infant born after prolonged shoulder dystocia, Apgar scores—1 at 1 minute, 3 at 5 minutes, 8 at 10 minutes—and an arterial cord gas of pH 6.98/CO_2 88 mmHG/PaO_2 24 mmHg/ Bicarbonate 20 mmol/L/base excess–17 who at 1 hour of age appears hyperalert, with mildly increased tone, a weak suck, HR of 190 beats/min, and respiratory rate (RR) of 75 breaths/min.
   c. 39-week infant born after uterine rupture, Apgar scores—1 at 1 minute, 3 at 5 minutes, 8 at 10 minutes—and an arterial cord gas of pH 6.98/CO_2 88 mmHG/PaO_2 24 mmHg/ Bicarbonate 20 mmol/L/base excess–17 who at 1 hour of age appears comatose, remains intubated, is lethargic, with decreased activity, hypotonia, incomplete Moro reflex and suck, and intermittent spontaneous respirations on the ventilator.
   d. 37-week infant, now 12 hours old, found in mother's room to be unresponsive and received CPR with two doses of epinephrine before spontaneous return of circulation.

3. Which of the following is the preferred dose of epinephrine to be given during a neonatal resuscitation?
   a. 0.01-mL/kg/dose of a 1:10,000 solution IV
   b. 0.5-mL/kg/dose of a 1:1000 solution via ETT
   c. 0.0-mL/kg/dose of a 0.1-mg/mL solution (1:10,000) IV
   d. 1-mL/kg/dose of a 1:10,000 solution via ETT

4. Which of the following is an advantage of a self-inflating bag over a T-piece resuscitator?
   a. It can administer PPV without a source of compressed air or oxygen
   b. It can provide PEEP when applied continuously to the face
   c. It provides consistent PIP and PEEP with each breath, with minimal variation between breaths
   d. It can be used to deliver oxygen concentrations > FiO_2 21%

5. The hypercapnia, hypoxemia, and acidosis that result from asphyxia will initially cause a redistribution of blood flow to which organs?
   a. Heart, kidneys, and adrenal glands
   b. Heart, intestines, and brain
   c. Heart, brain, and adrenal glands
   d. Brain, intestines, and kidneys
   e. Brain, kidneys, and heart

6. Which of the following is a feature of primary energy failure from hypoxic brain injury?
   a. Occurs 6–48 hours after hypoxic injury
   b. Necrotic cell death
   c. Apoptosis
   d. Decreased glutamate reuptake by damaged cells
   e. Increases in cerebral ATP stores

SECTION 3

Cardiovascular

KIMBERLY VERA

6 Cardiac Development

KIMBERLY VERA

Normal Cardiac Morphogenesis

- Cardiac progenitor cells migrate from the mesoderm to form a crescent shape in the lateral plate mesoderm (Fig. 6.1).
- The first heart field cells fuse in the midline to form the primitive heart tube, which begins to beat around day 17, becoming the first organ to function (Fig. 6.2).
- The cephalad portion of the primitive heart tube will become the future outflow region, and the caudal portion will become future atria.
- The primitive heart tube folds to the right as the second heart field cells migrate into the tube.
- First heart field cells give rise to the left ventricle and some of the atria; the second heart field cells give rise to the remaining atria, right ventricle, and outflow tracts (Fig. 6.3).
- Folding of the heart tube places the outflow portion, or conotruncal portion, of the tube adjacent to the inflow portions and creates an outer curve, which develops into ventricles, and an inner curve, which develops into the atrioventricular canal and atrioventricular septum (Fig. 6.4).
- The atrioventricular septum develops from the endocardial cushions to divide the primitive common atrioventricular valve into a tricuspid and mitral valve and must shift to the right. It aligns with the developing ventricular septum and positions the future tricuspid valve over the right ventricle and the future mitral valve over the left ventricle (Fig. 6.5).
- Conotruncal development:
  - The early common outflow tract, the conotruncus, is septated into an aorta and pulmonary artery, which rotates and then shifts to the left to align the conotruncal septum over the developing ventricular septum. This allows the aorta to arise from the left ventricle and the pulmonary artery to arise from the right ventricle (Fig. 6.6).
  - Conotruncal development requires extensive interaction between second heart field cells, neural crest cells, and pharyngeal tissues.
- Development of the great arteries:
  - The aortic sac contains six bilateral arches, which undergo complex remodeling.
  - The third, fourth, and sixth arches become mature arches and proximal pulmonary arteries.
  - Most of the right arches undergo programmed cell death to leave a left-sided mature arch.

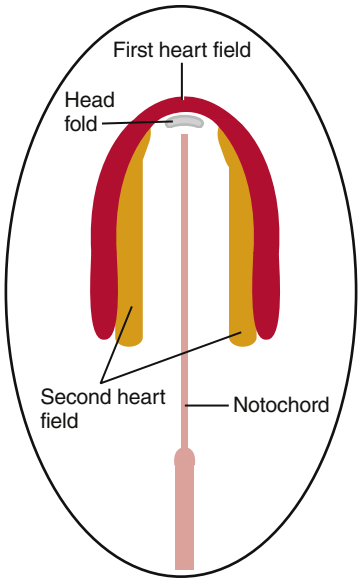

Fig. 6.1 Development of first and second heart Field. Crescent-like shape is caused by progenitor migration pattern and cardiogenic induction signals. (From Schoenwolf GC. *Larsen's Human Embryology.* 5th ed. Philadelphia: Elsevier; 2015.)

Regulators of Cardiac Embryology

See Box 6.1.

- Nkx2.5, GATA4, and TBx5 are major transcription regulators that drive the expression of myocardial-specific genes and lead cells to myocardial commitment.
- Islet1 (Isl1) is expressed in both the first and second heart field cells but is maintained for longer in the second heart field cells. It is needed for expansion and migration into the heart tube.
  - o Isl1 is critical for right ventricle development.
- Left-right asymmetry is mediated by the expression of Sonic hedgehog (Shh) in the left lateral mesoderm, which induces the expression of nodal and lefty proteins (members of the transforming growth factor beta [TGF-β] family). This drives the rightward folding of the primitive heart tube.
  - Nodal pathways induce the transcription factor Pitx2c in the left limb of the cardiac crescent and also contribute to left-right differentiation.
- Left ventricular development is driven by Nkx2.5, Hand1, and Tbx5.
- Tbx5 and Coup-TFII are important in atrial development.
- Tbx1 plays an important role in outflow tract development.

Box 6.1 Major Transcription Factors in Cardiac Development

Isl1—Right ventricle
Nkx2.5— Left ventricle
Hand1—Left ventricle
Tbx5—Left ventricle, atria
Coup-TGII—Atria
Tbx1—Outflow tract
Shh—Left-right differentiation
Pitx2c—Left-right differentiation

Abnormal Cardiac Morphogenesis

- Failure of the atrioventricular septum to shift to the right will lead to a double-inlet left ventricle.
- Incomplete shifting leads to an unbalanced atrioventricular (AV) septal defect, with the right AV valve only partially over the right ventricle.
- If the conotruncus does not shift to the left, a double-outlet right ventricle forms.
- If the conotruncus does not septate, a truncus arteriosus forms.

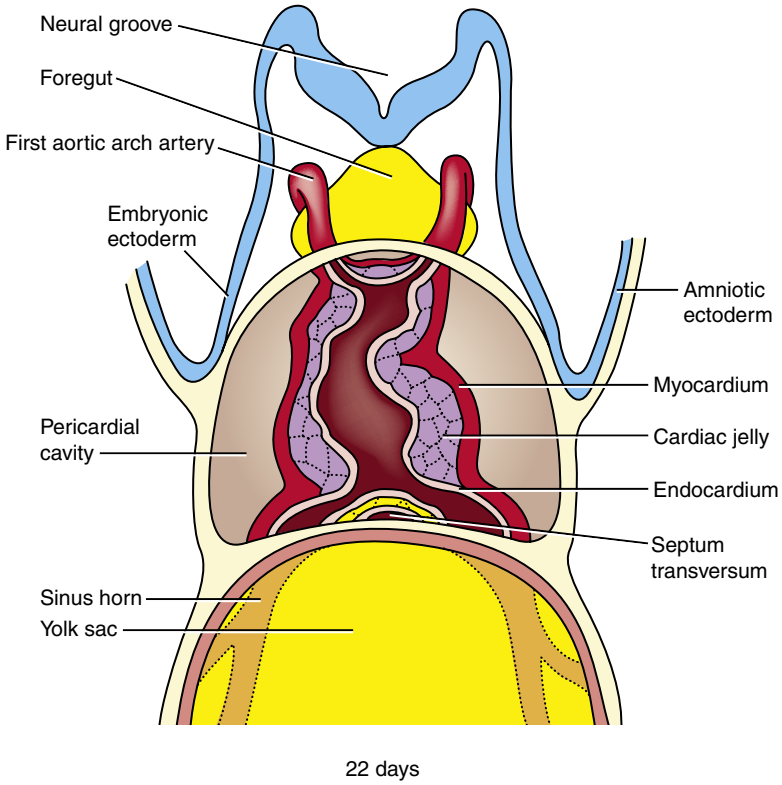

Fig. 6.2 Primitive heart tube. (From Schoenwolf GC. *Larsen's Human Embryology.* 5th ed. Philadelphia: Elsevier; 2015.)

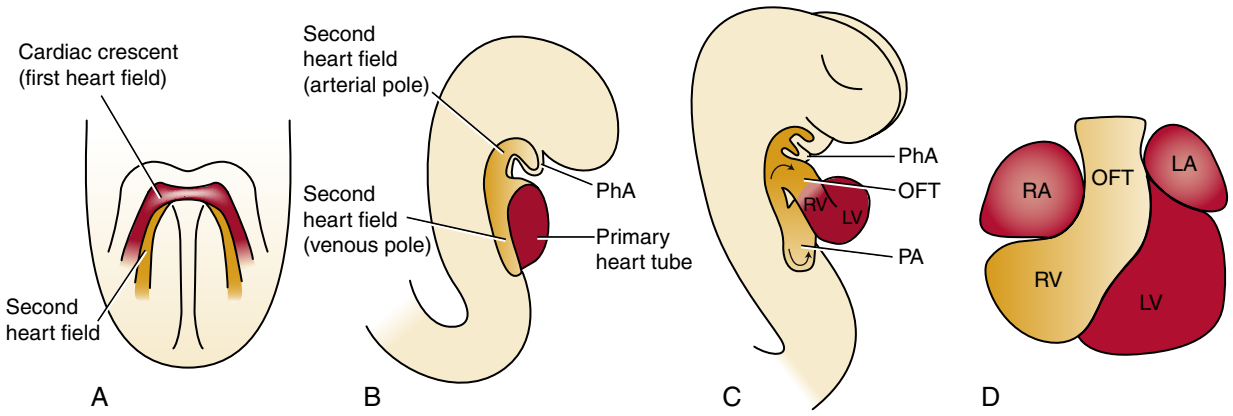

Fig. 6.3 Structures derived from the first and second heart fields. (A) Location of the second heart field relative to the first heart field before body folding. The second heart field is located within the splanchnic mesoderm just medial and slightly caudal to the first heart field (first heart field shown in red). (B) After formation of the primary heart tube, the second heart field becomes located dorsal to the dorsal mesocardium and runs along the craniocaudal axis. (C) With rupture of the dorsal mesocardium, the second heart field is divided into a caudal segment, responsible for adding to the venous pole of the heart, and a cranial segment, responsible for lengthening the heart tube at the arterial pole. (D) Ventral view of the looped heart shows the contributions of the first and second heart fields (contributions of the second heart field to the atria are not visible in this view). *LA,* Left atrium; *LV,* left ventricle; *OFT,* outflow tract; *PA,* primitive atria; *PhA,* pharyngeal arch tube; *RA,* Right atrium; *RV,* Right ventricle. (From Schoenwolf GC. *Larsen's Human Embryology.* 5th ed. Philadelphia: Elsevier; 2015.)

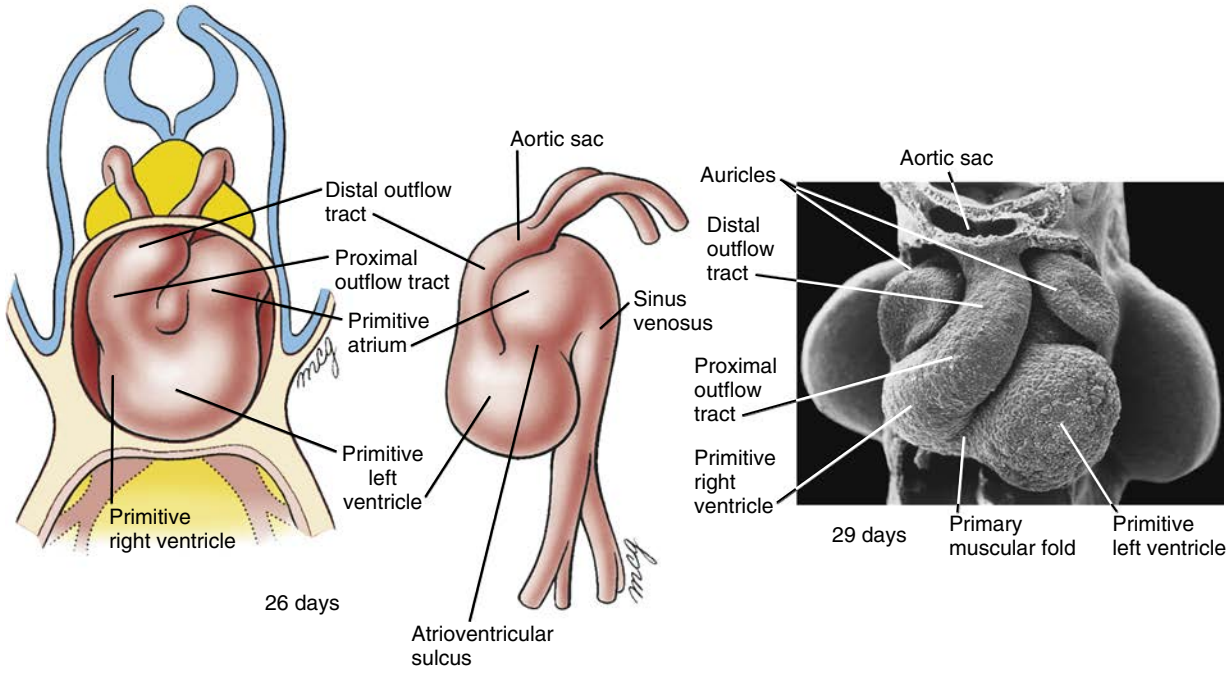

Fig. 6.4 Primitive heart tube folds to the right, creating an inner and outer curvature. (From Schoenwolf GC. *Larsen's Human Embryology.* 5th ed. Philadelphia: Elsevier; 2015.)

- If the conotruncus does not rotate, transposition of the great arteries develops.
- Incomplete rotation of the conotruncus can lead to tetralogy of Fallot because the conal septum is no longer aligned with the ventricular septum, leading to a ventricular septal defect, with the conal septum causing obstruction to pulmonary outflow.
- Arch anomalies arise from abnormal persistence and/or cell death of the six embryonic arches.
  - An interrupted arch develops with abnormalities of the fourth arch.
  - Abnormalities of the pulmonary arteries develop from abnormalities of the sixth arch.
  - Failure of the right-sided dorsal and aortic arches to regress, with abnormal regression on the left, leads to a right-sided aortic arch.
- Abnormal development of proximal structures leading to decreased flow can cause secondary hypoplasia of downstream structures.

Developmental Changes of the Myocyte and Contraction

- The contractile unit of the myocyte is the sarcomere. which is made of myofibrils.
- Contraction of the sarcomere is triggered by calcium binding to troponin.
- In the mature myocyte, membrane depolarization triggers calcium influx at L-type calcium channels found in the T tubules of the cell membrane. This small influx of calcium binds to the ryanodine receptor of the sarcoplasmic reticulum due to the close physical relationship of the T tubules and sarcoplasmic reticulum in the mature myocyte. The sarcoplasmic reticulum then releases a large amount of calcium into the cytosol. allowing calcium binding to troponin. This is termed *calcium-induced calcium release.*
- Immature myocytes have more physical separation of the sarcoplasmic reticulum and the cell membrane, as well as the absence of T tubules, leaving the cell dependent on calcium influx at the cell membrane alone. Calcium-induced calcium release does not occur in the immature myocyte. The sodium-calcium exchanger is primarily responsible for calcium influx into the cytosol of the immature myocyte.
- Several structural differences of the immature myocyte lead to less force generated with sarcomeric contraction:
  - Myofibrils are disorganized in fetal and early newborn hearts.
    - Organization of myofibrils along the long axis of the cell occurs with development.
  - Sarcomeric protein isoform expression changes with development.
    - The troponin I (TnI) isoform TnI-s is predominant in fetal life and changes to TnI-c by 9 months of age, allowing for increased force of contraction.
  - Mitochondria aggregate in the center of the immature myocyte and then become regularly distributed along the myofibrils with maturation.
- In immature hearts, lactate and carbohydrates are the primary energy sources, with transition to long-chain fatty acid in mature hearts.
- Cardiac growth in fetal life is primarily due to cell division, with resultant increase in cell number. After birth, cardiac growth is primarily secondary to hypertrophy in existing myocytes.

Maternal Diseases With Fetal Cardiac Manifestations

- Diabetes mellitus:
  - There is a five-fold increase of cardiac anomalies in infants of diabetic mothers.

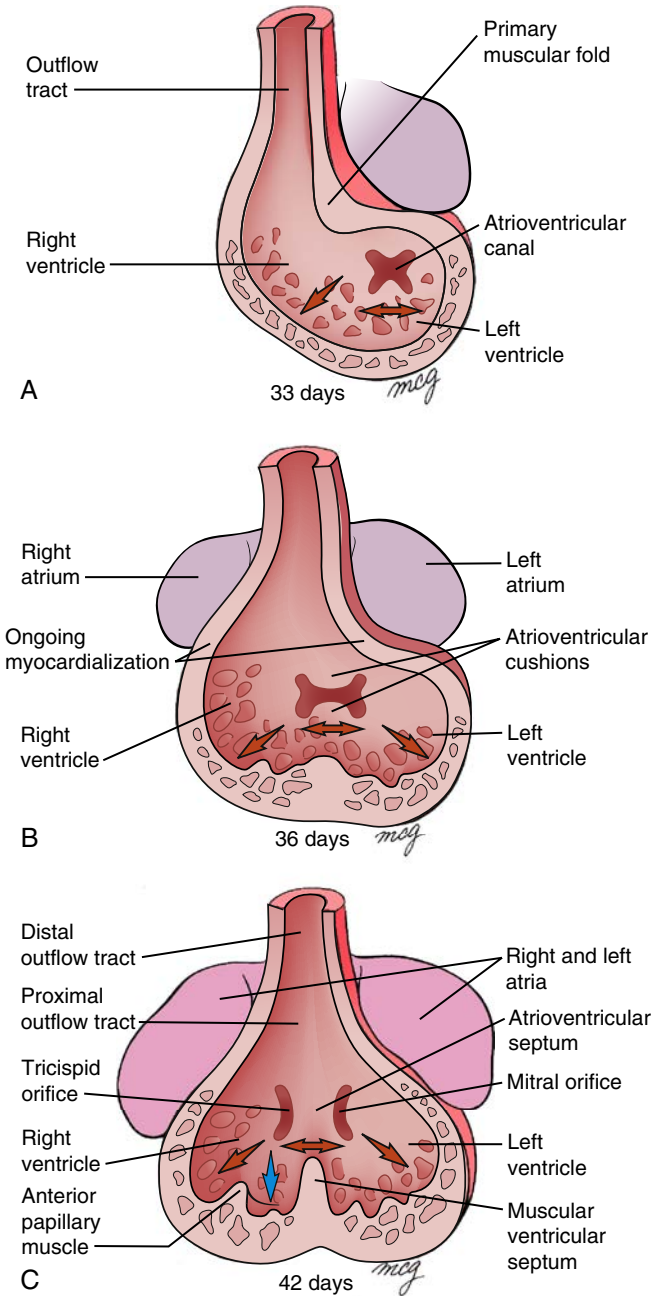

Fig. 6.5 Developing atrioventricular valve shifting to the right. (A-C) Realignment of the heart. As the atrioventricular septum forms during the fifth and sixth weeks, the heart is remodeled to align the developing left atrioventricular canal with the left atrium and ventricle, and the right atrioventricular canal with the right atrium and ventricle. Red arrows indicate the direction of realignment of the atrioventricular canal and outflow tract and formation of the muscular interventricular septum. The blue arrow in C indicates formation of an enlarging slit carved out of the muscular ventricular septum; this is responsible in part for repositioning of the tricuspid orifice to the right, as well as for formation of the moderator band. (From Schoenwolf GC. *Larsen's Human Embryology*. 5th ed. Philadelphia: Elsevier; 2015.)

- Ventricular septal defects are the most common cardiac defect.
- Transposition of the great arteries is markedly increased.
- Other defects seen include hypoplastic left heart syndrome (HLHS), coarctation of the aorta, and atrial septal defects.
- The frequency of anomalies increases with increasing first-trimester maternal hemoglobin A1c.
- Hypertrophic cardiomyopathy can develop in response to maternal hyperglycemia in the third trimester.
  - Hypertrophy gradually resolves within 6 months.

- Systemic lupus erythematosus:
  - Maternal antibodies to Ro (SS-A) and La (SS-B) cross the placenta and can cause cardiac inflammation.
  - This occurs in less than 5% of pregnancies with antibodies.
  - It can occur in asymptomatic mothers.
  - Isolated complete heart block is the most common fetal cardiac effect.
  - It usually presents with fetal bradycardia at 20 to 24 weeks of gestation.
  - Poor cardiac function and valvular regurgitation can also occur.
  - Fetal hydrops can occur.

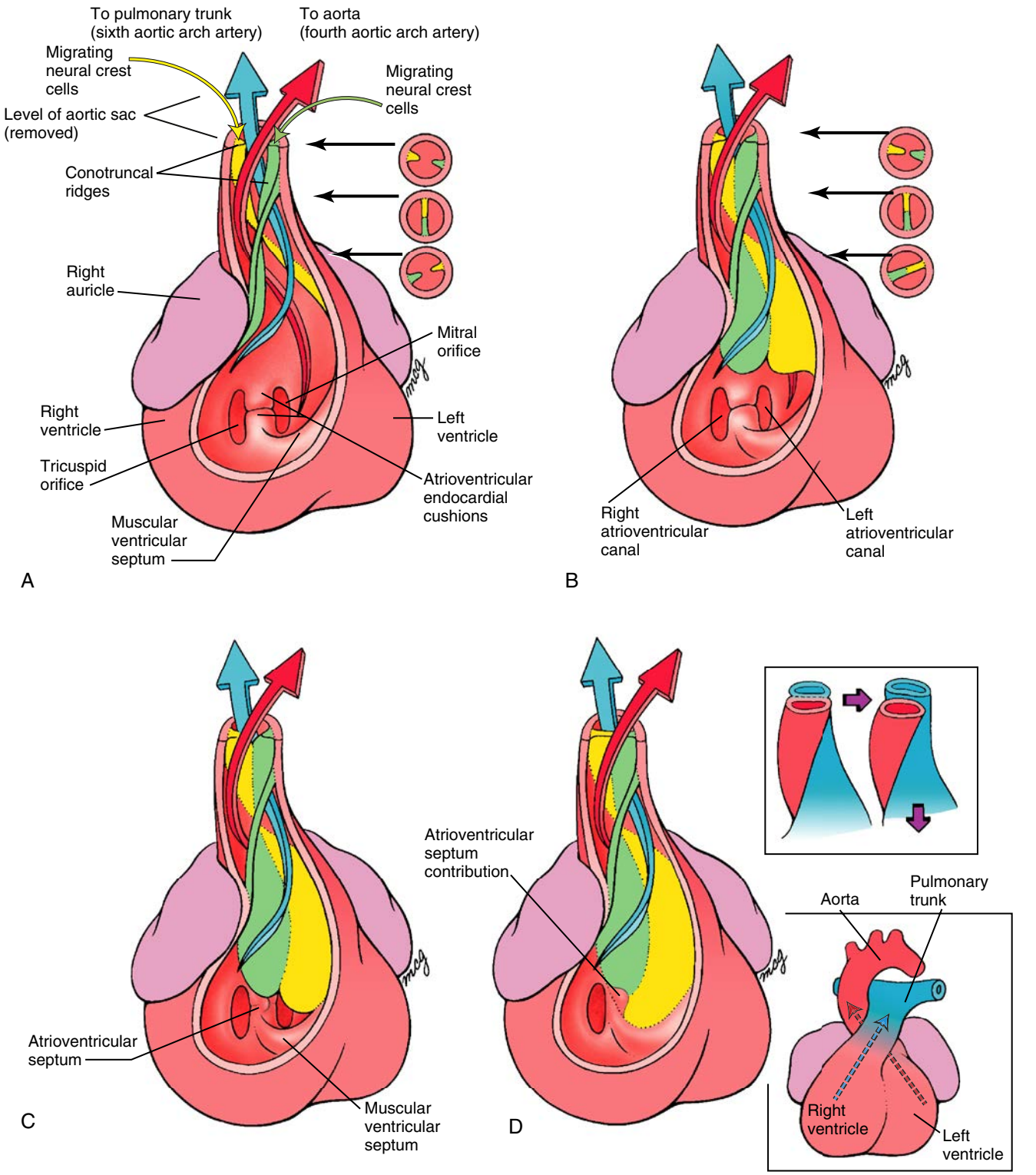

Fig. 6.6 Septation and rotation of primitive outflow tract and alignment with the developing ventricular septum. Septation of the cardiac outflow tract and completion of ventricular separation. Right oblique view. The cranial-lateral wall of the right ventricle has been removed to show the interior of the right ventricular chamber and the presumptive outflow tracts of both ventricles. (A and B) Starting in the fifth week, the right and left conotruncal ridges grow out from the walls of the common outflow tract. These swellings are populated by endocardial and neural crest cell -derived cushion cells and develop in a spiraling configuration. They fuse with one another in a cranial-to-caudal direction, forming the conotruncal septum, which separates the aortic and pulmonary outflow tracts. The circular structures to the right of the developing outflow tract illustrate drawings of cross sections at three proximodistal levels. (C and D) By the ninth week, the caudal end of the conotruncal septum has reached the level of the muscular portion of the ventricular septum and the atrioventricular septum. Here it fuses with these others to complete the ventricular septum. (From Schoenwolf GC. *Larsen's Human Embryology.* 5th ed. Philadelphia: Elsevier; 2015.)

- Maternal treatment with dexamethasone can be used to treat the fetus with complete heart block with evidence of endocardial fibroelastosis, congestive heart failure, or hydrops.
- Maternal B-mimetics such as terbutaline can be used to treat a fetus with a critically low heart rate.
  - Some neonates with complete heart block require postnatal permanent pacemakers.

- Maternal phenylketonuria:
  - A strict diet followed during the mother's childhood no longer needs to be followed during adult childbearing years; however, elevated levels of maternal phenylalanine can cause a wide array of abnormalities in a developing fetus.
  - Cardiac malformations include tetralogy of Fallot, ventricular septal defect (VSD), aortic coarctation, and hypoplastic left heart syndrome.
  - Maternal serum phenylalanine levels correlate to the risk of cardiac anomalies.
- Maternal infections during pregnancy:
  - Parvovirus can cause fetal myocarditis, with poor ventricular contractility and/or high output cardiac failure due to severe anemia.
  - Congenital rubella is associated with patent ductus arteriosus and pulmonary artery stenosis.

Suggested Readings

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Questions

1. An infant was born with truncus arteriosus. What embryologic event led to this anomaly?
   a. Failure of the conotruncus to septate
   b. Failure of the second heart field cells to migrate
   c. Failure of the conotruncus to rotate
   d. Abnormal development of the 6th arch

2. The most common cyanotic congenital heart defect seen in infants of diabetic mothers is which of the following?
   a. D-Transposition of the great arteries
   b. Hypoplastic left heart syndrome
   c. Tricuspid atresia
   d. Tetralogy of Fallot

7 Cardiovascular Physiology

KIMBERLY VERA

Fetal circulation is optimized to send oxygenated blood from the placenta to the left ventricle for distribution to the most metabolically active fetal organs and deoxygenated blood to the right ventricle to be pumped to the placenta (Fig. 7.1).

- Venous return to the fetal heart:
  - Deoxygenated blood from the upper body returns to the heart via the superior vena cava and is directed by the foramen ovale and eustachian valve, across the tricuspid valve and into the right ventricle.
  - Deoxygenated blood from the coronary sinus streams across the tricuspid valve to the right ventricle due to its location adjacent to the tricuspid valve.
  - Deoxygenated blood from the lower body returns via the inferior vena cava and streams across the tricuspid valve.
  - Oxygenated blood from the placenta goes from the umbilical vein primarily into the ductus venosus, with a smaller amount directed to the left portal vein.
  - The ductus venosus joins the inferior vena cava (IVC) near the entrance of the left hepatic vein into the IVC.
  - These oxygenated streams within the IVC are baffled by the foramen ovale into the left atrium, resulting in more oxygenated blood entering the left ventricle.
- Ventricular output of the fetal heart:
  - The right ventricle is dominant in fetal life, pumping 55% to 65% of the cardiac output.
    - The right ventricle has greater mass and thus directly affects the filling and ejection of the left ventricle in the fetus.
  - Most of the right ventricular output is directed away from the lungs due to the very high pulmonary vascular resistance in fetal life. Blood is directed across the ductus arteriosus, with one-third delivered to the lower body and two-thirds delivered to the placenta via the umbilical artery for oxygen uptake.
  - Left ventricular output supplies the oxygenated blood from the ascending aorta to the coronary arteries (7% of left ventricular output) and to the brain (55% of the left ventricular output).

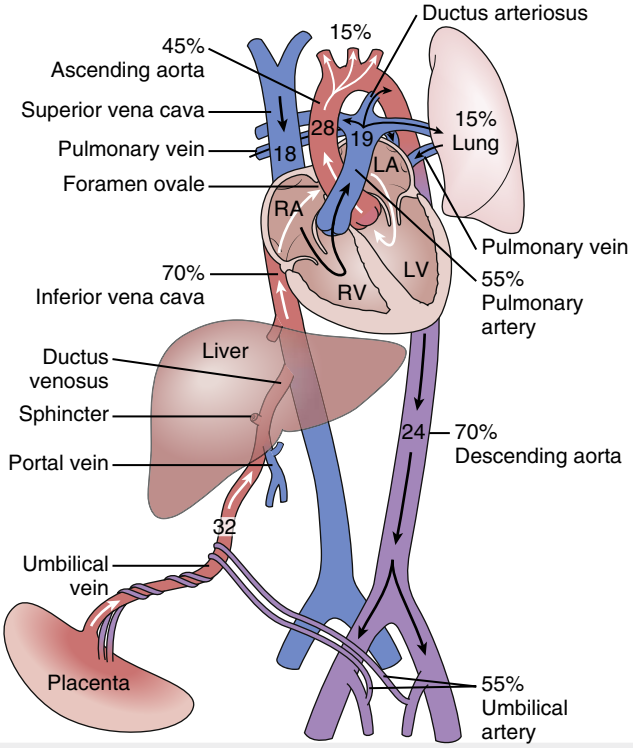

Fig. 7.1 Fetal circulation. Numbers within the vessels denote PaO_2. Numbers outside the vessels denote the percentage of cardiac output. *LA,* Left atrium; *LV,* left ventricle; *RA,* right atrium; *RV,* right ventricle. (From Park MK. *Park's Pediatric Cardiology for Practitioners.* 6th ed. Philadelphia: Saunders; 2014.)

Transition of Circulation With Birth

- Pulmonary blood flow greatly increases due to rapid decrease in pulmonary vascular resistance:
  - Ventilation alone induces a two-thirds decrease in pulmonary vascular resistance.
  - Oxygen further decreases pulmonary vascular resistance.
  - Prostacyclin is produced by lung distention and is a potent pulmonary vasodilator.
  - Remodeling of the pulmonary vascular bed decreases the muscularity of the proximal arterioles and leads to mature levels of pulmonary vascular resistance by 2 months of age.
- Fetal central shunts close (e.g., ductus arteriosus, ductus venosus, foramen ovale), creating a circulation in series:
  - Ductus venosus flow dramatically decreases with cord clamping. Anatomic closure is completed within hours to days after birth.
  - The flap of the foramen ovale is functionally closed at birth, with the dramatic increase in pulmonary venous return causing left atrial pressure to exceed right atrial pressure.
    - Anatomic closure may not occur for months after birth and remains open in 25% of people.

- The ductus arteriosus typically closes at 12 to 48 hours of life.
  - Flow across the ductus arteriosus typically changes from right to left to left to right due to the decrease in pulmonary vascular resistance and increase in systemic vascular resistance after birth.
  - Ductus arteriosus closure is initiated by increased oxygen content and decreased levels of prostaglandins after birth.
- Ventricular output dramatically increases to meet new increased energy demands due to the work of breathing and thermoregulation:
  - Oxygen consumption triples at birth.
  - Left ventricular output increases by increases in heart rate and stroke volume.
  - The left ventricle becomes the dominant ventricle in the transitional circulation as it pumps at higher pressure and ejects more blood due to the continued patency of the ductus arteriosus.
  - Cardiac output (CO) = heart rate × stroke volume (or CO) = (systemic blood pressure)/(total peripheral vascular resistance)
  - Stroke work = mean arterial pressure × stroke volume
- The systemic vascular resistance increases after birth due to removal of the low-resistance placenta and the constriction of systemic vascular beds, especially the cerebral and coronary beds, in response to the higher oxygen content of blood.

Monitoring Cardiovascular Function in the Fetus

- The fetal echocardiogram can assess for wall motion and valvar dysfunction.
- In response to stress, fetal arterial output is redistributed, with increased resistance in the placental and lower body vascular beds to maintain cerebral and cardiac oxygen delivery.
  - End-diastolic velocities decrease in the umbilical artery (Figs. 7.2 and 7.3).
  - End-diastolic velocities increase in the cerebral arteries (Fig. 7.4).
- When the arterial compensatory mechanisms are exceeded, and fetal heart failure develops, abnormalities are seen in the venous system:
  - The first sign of decompensation is a larger A wave in the inferior vena cava Doppler signal.
  - Development of a reverse A wave in the ductus venosus Doppler trace develops as heart failure progresses.
  - Atrial pulsations in the umbilical venous Doppler trace occur in end-stage fetal heart failure.

Hemodynamic Consequences of Perinatal Events

- Asphyxia impairs the transition of fetal to postnatal circulation:
  - Hypoxia keeps the ductus arteriosus open and promotes pulmonary vasoconstriction.

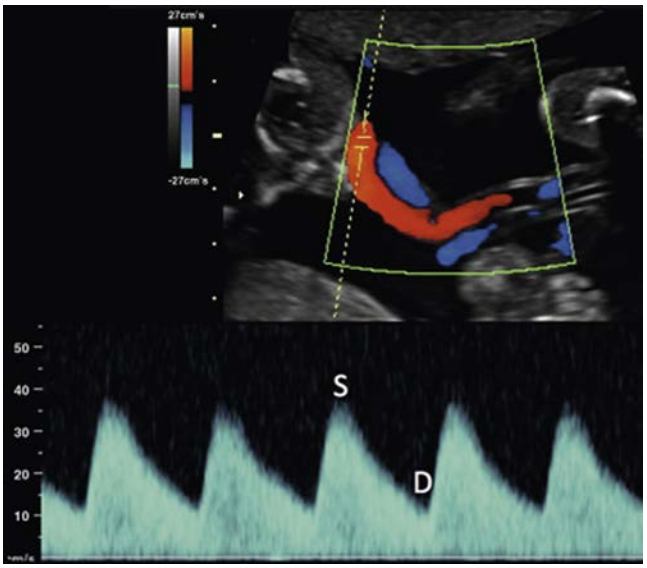

Fig. 7.2 Normal umbilical artery Doppler trace. *D,* Diastolic; *S,* Systolic. (From Norton ME. *Callen's Ultrasonography in Obstetrics and Gynecology.* 6th ed. Philadelphia: Elsevier; 2017.)

  - Metabolic acidosis worsens pulmonary vasoconstriction.
  - Increased pulmonary vascular resistance promotes tricuspid insufficiency, which increases right atrial pressure and promotes continued right to left shunting at the patent foramen ovale.
  - Cardiac output is maintained in early asphyxia due to systemic vasoconstriction shunting flow away from less vital organs, such as the gut, muscle, and skin, and toward the heart and brain.
    - This redistribution maintains oxygen delivery to critical organs and leaves the less vital organs to rely on increased oxygen extraction.
  - Skin pallor is the clinical finding that occurs secondary to this redistribution of flow.
  - Bradycardia and hypertension result from the reflexes that drive the flow redistribution.
  - Central venous pressure rises in early asphyxia secondary to the vasoconstriction of capacitance vessels.
  - As hypoxia and acidosis worsen, cardiac function declines, causing hypotension, worsening bradycardia, and leading to further increases in the central venous pressure.
  - Correction of asphyxia sequelae in the early stages can be done by establishing adequate ventilation and oxygenation.
  - If cardiac failure has developed, treatment must include rapid correction of the acidosis to improve the poor cardiac wall motion.
- Perinatal hypovolemia results in similar hemodynamic responses to asphyxia, including redistribution of the cardiac output to vital organs.
  - Acidosis and bradycardia can also be seen in hypovolemia.
  - Central venous pressure, however, is typically low in infants in the early stages of hypovolemia.

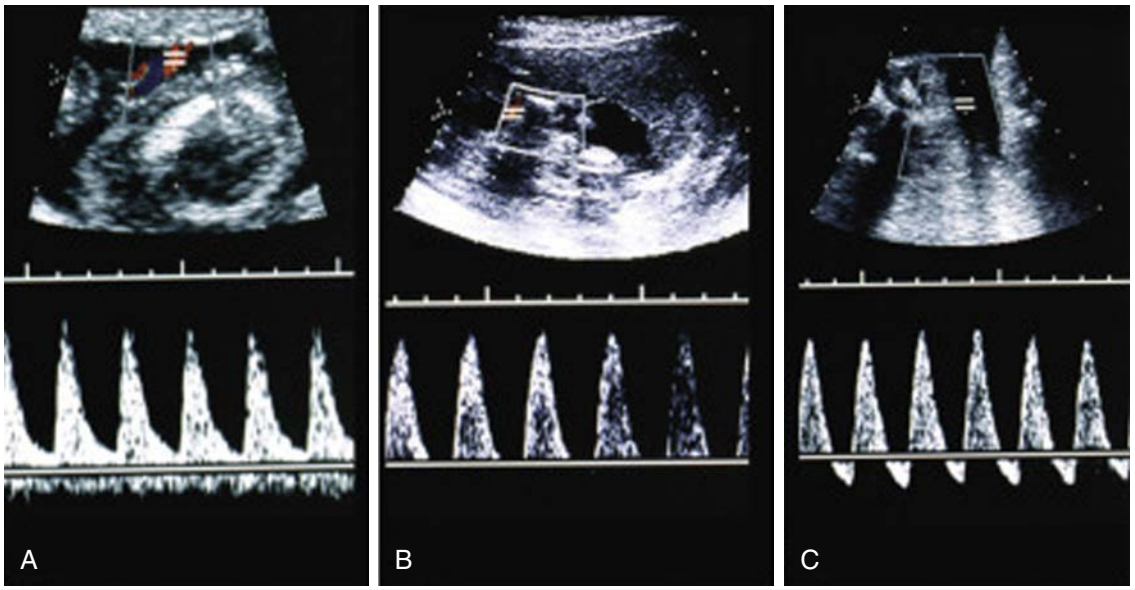

Fig. 7.3 Umbilical artery traces in fetal distress. (A) End-diastolic velocity decreases in response to fetal distress. (B) It proceeds to absent end-diastolic flow and ultimately reverse end-diastolic flow (C) as fetal distress progresses. (From Norton ME. *Callen's Ultrasonography in Obstetrics and Gynecology*. 6th ed. Philadelphia: Elsevier; 2017.)

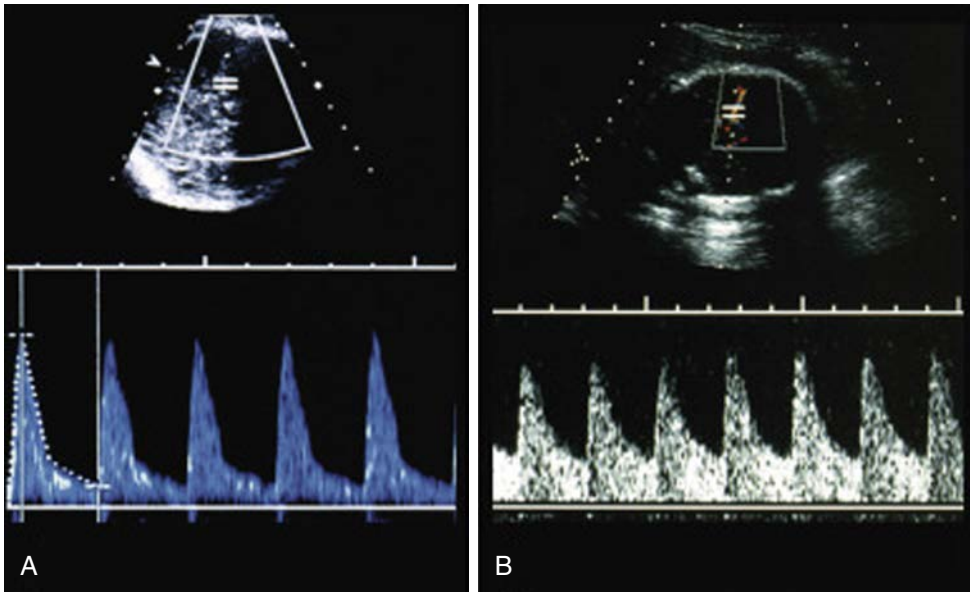

Fig. 7.4 Normal and abnormal cerebral arterial Doppler. (A) Normal cerebral arterial Doppler. (B) Increase in end-diastolic velocity in response to fetal stress. (From Norton ME. *Callen's Ultrasonography in Obstetrics and Gynecology*. 6th ed. Philadelphia: Elsevier; 2017.)

Suggested Readings

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Question

1. Physiologic responses to asphyxia include which of the following?
   a. Tachycardia, decreased central venous pressure, vasoconstriction of the cerebral vessels
   b. Bradycardia, increased central venous pressure, vasoconstriction of the skeletal muscle vessels
   c. Bradycardia, decreased central venous pressure, vasodilation of the cerebral vessels
   d. Tachycardia, increased central venous pressure, vasoconstriction of the skeletal muscle vessels

8 Presentation of Congenital Heart Disease

KIMBERLY VERA

Congenital heart disease occurs in 1% of live births and can be associated with genetic syndromes or maternal medications (Table 8.1). The presentation of congenital heart disease in neonatal life is typically with cyanosis, poor perfusion, tachypnea, or some combination of these symptoms.

- Cyanosis
  - Cyanosis due to heart disease develops secondary to inadequate pulmonary blood flow or intracardiac mixing.
  - Cyanosis is appreciated clinically when 5 g/dL of hemoglobin are deoxygenated.
  - It is typically not clinically apparent until oxygen saturation is <85%.
  - The differential for a cyanotic infant is congenital heart disease, persistent primary pulmonary hypertension of the newborn, and primary parenchymal lung disease.
  - Congenital heart disease is very likely in a cyanotic infant with mild tachypnea but no significant respiratory distress.
- Poor perfusion
  - Poor perfusion due to congenital heart disease occurs secondary to left-sided obstruction or decreased ventricular function.
  - It typically presents when the ductus arteriosus closes in the first days of life; however ductal closure can occur as late as 3 to 4 weeks of age.
- Tachypnea
  - Tachypnea due to congestive heart failure develops slowly over the first weeks to months of life as the pulmonary vascular resistance drops and allows significant left-to-right shunting.

Evaluation of an Infant With Suspected Congenital Heart Disease

Cardiac auscultation includes identifying normal and abnormal sounds and can give indications to underlying pathology.

- S1 indicates the closure of the mitral and tricuspid valves and is best heard at the apex or left lower sternal border (LLSB).
- S2 indicates closure of the of the aortic and pulmonary valves. It is normally split into A2 (aortic closure) and P2 (pulmonary closure). The time between A2 and P2 normally increases with inspiration and decreases with expiration, causing the normal splitting of S2.
  - A narrowly split S2 occurs with pulmonary hypertension.
  - A widely split S2 occurs with volume overload that is seen in conditions such as an atrial septal defect or anomalous pulmonary veins.
  - A single S2 is found in anomalies with only one semilunar valve.
- S3 is a low-frequency, early diastolic sound best heard at the apex or LLSB. It is the sound of rapid filling of the ventricle.
  - It can be a normal finding; however, a loud S3 is abnormal and is seen in conditions with poor ventricular compliance, such as a cardiomyopathy.
- S4 is a low-frequency late diastolic sound that is always pathologic. An S4, also called a *gallop*, indicates poor ventricular compliance in conditions such as cardiomyopathy.
- An ejection click follows S1 closely and indicates pathology of one of the semilunar valves.
  - A pulmonary click is best heard at the second or third left intercostal space and is louder with expiration.
  - An aortic click is best heard at the second right intercostal space, apex, or mid–left sternal border.
- Murmurs should be graded by intensity (1–6), timing (systolic versus diastolic), location, transmission, and quality.
- Systolic murmurs occur between S1 and S2.
  - Systolic ejection murmurs have intensity that grows from S1 and peaks at a midpoint before decreasing at S2.
    - Created by pathology of the semilunar valves and physiologic murmurs
  - Regurgitant systolic murmurs begin from S1 with peak intensity and continue with variable duration throughout systole.
    - Created by ventricular septal defects, mitral regurgitation, and tricuspid regurgitation
  - Location of the murmur is associated with the lesion
    - Upper left sternal border (pulmonary area): pulmonary stenosis, atrial septal defect, and anomalous pulmonary veins
    - Upper right sternal border (aortic area): aortic stenosis
    - Lower left sternal border: ventricular septal defects, tricuspid regurgitation
    - Apex: mitral regurgitation, aortic stenosis
- Diastolic murmurs occur between S2 and S1 and signify aortic or pulmonary insufficiency.
- Continuous murmurs begin in systole and continue past S2 into some or all of diastole.
  - Patent ductus arteriosus as well as coarctation of the aorta can present with a continuous murmur.

Table 8.1 Syndromes and Medications Associated With Congenital Heart Disease

Disorder	Cardiovascular (CV) Abnormalities: Frequency and Types	Major Features	Etiology
Alagille syndrome (arteriohepatic dysplasia)	Frequent (85%), peripheral PA stenosis, with or without complex CV abnormalities	Peculiar facies (95%) consisting of deep-set eyes, broad forehead, long, straight nose with flattened tip, prominent chin, and small, low-set, malformed ears; paucity of intrahepatic interlobular bile duct with chronic cholestasis (91%), hypercholesterolemia, butterfly-like vertebral arch defects (87%); growth retardation (50%) and mild mental retardation (16%)	AD chromosome 22q11.2
CHARGE association	Common (65%); TOF, truncus arteriosus, aortic arch anomalies (e.g., vascular ring, interrupted aortic arch)	*C*oloboma, *h*eart defects, choanal *a*tresia, growth or mental *r*etardation, *g*enitourinary anomalies, *e*ar anomalies, genital hypoplasia	8q12 deletion
Carpenter syndrome	Frequent (50%); PDA, VSD, PS, TGA	Brachycephaly with variable craniosynostosis, mild facial hypoplasia, polydactyly and severe syndactyly ("mitten hands")	AR
Cockayne syndrome	Accelerated atherosclerosis	Senile-like changes beginning in infancy, dwarfing, microcephaly, prominent nose and sunken eyes, visual loss (retinal degeneration) and hearing loss	AR
Cornelia de Lange (de Lange) syndrome	Occasional (30%); VSD	Synophrys and hirsutism, prenatal growth retardation, microcephaly, anteverted nares, downturned mouth, mental retardation	Unknown; AD?
Cri du chat syndrome (deletion 5p syndrome)	Occasional (25%); variable CHD (VSD, PDA, ASD)	Cat-like cry in infancy, microcephaly, downward slant of palpebral fissures	Partial deletion, short arm of chromosome 5
Crouzon disease (craniofacial dysostosis)	Occasional; PDA, COA	Ptosis with shallow orbits, premature craniosynostosis, maxillary hypoplasia	AD
DiGeorge syndrome (overlap with velocardiofacial syndrome)	Frequent; interrupted aortic arch, truncus arteriosus, VSD, PDA, TOF	Hypertelorism, short philtrum, downslanting eyes, hypoplasia or absence of thymus and parathyroid, hypocalcemia, deficient cell-mediated immunity	Microdeletion of 22q11.2
Down syndrome (trisomy 21)	Frequent (40%–50%); ECD, VSD	Hypotonic, flat facies, slanted palpebral fissure, small eyes, mental deficiency, simian crease	Trisomy 21
Ehlers-Danlos syndrome	Frequent; ASD, aneurysm of aorta and carotids, intracranial aneurysm, MVP	Hyperextensive joints, hyperelasticity, fragility and bruisability of skin, poor wound healing with thin scar	AD
Ellis-van Creveld syndrome (chondroectodermal dysplasia)	Frequent (50%); ASD, single atrium	Short stature of prenatal onset, short distal extremities, narrow thorax with short ribs, polydactyly, nail hypoplasia, neonatal teeth	AR
Fetal alcohol syndrome	Occasional (25%–30%); VSD, PDA, ASD, TOF	Prenatal growth retardation, microcephaly, short palpebral fissure, mental deficiency, irritable infant or hyperactive child	Ethanol or its byproducts
Fetal trimethadione syndrome	Occasional (15%–30%); TGA, VSD, TOF	Ear malformation, hypoplastic midface, unusual eyebrow configuration, mental deficiency, speech disorder	Exposure to trimethadione
Fetal warfarin syndrome	Occasional (15%–45%); TOF, VSD	Facial asymmetry and hypoplasia, hypoplasia, or aplasia of the pinna with blind or absent external ear canal (microtia); ear tags; cleft lip or palate; epitubular dermoid; hypoplastic vertebrae	Exposure to warfarin
Friedreich ataxia	Frequent; hypertrophic cardiomyopathy progressing to heart failure	Late-onset ataxia, skeletal deformities	AR
Goldenhar syndrome (oculoauriculovertebral spectrum)	Frequent (35%); VSD, TOF	Facial asymmetry and hypoplasia, microtia, ear tag, cleft lip or palate, hypoplastic vertebrae	Unknown; usually sporadic
Glycogen storage disease II (Pompe disease)	Very common; cardiomyopathy	Large tongue and flabby muscles, cardiomegaly; LVH and short PR on ECG, severe ventricular hypertrophy on echocardiography; normal FBS and GTT	AR
Holt-Oram syndrome (cardio-limb syndrome)	Frequent; ASD, VSD	Defects or absence of thumb or radius	AD
Homocystinuria	Frequent; medial degeneration of aorta and carotids, atrial or venous thrombosis	Subluxation of lens (usually by 10 yr), malar flush, osteoporosis, arachnodactyly, pectus excavatum or carinatum, mental defect	AR

Table 8.1 Syndromes and Medications Associated With Congenital Heart Disease—cont'd

Disorder	Cardiovascular (CV) Abnormalities: Frequency and Types	Major Features	Etiology
Infant of mother with diabetes	CHDs (3%–5%); TGA, VSD, COA; cardiomyopathy (10%–20%); PPHN	Macrosomia, hypoglycemia and hypocalcemia, polycythemia, hyperbilirubinemia, other congenital anomalies	Fetal exposure to high glucose levels
Kartagener syndrome	Dextrocardia	Situs inversus, chronic sinusitis and otitis media, bronchiectasis, abnormal respiratory cilia, immotile sperm	AR
LEOPARD syndrome (multiple lentigenes syndrome)	Very common; PS, HOCM, long PR interval	*L*entiginous skin lesion, *E*CG abnormalities, *o*cular hypertelorism, *p*ulmonary stenosis, *a*bnormal genitalia, *r*etarded growth, *d*eafness	AD
Long QT syndrome: Jervell and Lange-Nielsen syndrome Romano-Ward syndrome	Very common; long QT interval on ECG, ventricular tachyarrhythmia	Congenital deafness (not in Romano-Ward syndrome), syncope resulting from ventricular arrhythmias, family history of sudden death (±)	AR, AD
Marfan syndrome	Frequent; aortic aneurysm, aortic or mitral regurgitation	Arachnodactyly with hyperextensibility, subluxation of lens	AD
Mucopolysaccharidosis; Hurler syndrome (type I); Hunter syndrome (type II); Morquio syndrome (type IV)	Frequent; aortic or mitral regurgitation, coronary artery disease	Coarse features, large tongue, depressed nasal bridge, kyphosis, retarded growth, hepatomegaly, corneal opacity (not in Hunter syndrome), mental retardation; most patients die by 10 to 20 yr of age	AR, XR
Muscular dystrophy (Duchenne type)	Frequent; cardiomyopathy	Waddling gait, "pseudohypertrophy" of calf muscle	XR
Neurofibromatosis (von Recklinghausen disease)	Occasional; PS, COA, pheochromocytoma	Café au lait spots, multiple neurofibroma, acoustic neuroma, variety of bone lesions	AD
Noonan syndrome (Turner-like syndrome)	Frequent; PS (dystrophic pulmonary valve), LVH (or anterior septal hypertrophy)	Similar to Turner syndrome but may occur in both males and females, without chromosomal abnormality	Usually sporadic; apparent AD?
Pierre Robin syndrome	Occasional, VSD, PDA; less commonly, ASD, COA, TOF	Micrognathia, glossoptosis, cleft soft palate	In utero mechanical constraint?
Osler-Weber-Rendu syndrome (hereditary hemorrhagic telangiectasia)	Occasional; pulmonary arteriovenous fistula	Hepatic involvement, telangiectases, hemangioma or fibrosis	AD
Osteogenesis imperfecta	Occasional; aortic dilation, aortic regurgitation, MVP	Excessive bone fragility with deformities of skeleton, blue sclera, hyperlaxity of joints	AD or AR
Progeria (Hutchinson-Gilford syndrome)	Accelerated atherosclerosis	Alopecia, atrophy of subcutaneous fat, skeletal hypoplasia and dysplasia	Unknown; occasional AD or AR
Rubella syndrome	Frequent (>95%); PDA and PA stenosis	Triad of the syndrome: deafness, cataract, and CHDs; others include intrauterine growth retardation, microcephaly, microphthalmia, hepatitis, neonatal thrombocytopenic purpura	Maternal rubella infection during the first trimester
Rubinstein-Taybi syndrome	Occasional (25%); PDA, VSD, ASD	Broad thumbs or toes, hypoplastic maxilla with narrow palate, beaked nose, short stature, mental retardation	Sporadic; 16p13.3 deletion
Smith-Lemli-Opitz syndrome	Occasional; VSD, PDA, others	Broad nasal tip with anteverted nostrils, ptosis of eyelids, syndactyly of second and third toes, short stature, mental retardation	AR
Thrombocytopenia–absent radius (TAR) syndrome	Occasional (30%); TOF, ASD, dextrocardia	Thrombocytopenia, absent or hypoplastic radius, normal thumb; "leukemoid" granulocytosis and eosinophilia	AR
Treacher Collins syndrome	Occasional; VSD, PDA, ASD	Defects of lower eyelids, malar hypoplasia with downslanting palpebral fissure, malformation of auricle or ear canal defect, cleft palate	Fresh mutation; AD
Trisomy 13 syndrome (Patau syndrome)	Very common (80%); VSD, PDA, dextrocardia	Low birth weight, central facial anomalies, polydactyly, chronic hemangiomas, low-set ears, visceral and genital anomalies	Trisomy 13
Trisomy 18 syndrome (Edwards syndrome)	Very common (90%); VSD, PDA, PS	Low birth weight, microcephaly, micrognathia, rocker-bottom feet, closed fist with overlapping fingers	Trisomy 18

Continued

Table 8.1 Syndromes and Medications Associated With Congenital Heart Disease—cont'd

Disorder	Cardiovascular (CV) Abnormalities: Frequency and Types	Major Features	Etiology
Tuberous sclerosis	Frequent; rhabdomyoma	Triad of adenoma sebaceum (2–5 yr of age), seizures, and mental defect; cyst-like lesions in phalanges and elsewhere; fibrous-angiomatosis lesions (83%) with varying colors in nasolabial fold, cheeks, and elsewhere	AD
Turner syndrome (XO syndrome)	Frequent (35%); COA, bicuspid aortic valve, AS; hypertension, aortic dissection later in life	Short female, broad chest with widely spaced nipples, congenital lymphedema with residual puffiness over the dorsum of fingers and toes (80%)	XO with 45 chromosomes
VATER association (VATER or VACTERL syndrome)	Common (>50%); VSD, other defects	*V*ertebral anomalies, *a*nal atresia, *c*ongenital heart defects, *t*racheo*e*sophageal (TE) fistula, *r*enal dysplasia, *l*imb anomalies (e.g., radial dysplasia)	Sporadic
Velocardiofacial syndrome (Shprintzen syndrome)	Very common (85%); truncus arteriosus, TOF, pulmonary atresia with VSD, interrupted aortic arch type B), VSD, and d-TGA	Structural or functional palatal abnormalities, unique facial characteristics ("elfin facies" with auricular abnormalities, prominent nose with squared nasal root and narrow alar base, vertical maxillary excess with long face), hypernatal speech, conductive hearing loss, hypotonia, developmental delay and learning disability	Unknown; chromosome 22q11 (probably the same disease as DiGeorge syndrome)
Williams syndrome	Frequent; supravalvar AS, PA stenosis	Varying degree of mental retardation, so-called elfin facies (consisting of some of the following: upturned nose, flat nasal bridge, long philtrum, flat malar area, wide mouth, full lips, widely spaced teeth, periorbital fullness), hypercalcemia of infancy?	Sporadic, 7q23 deletion, AD?
Zellweger syndrome (cerebrohepatorenal syndrome)	Frequent; PDA, VSD, or ASD	Hypotonia, high forehead with flat facies, hepatomegaly, albuminemia	AR

AD, autosomal dominant; *AR,* autosomal recessive; *AS,* aortic stenosis; *ASD,* atrial septal defect; *CHD,* congenital heart defect; *COA,* coarctation of the aorta; *d-TGA,* d-transposition of the great arteries; *FBS,* fasting blood sugar; *GTT,* gamma-glutamyl transferase; *HOCM,* hypertrophic obstructive cardiomyopathy; *LVH,* left ventricular hypertrophy; *MVP,* mitral valve prolapse; *PDA,* patent ductus arteriosus; *PPHN,* persistent pulmonary hypertension of the newborn; *PS,* pulmonary stenosis; *TOF,* tetralogy of fallot; *VSD,* ventricular septal defect; *XR,* x-linked recessive.
From Park MK. *Park's Pediatric Cardiology for Practitioners*. 6th ed. Philadelphia: Elsevier, 2014.

- Pulse oximetry
  - Useful to measure oxygen saturation (<95% abnormal)
  - Simultaneous measurement in right hand (preductal) and lower extremity (postductal) useful to assess whether the ascending and descending aorta are being perfused by different ventricles via the ductus arteriosus (Table 8.2)
- Arterial blood gas
  - Should be determined if the pulse oximetry is abnormal to confirm low Po_2
  - Demonstrates metabolic acidosis in infants with left-sided obstructive lesions
- Oxygen challenge test (also called the *hyperoxia test*)
  - Arterial blood gases are measured on room air, after several minutes of inhaling 100% Fio_2. Failure to increase Po_2 dramatically (absolute Po_2 < 100 mm Hg on 100% Fio_2 or increase of Po_2 by <30 mm Hg on 100% Fio_2) is suggestive of hypoxia secondary to cardiac disease.
  - Oxygen may promote constriction of the ductus, which is often detrimental.
- Four extremity blood pressures
  - Systolic blood pressure in the upper extremities should be lower than in the lower extremities. If the lower extremities have lower systolic blood pressures, coarctation of the aorta should be suspected.

Table 8.2 Differential Diagnosis of Differences in Preductal and Postductal Saturations

Preductal Saturation > Postductal Saturation	Postductal Saturation > Preductal Saturation
Pulmonary hypertension Coarctation of the aorta Interrupted aortic arch Critical aortic stenosis	Transposition of the great arteries with a coarctation

- Electrocardiogram (ECG)
  - Very nonspecific in diagnosing most congenital heart disease
  - Normal neonate ECG will demonstrate right ventricular hypertrophy, with up right T waves in the right precordial leads
- Chest radiograph
  - Can demonstrate increased or decreased pulmonary vascular markings, heart size, and shape
  - Can also suggest thymic absence and right-sided arch, which would support the diagnosis of 22q11 syndrome (associated with conotruncal cardiac defects)
- Echocardiogram
  - Gold standard to define anatomy and diagnose specific lesions

Medical Interventions in Infants With Cyanotic Heart Disease

- Severely hypoxic infants (saturation <75%) due to inadequate pulmonary blood flow should be treated with prostaglandins to open or maintain the ductus arteriosus.
- Oxygen should be used sparingly to maintain saturation of 75% to 85% because the pulmonary vasodilatory response to oxygen can lead to excessive pulmonary blood flow and thus inadequate systemic blood flow in single-ventricle infants.

Common Surgical Interventions in Cyanotic and Single-Ventricle Infants

- Atrial balloon septostomy, also known as the *Rashkind procedure*
  - Atrial septum is enlarged in the cardiac catheterization laboratory to allow for atrial-level shunting, often performed emergently
  - Typically performed in infants with hypoplastic left heart syndrome with a restrictive atrial septum or in infants with transposition of the great arteries
- Systemic to pulmonary artery shunts
  - Typically performed in the first week of life in a prostaglandin-dependent infant to ensure stable pulmonary blood flow
  - Blalock-Taussig shunt (Fig. 8.1)
    - Gore-Tex tube placed to connect the subclavian artery to a branch of the pulmonary artery
  - Stenting of the ductus arteriosus via cardiac catheterization
  - Goal is to balance flow to the lungs (Qp) and flow to the body (Qs) to provide adequate oxygenation but not excessive pulmonary blood flow, which results in inadequate systemic perfusion and ventricular volume overload
    - Balance is typically achieved with oxygen saturations of 75% to 85%
- Bidirectional Glenn (Fig. 8.2A)
  - Anastomosis of the superior vena cava to the right pulmonary artery in an end-to-side fashion
  - Performed at 4 to 6 months of age
- Fontan (see Fig. 8.2B)
  - Direction of inferior vena cava flow to the pulmonary artery via an extracardiac conduit or via a baffle through the right atrium
  - Performed at 2 to 4 years of age

Left-to-Right Shunting Lesions

- Infant asymptomatic at birth and then develops signs of congestive heart failure as the pulmonary vascular resistance falls in the first weeks to months of life
  - Premature infants may develop symptoms earlier because they are born with lower pulmonary vascular resistance.

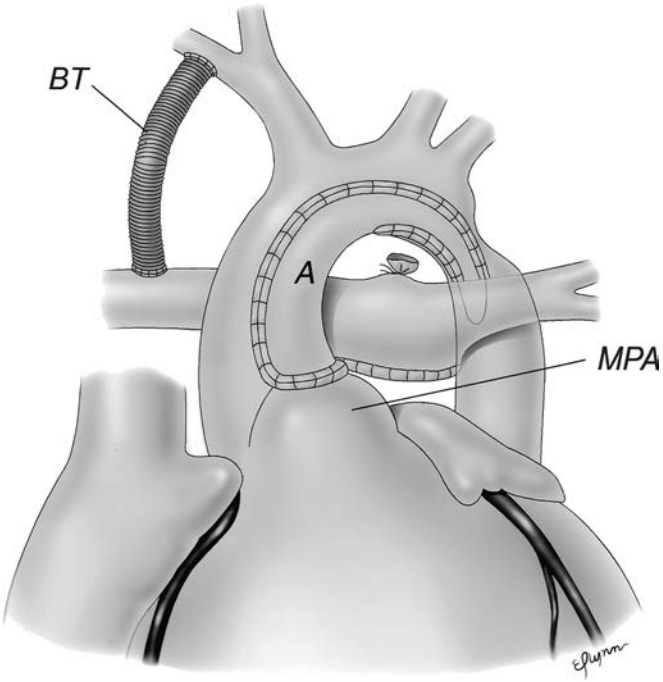


Fig. 8.1 Blalock-Taussig shunt (BT). *A,* NeoAorta; *MPA,* middle pulmonary artery. (From Keane JF. *Nadas' Pediatric Cardiology.* 2nd ed. Philadelphia: Saunders; 2006.)

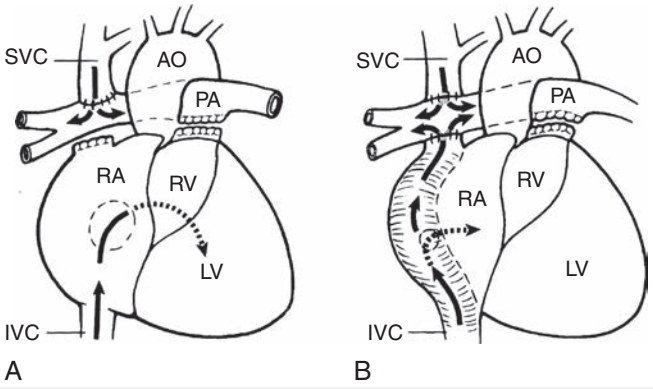


Fig. 8.2 Single-ventricle palliation. (A) The Glenn operation. (B) The Fontan operation. *AO,* aorta; *IVC,* inferior vena cava; *LV,* left ventricle; *PA,* pulmonary artery; *RA,* right atrium; *RV,* right ventricle; *SVC,* superior vena cava. (From Park MK. *Park's Pediatric Cardiology for Practitioners.* 6th ed. Philadelphia: Elsevier; 2014.)

- Lesions can be divided into those with pure left-to-right shunting and thus have normal oxygen saturations and lesions that have bidirectional shunting but with excessive pulmonary blood flow leading to mild desaturation (Table 8.3).
- Symptoms of congestive heart failure: tachypnea, diaphoresis, failure to thrive
- Chest x-ray demonstrates cardiomegaly with increased pulmonary vascular markings.
- Ventricular septal defect
  - There are several anatomically different places for ventricular septal defects to occur—perimembranous, outlet, inlet, and muscular (Fig. 8.3).
  - Symptoms of congestive heart failure develop at several weeks to months of age with medium to large defects, but small defects are asymptomatic.

Table 8.3 Left-to-Right Shunting Lesions

Exclusive Left-to-Right Shunting	Bidirectional Shunting Present but Not Left-to-Right Shunt
Ventricular septal defect (VSD)	Double-inlet left ventricle with unobstructed outflow tracts
Atrioventricular septal defect	Truncus arteriosus
Anteroposterior window	Total anomalous venous pulmonary return without obstruction
Patent ductus arteriosus	
Atrial septal defect	

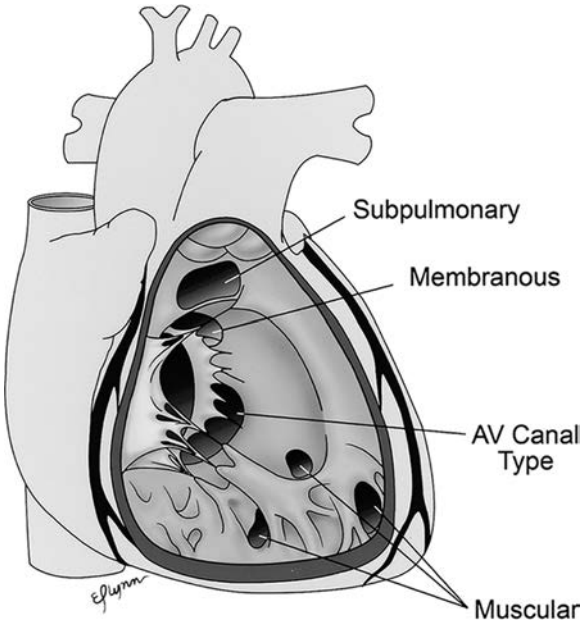
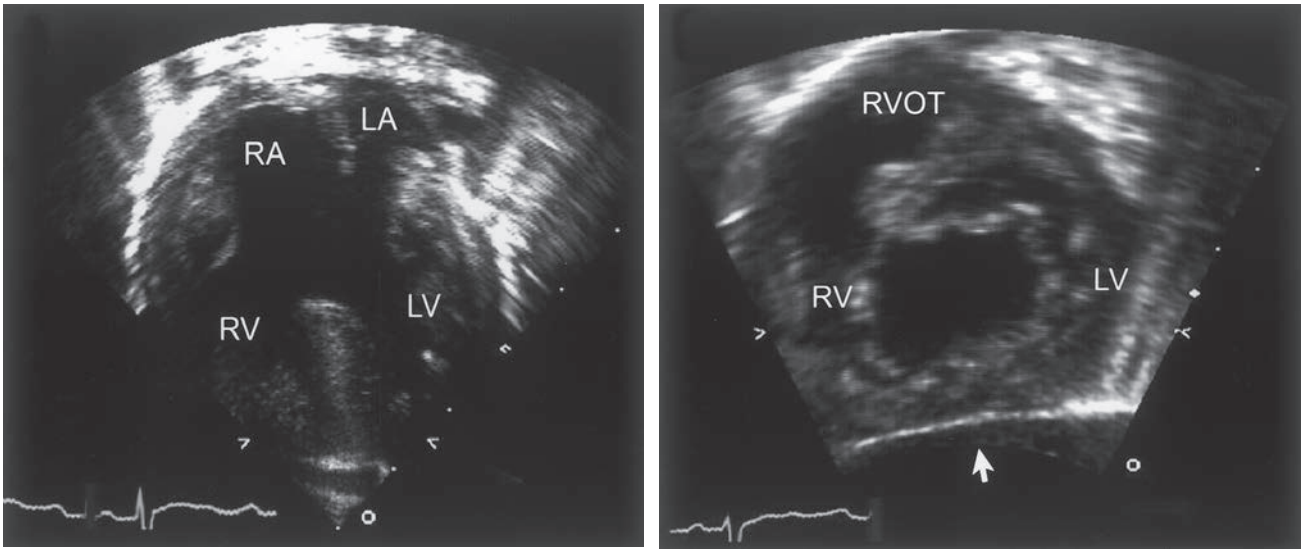


Fig. 8.3 Types of ventricular septal defects. (From Keane JF. *Nadas' Pediatric Cardiology.* 2nd ed. Philadelphia: Saunders; 2006.)

- Small defects have a loud, high-pitched murmur; large defects have a lower frequency holosystolic murmur and can have a diastolic rumble.
- Medical management of congestive heart failure includes diuretics, digoxin, angiotensin-converting enzyme inhibitors, and maximization of nutrition.
- Surgical repair is preferably delayed until 4 to 6 months of age but can be done earlier if congestive heart failure symptoms are refractory to medical management.
- Small perimembranous and muscular defects can spontaneously close.

- Atrial septal defects
  - Secundum atrial septal defects occur in the fossa ovalis and are the most common defects.
  - Primum atrial septal defects are found in the inferior portion of the atrial septum and are part of the atrioventricular septal defect spectrum.
  - Sinus venosus atrial septal defects are found adjacent to the inferior or superior vena cava and are often found in association with partial anomalous pulmonary venous return.
  - Atrial septal defects rarely cause symptoms in infancy because the right ventricular compliance does not typically allow for significant left-to-right shunting.
  - Auscultatory finding can include a pulmonary outflow murmur at the left upper sternal border and a fixed split S2.
  - Surgical repair is indicated for any symptomatic infant or toddler, and during childhood, for significant asymptomatic defects to avoid pulmonary vascular disease in adulthood.
- Atrioventricular septal defects (AVSDs)
  - Class of cardiac lesions with endocardial cushion defects resulting in a common atrioventricular valve
  - Incomplete AVSD
    - Primum atrial septal defect with a cleft mitral valve
  - Complete AVSD (Fig. 8.4)
    - Primum atrial septal defect, common atrioventricular valve, inlet ventricular septal defect



A B

Fig. 8.4 Echo images of a complete atrioventricular septal defect. (A) Demonstrates the large inlet ventricular septal defect and large primum atrial septal defect. (B) Demonstrates the common atrioventricular valve. *LA,* left atrium; *LV,* left ventricle; *RA,* right atrium; *RV,* right ventricle; *RVOT,* right ventricular outflow tract. (From Keane JF. *Nadas' Pediatric Cardiology.* 2nd ed. Philadelphia: Saunders; 2006.)

- Atrioventricular valves are always abnormal and can have significant regurgitation.
- About half of the infants with a complete AVSD will have Down syndrome.
- The ECG shows a left superior QRS axis.
- Congestive heart failure symptoms develop at a few weeks to months of age.
- Infants with complete AVSDs often have mild cyanosis.
- Auscultatory findings vary widely, depending on the degree of atrioventricular valve insufficiency and the degree of left-to-right shunting at the ventricular level. Murmur may not be present.
- Medical management with diuretics and afterload reduction and nutritional support is first-line therapy.
- Surgical repair is optimally done at 3 to 6 months of age.

- Patent ductus arteriosus
  - Ductus arteriosus arises from the sixth dorsal arch and connects the pulmonary artery to the dorsal aorta at the isthmus (Fig. 8.5).
  - A patent ductus arteriosus (PDA) is a common complication of hyaline membrane disease and is a common additional lesion in congenital heart disease.
  - Moderate to large PDAs result in significant left-to-right shunting as the pulmonary vascular resistance falls after birth.
  - As the pulmonary vascular resistance decreases in the first weeks of life, increased pulmonary blood flow, increased pulmonary artery pressure, and increased left ventricular and atrial volume and pressure develop, leading to congestive heart failure symptoms, with pulmonary edema.
  - Premature infants can develop heart failure symptoms earlier than term infants due to the incomplete development of the medial musculature of small pulmonary arteries causing decreased pulmonary vascular resistance. The immature contractile function of the ventricles makes volume load more difficult to handle.
  - A crescendo systolic murmur or continuous murmur is often present, but some premature infants have no murmur.

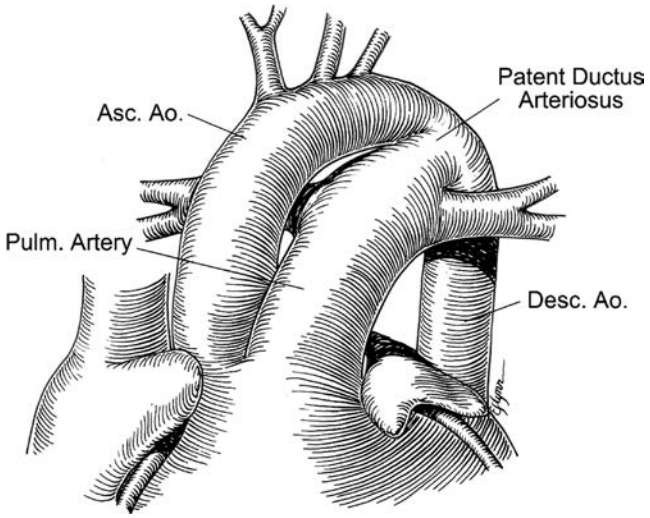


Fig. 8.5 Patent ductus arteriosus. *Ao,* aorta. (From Keane JF. *Nadas' Pediatric Cardiology.* 2nd ed. Philadelphia: Saunders; 2006.)

  - Runoff from the aorta into the pulmonary artery lowers the diastolic blood pressure and leads to wide pulse pressure.
    - Necrotizing enterocolitis and renal dysfunction may result from the aortic runoff, causing ischemia.
  - Treatment
    - Term symptomatic infants can be managed medically with diuretics and afterload reduction but, ultimately, symptomatic PDAs should be closed in the operating room.
    - Asymptomatic term infants can be monitored without treatment but PDAs are closed, often in the cardiac catheterization laboratory, in toddlers or children to remove the risk of endocarditis.
    - Preterm infants with PDAs are medically treated with indomethacin.
      - Indomethacin inhibits prostaglandin synthesis leading to ductal constriction.
      - Indomethacin produces PDA closure in about 85% of preterm infants but is not effective in term infants.
      - Indomethacin can inhibit renal and platelet function.
    - Ibuprofen is a newer agent that can also medically close PDAs in premature infants.
    - Surgical closure is indicated in premature infants with symptomatic PDAs, despite medical treatment.

Left-Sided Obstructive Lesions

- Aortic stenosis
  - The aortic valve is often bicuspid and may have thickened and doming leaflets.
  - Critical aortic stenosis occurs when systemic output cannot be maintained without a patent ductus arteriosus.
  - Mild to moderate aortic stenosis is often asymptomatic, but severe stenosis is clinically apparent. Symptoms include congestive heart failure with pulmonary edema and potential cardiogenic shock in critical aortic stenosis with ductal closure.
  - The murmur can be heard as a systolic murmur at the upper sternal borders, with a possible click.
    - A murmur may not be present if only a minimal amount of blood is passing through the aortic valve.
  - A chest x-ray demonstrates cardiomegaly and pulmonary edema.
  - Decreased left ventricular wall motion is common in critical aortic stenosis.
  - Medical management for critical aortic stenosis includes prostaglandin E1 infusion and inotropic support.
  - Critical aortic stenosis is treated urgently with balloon valvuloplasty in the cardiac catheterization laboratory.
  - Milder degrees of stenosis do not need intervention in the neonatal period.
- Coarctation of the aorta
  - Discrete coarctation occurs at the isthmus at the insertion of the ductus arteriosus.
    - Contractile tissue from the ductus can extend around the isthmus, resulting in further narrowing of the isthmus with ductal constriction.
  - Long-segment coarctation involves a long tubular narrowing of both the transverse arch and isthmus.

- In severe discrete coarctation and long-segment coarctation, adequate perfusion of the lower body is dependent on maintaining patency of the ductus arteriosus so that presentation occurs with ductal restriction and closure.
- A continuous murmur can sometimes be heard in the back with coarctation of the aorta.
- Differential cyanosis can occur with postductal saturations being lower than preductal saturations.
- Symptomatic infants have congestive heart failure, decreased lower extremity pulses compared to upper extremity pulses, and leg blood pressures 10 to 15 mm Hg less than arm blood pressures. Cardiogenic shock can develop.
- Medical treatment includes stabilization with prostaglandin E1 infusion and inotropic support before surgical repair.
- Surgical treatment is required to augment the aortic arch.
  - Discrete coarctation can be treated with an end-to-end anastomosis from a thoracotomy without cardiopulmonary bypass.
  - Long-segment coarctations require arch augmentation from a sternotomy with cardiopulmonary bypass.
- Balloon angioplasty of discrete coarctations can be used in infants who have a contraindication to operative repair; however, redevelopment of coarctation over time is common after angioplasty of a native coarctation.

- Interrupted aortic arch
  - Complete interruption of the arch
  - Type A—interrupted after the left subclavian artery (Fig. 8.6)

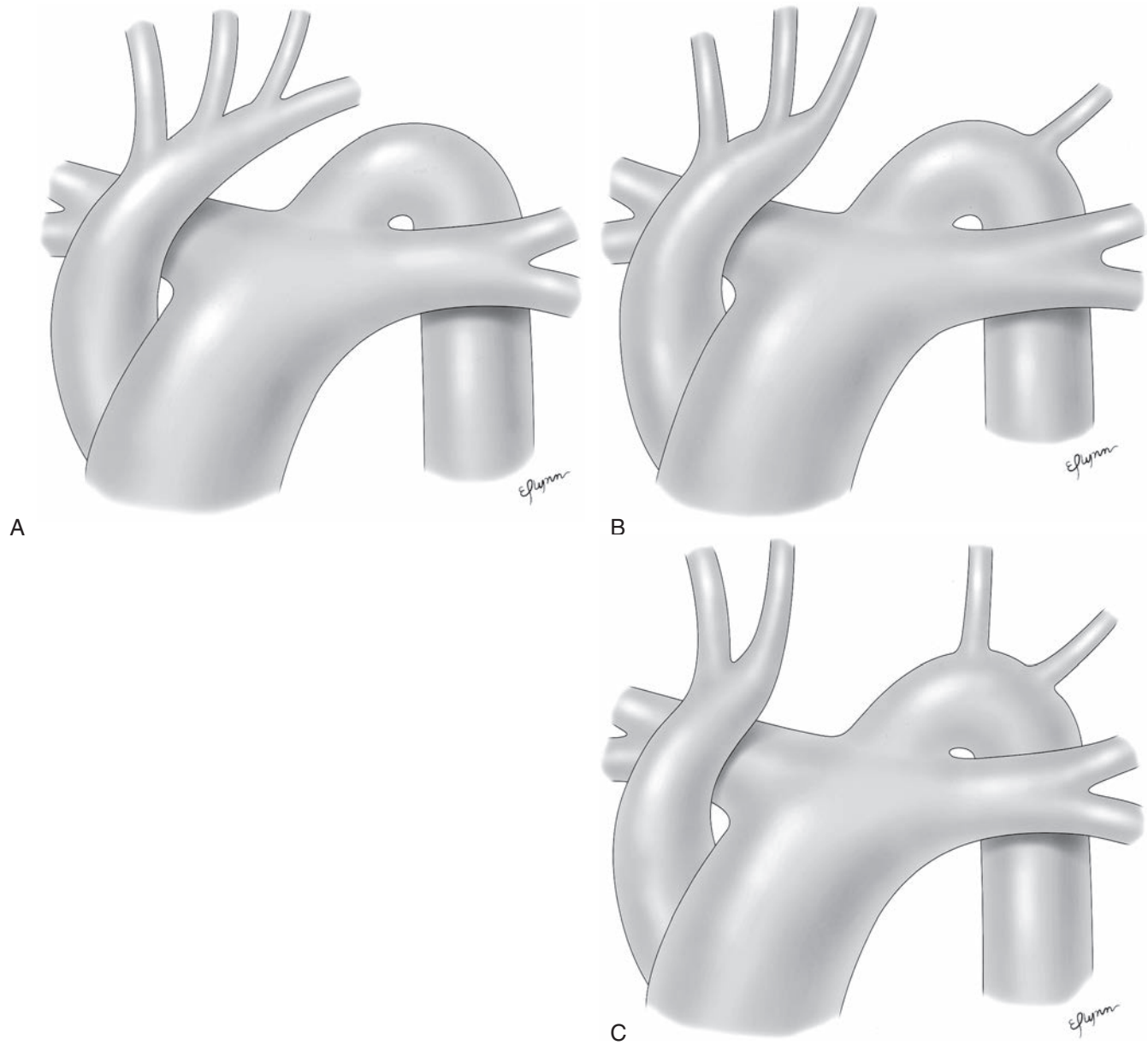


Fig. 8.6 Types of interrupted aortic arches. (A) Type A. (B) Type B. (C) Type C. (From Keane JF. *Nadas' Pediatric Cardiology.* 2nd ed. Philadelphia: Saunders; 2006.)

- Type B—interrupted after the left carotid artery (see Fig. 8.6)
  - Most common type of interruption
  - Chromosome 22q11 deletion found in 60% of infants with type B interruption
- Type C—interrupted after the innominate artery (see Fig. 8.6)
- Interrupted aortic arch—almost always occurs with a ventricular septal defect
- Presents with congestive heart failure leading to cardiogenic shock, with ductal closure
- Medical treatment with prostaglandin E1 infusion until surgical arch repair can be performed

- Hypoplastic left heart syndrome
  - Hypoplasia of the mitral valve, left ventricle, aortic valve, and aortic arch so that the left-sided structures are unable to meet the systemic needs (Fig. 8.7)

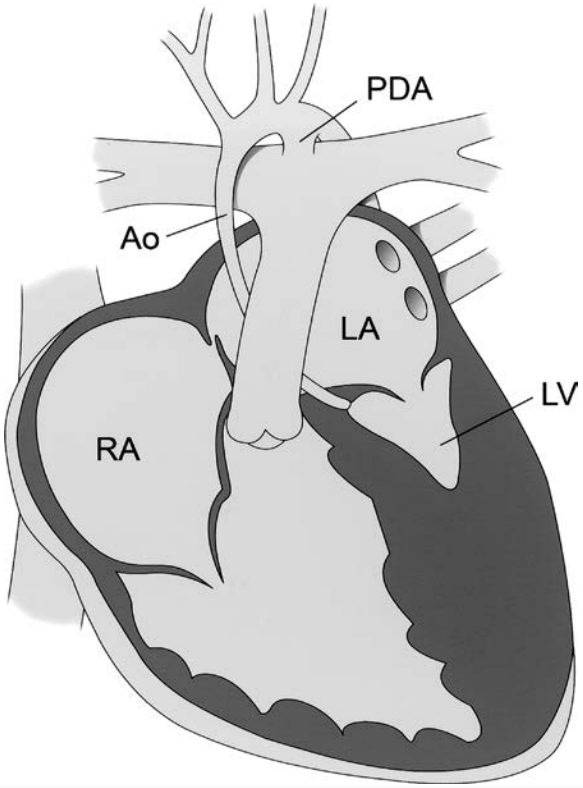


Fig. 8.7 Hypoplastic left heart syndrome. *Ao,* aorta; *LA,* left atrium; *LV,* left ventricle; *PDA,* patent ductus arteriosus; *RA,* right atrium. (From Keane JF. *Nadas' Pediatric Cardiology.* 2nd ed. Philadelphia: Saunders; 2006.)

  - To maintain hemodynamic stability, a PDA must be present to maintain systemic output, and a patent foramen ovale must be present to decompress the left atrium.
    - Infants with a restrictive or closed patent foramen ovale at birth will quickly develop profound cyanosis, pulmonary edema, and shock.
    - Emergent balloon atrial septostomy (Rashkind procedure) can be performed.
  - Infants with an unrestrictive atrial septum are generally hemodynamically stable after birth.
  - Prostaglandin E1 infusion is required to maintain ductal patency.
  - With a widely patent ductus arteriosus, the examination can be almost normal, with a single S2 as the only indication of disease.
  - Continued hemodynamic stability is dependent on the Qp/Qs (ratio of pulmonary to systemic blood flow) being roughly equal to 1.
  - Qp/Qs approximates 1 with oxygen saturations between 75% and 85%.
  - In the days after birth, the pulmonary vascular resistance falls, leading to increased pulmonary flow and resultant decreased systemic flow.
  - This leads to poor end-organ perfusion, with resultant lactic acidosis. Untreated, this leads to cardiovascular collapse.
  - Supplemental oxygen should be avoided if saturations are greater than 75% to avoid stimuli for the pulmonary vascular bed to relax.
- Infants with high saturations and evidence of decreasing systemic perfusion whose ductus arteriosus is confirmed to be patent should be treated with measures to increase the pulmonary vascular resistance.
  - Subambient oxygen with inspired nitrogen
  - Supplemental carbon dioxide
  - Induced hypoventilation via the ventilator, with sedation and paralysis
- Feeding of the infants with hypoplastic left heart syndrome must be done with caution, given the potential for decreased gut perfusion.
- Hypoplastic left heart syndrome can be addressed by palliative care, heart transplantation, or a three-stage, single-ventricle palliation. Most centers' first-line treatment is single-ventricle palliation.
- The Norwood operation is the first operation typically performed in the first week of life (Fig. 8.8).
  - The Norwood includes arch reconstruction, Damus-Kaye-Stansel anastomosis, atrial septectomy, and a Blalock-Taussig or Sano shunt (right ventricle to pulmonary artery).

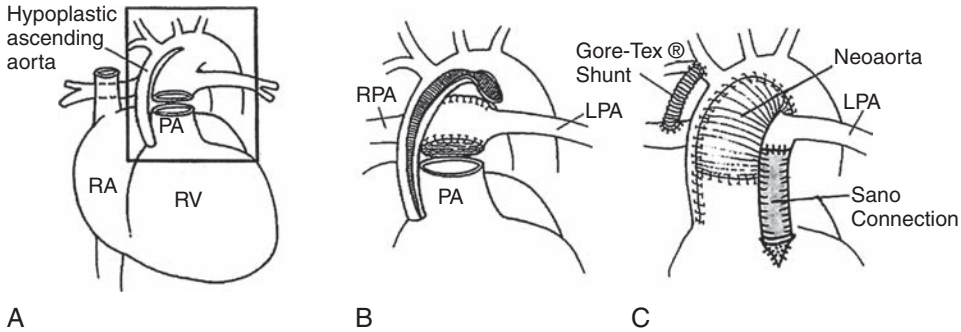


Fig. 8.8 Norwood operation. (A) MPA is transected; (B) native aorta is opened (C) aortic arch augmented and MPA is anastomosed to the arch, Sano connects the RV to the PA. *LPA,* left pulmonary artery; *RA,* right atrium; *RPA,* right pulmonary artery; *PA,* main pulmonary artery. (From Park MK. *Park's Pediatric Cardiology for Practitioners.* 6th ed. Philadelphia: Elsevier; 2014.)

- Second-stage palliation is the Glenn procedure, which is performed at 4 to 6 months of age.
- Third-stage palliation is the Fontan procedure, which is performed at 3 to 4 years of age.

Right-Sided Obstructive Lesions

- Pulmonary stenosis
  - Narrowing can be subvalvar or supravalvar, but the most common level of obstruction is at the pulmonary valve, with thickened and doming leaflets.
  - Supravalvar pulmonary stenosis is associated with Williams syndrome and congenital rubella.
  - The degree of obstruction can vary from mild to severe.
  - Critical pulmonary stenosis requires ductus arteriosus patency to maintain adequate pulmonary blood flow.
  - Severe forms of pulmonary stenosis generally result in some degree of right ventricular hypertrophy.
  - A systolic ejection murmur with radiation to the suprasternal notch is common, and a click may be present as well.
  - Severe obstruction results in cyanosis, with ductal restriction and/or closure.
  - Mild valvar pulmonary stenosis only requires monitoring and rarely progresses.
  - Moderate forms of pulmonary stenosis require close monitoring as progression can occur.
  - Severe forms of valvar pulmonary stenosis require prostaglandin E infusion until balloon valvuloplasty can be performed.
    - Dynamic subvalvar obstruction from right ventricular hypertrophy may limit pulmonary blood flow after a successful pulmonary valvuloplasty. Prostaglandins may be needed for a time to ensure adequate pulmonary blood flow as the right ventricular hypertrophy regresses after the fixed obstruction is relieved.
  - Subvalvar and supravalvar forms of pulmonary stenosis are not amenable to catheter-based intervention, and severe forms require operative intervention.
- Tetralogy of Fallot
  - This is the most common cyanotic congenital heart lesion.
  - The defect includes pulmonary stenosis, anteriorly malaligned ventricular septal defect, aortic override, and right ventricular hypertrophy.
    - Aortic arch is rightward in 25% of patients.
  - Chromosome 22a11 deletion is present in 15% of patients and is even more common in those with right-sided aortic arches.
  - A wide spectrum of presentations is possible, depending on the degree of right ventricular outflow tract (RVOT) obstruction.
    - Infants with significant RVOT obstruction present with cyanosis and/or hypoxia:
      - Initial management with prostaglandins is needed to maintain adequate saturation (<75%).
    - Infants with minimal RVOT obstruction will be normally saturated and may develop some signs of congestive heart failure.
    - A murmur is the systolic ejection murmur of pulmonary stenosis along the left sternal border.
    - Progressive development of an increased RVOT is common; these normally saturated infants often develop cyanosis or hypercyanotic spells later in infancy.
    - The chest x-ray demonstrates a boot-shaped heart with decreased pulmonary vascular markings.
  - Hypercyanotic spells, or TET spells, are an acute and dramatic decrease in pulmonary blood flow that leads to progressive cyanosis and acidosis.
    - Can be triggered by agitation and/or medical procedures
    - Theorized to be caused by infundibular spasm, tachycardia, and an imbalance between the systemic and pulmonary vascular resistances
    - Loss of murmur is hallmark of true hypercyanotic spell
    - Treatment of a hypercyanotic spell—includes measures to increase systemic vascular resistance, decrease pulmonary vascular resistance, and decrease agitation (Table 8.4)
  - Surgical repair in acyanotic infants occurs at 4 to 6 months of age.
    - The development of hypercyanotic spells is an indication for surgical repair.
  - Cyanotic neonates can undergo complete repair but may be palliated with a Blalock-Taussig shunt or ductal stenting in the cardiac catheterization laboratory.
  - Complete surgical repair includes ventricular septal defect closure and relief of the RVOT obstruction (Fig. 8.9).
- Tetralogy of Fallot with absent pulmonary valve
  - Rudimentary pulmonary valve is present, creating pulmonary stenosis and significant pulmonary insufficiency.
    - Marked dilation of the right ventricle and pulmonary arteries
    - Associated with significant airway anomalies secondary to compression from the pulmonary arteries
  - It is associated with 22q11 deletion syndrome.
  - A to-fro murmur is present due to pulmonary stenosis and insufficiency.
  - Varying degrees of cyanosis can be present, depending on the degree of RVOT obstruction.
  - Airway obstruction requiring mechanical ventilation, and sometimes prone ventilation, is necessary in more severe cases with significant airway obstruction.

Table 8.4 Treatment Options for Hypercyanotic Spells

Treatment	Effect
Knee-chest position	Increased systemic vascular resistance
Oxygen	Decreased pulmonary vascular resistance
Morphine	Decreased agitation
Propranolol	Decreased heart rate and infundibular spasm
Sodium bicarbonate	Decreased acidosis
Phenylephrine	Increased systemic vascular resistance
Ketamine	Increased systemic vascular resistance and decrease agitation
Extracorporeal membrane oxygenation	Rescue in refractory patients

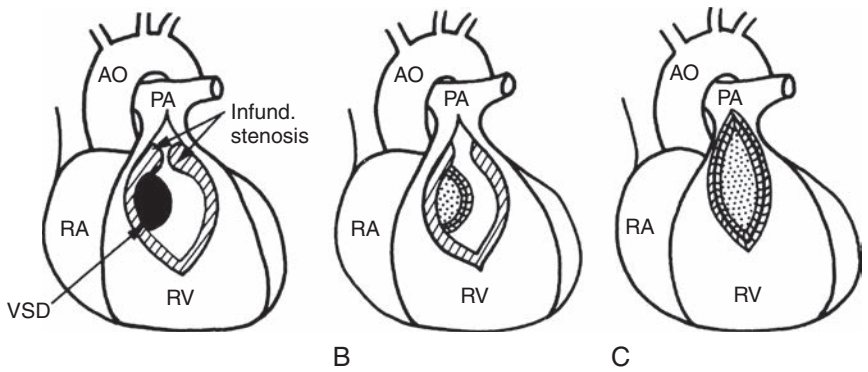


Fig. 8.9 Transannular patch repair of tetralogy of Fallot. (A) Anatomy of TOF showing a large ventricular septal defect (VSD) and infundibular stenosis seen through a right ventriculotomy. Note that the size of the ventriculotomy has been expanded to show the VSD. (B) Patch closure of the VSD and resection of the infundibular stenosis. (C) Placement of a fabric patch on the outflow tract of the right ventricle (RV). *AO,* aorta; *PA,* pulmonary artery; *RA,* right atrium; *RV,* right ventricle; *VSD,* ventricular septal defect. (From Park MK. *Park's Pediatric Cardiology for Practitioners.* 6th ed. Philadelphia: Elsevier; 2014.)

- Prostaglandins may be needed if pulmonary blood flow is inadequate.
- Urgent surgical repair is needed in severe cases, which include ventricular septal defect (VSD) closure, right ventricular and pulmonary artery plication, and RVOT augmentation with a right ventricle to pulmonary artery homograft.
- Outcomes are related to the degree of airway obstruction.

- Tricuspid atresia (Fig. 8.10)
  - The tricuspid valve remains unformed as a plate so that all systemic venous return must pass through the patent foramen ovale into the left atrium.
  - Nearly all patients have a VSD.
  - If the VSD is large, the pulmonary valve is often normal in size, so that there is adequate pulmonary blood flow without a PDA.
  - If the VSD is small, the pulmonary valve is often hypoplastic, so that a PDA is needed for adequate blood flow.
  - The VSD can become smaller during infancy, causing the saturations to decrease later in infancy.
  - Transposition of the great arteries can occur, which can result in a small aorta and inadequate systemic blood flow in the absence of a PDA.
  - The presentation is varied, depending on the degree of obstruction to pulmonary or systemic blood flow, but cyanosis and/or hypoxia is the most common presentation.
  - The ECG demonstrates left axis deviation and left ventricular hypertrophy.
  - Initial medical treatment uses prostaglandins if the pulmonary or systemic blood flow is inadequate. Some infants have adequate pulmonary blood flow, making initial treatment unnecessary.
  - For tricuspid atresia with normally related great arteries and inadequate pulmonary blood flow, initial surgical palliation involves a Blalock-Taussig shunt, followed by a Glenn and Fontan procedure later in infancy. Infants with adequate initial pulmonary blood flow undergo a Glenn procedure as their first operative intervention.
  - For tricuspid atresia with transposed great arteries and a hypoplastic aorta, the initial operative intervention is a Norwood procedure followed by a Glenn and Fontan procedure later in infancy.

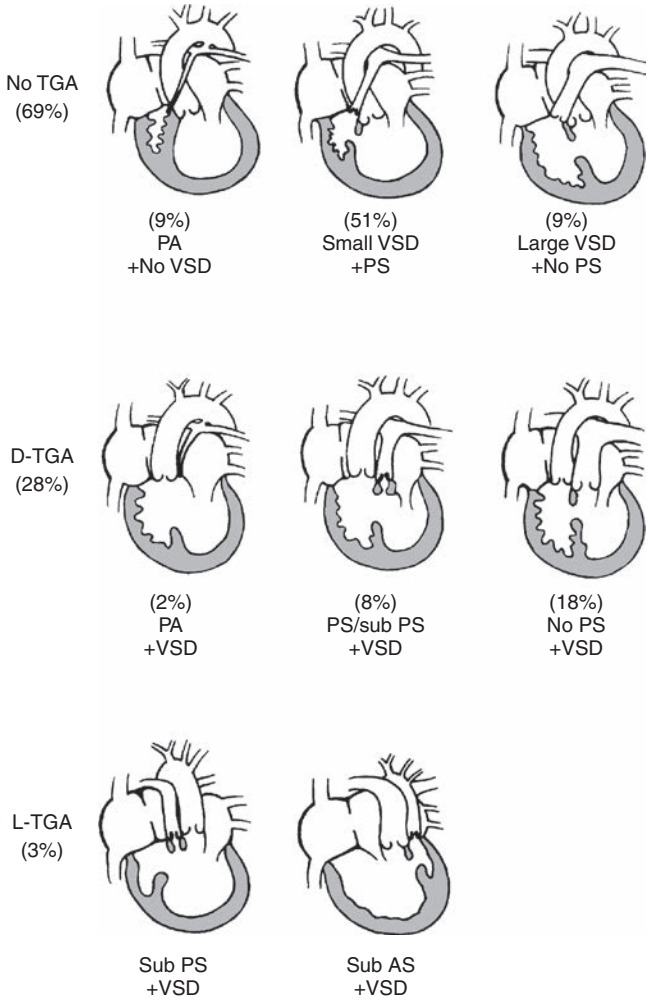


Fig. 8.10 Anatomic variations of tricuspid atresia. (From Park MK. *Park's Pediatric Cardiology for Practitioners.* 6th ed. Philadelphia: Elsevier; 2014.)

- Ebstein anomaly
  - Apical displacement of the septal and posterior leaflets of the tricuspid valve, with a large anterior leaflet (Fig. 8.11)
  - Wide range of severity, from very mild and asymptomatic throughout life to severe, causing in utero demise

- More severe cases—include severe dilation of the right atrium with "atrialization" of the right ventricle, right ventricular hypoplasia, functional or anatomic pulmonary atresia, and severe tricuspid valve insufficiency
- Associated with Wolff-Parkinson-White syndrome with delta waves on the ECG
- Associated with maternal lithium use

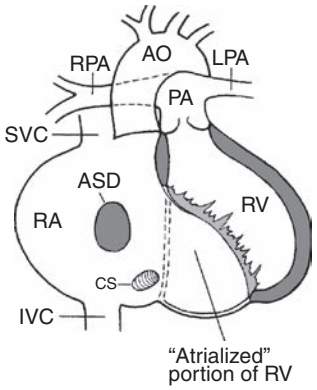


Fig. 8.11 Ebstein anomaly. *AO,* aorta; *ASD,* atrial septal defect; *CS,* coronary sinus; *IVC,* inferior vena cava; *LPA,* left pulmonary artery; *PA,* main pulmonary artery; *RA,* right atrium; *RPA,* right pulmonary artery; *RV,* right ventricle; *SVC,* superior vena cava. (From Park MK. *Park's Pediatric Cardiology for Practitioners.* 6th ed. Philadelphia: Elsevier; 2014.)

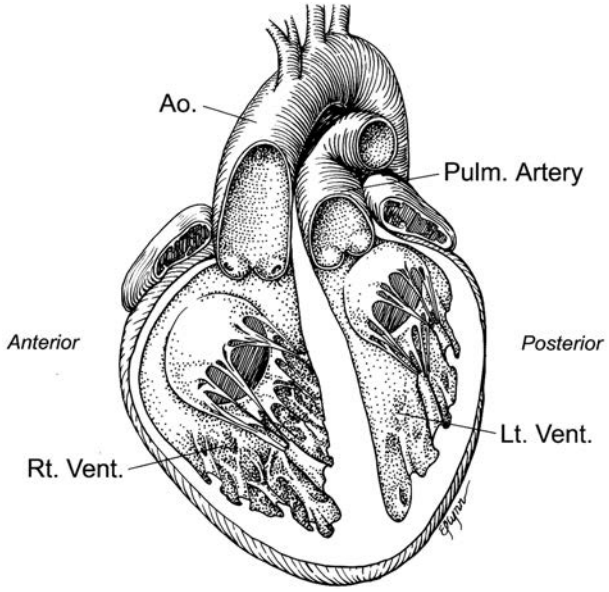


Fig. 8.12 d-Transposition of the great arteries. *Ao,* aorta. (From Keane JF. *Nadas' Pediatric Cardiology.* 2nd ed. Philadelphia: Saunders; 2006.)

- Infants with severe tricuspid valve insufficiency—have a holosystolic murmur at lower left sternal border, often a click and/or gallop
- Significant cardiomegaly is seen on chest x-ray
- Severely affected infants—have both cyanosis and congestive heart failure
- Initial medical management in severe cases includes:
  Prostaglandins to supplement pulmonary blood flow
  Also, measures to decrease the pulmonary vascular resistance, such as oxygen, nitric oxide, and inducing a respiratory alkalosis with ventilation
  Some patients may be able to generate sufficient pulmonary blood flow through their right heart when the pulmonary vascular resistance drops.
  If the infant continues to be ductal dependent, a Blalock-Taussig shunt can be placed.
- Long-term surgical treatment varies based on the degree of right-sided hypoplasia; it can range from tricuspid valve repair later in life to single-ventricle palliation

Mixing Lesions

- d-Transposition of the great arteries
  - The aorta arises from the right ventricle, and the pulmonary artery arises from the left ventricle (Fig. 8.12).
  - Circulation is parallel, with deoxygenated systemic venous blood flow being pumped back to the body, and oxygenated pulmonary blood flow being pumped back to the lungs.
  - Survival depends on shunting taking place at the level of the patent foramen ovale and PDA.
  - Infants present with cyanosis-hypoxia.
  - Infants with an intact atrial septum present with profound cyanosis after birth.
    - Emergent balloon atrial septostomy is required for survival
  - A single S2 is present as the anterior aortic valve obscures the sound of the pulmonary valve closing.
  - The chest x-ray demonstrates a narrow mediastinum or so-called egg on a string appearance.
  - Prostaglandins are initiated to augment shunting between the two circulations.
  - Surgical repair is the arterial switch operation performed in the first weeks of life (Fig. 8.13).
    - The aorta and coronary arteries are removed from their native root, as is the pulmonary artery. The two are then switched, so that the aorta and coronary arteries arise from the left ventricle, and the pulmonary artery arises from the right ventricle.

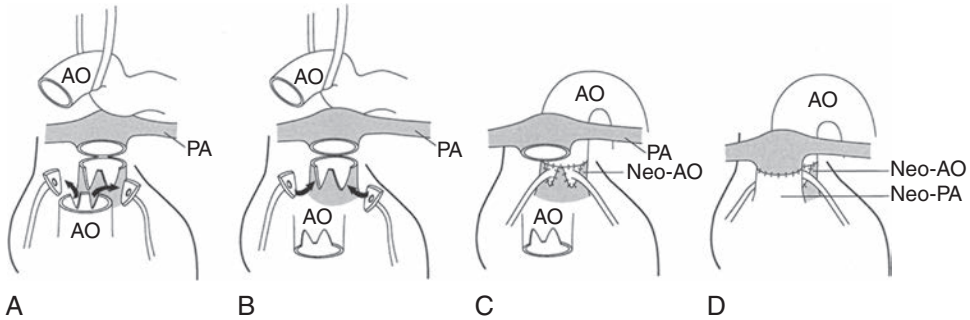


Fig. 8.13 Arterial switch operation. (A) Ao and PA are transected and coronary buttons are removed (B) coronary buttons are moved to the native PA (C) coronary buttons and arch are attached to the native pulmonary arteries D. PAs are attached to the native aorta. *AO,* aorta; *PA,* pulmonary artery. (From Park MK. *Park's Pediatric Cardiology for Practitioners.* 6th ed. Philadelphia: Elsevier; 2014.)

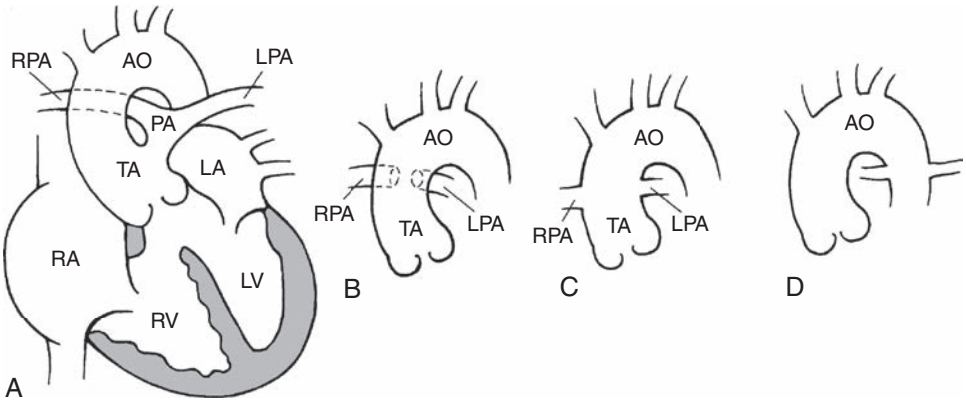


Fig. 8.14 Types of truncus arteriosus. The anatomic type of persistent truncus arteriosus (TA) is determined by the branching patterns of the pulmonary arteries. (A) In type I, the main pulmonary artery (PA) arises from the truncus and then divides into the right (RPA) and left pulmonary artery (LPA) branches. (B) In type II, the RPA and LPA arise separately from the posterior aspect of the truncus. (C) In type III, the PAs arise separately from the lateral aspects of the truncus. (D) In type IV, or pseudotruncus arteriosus, arteries arising from the descending aorta (AO) supply the lungs. *Ao,* aorta; *LV,* left ventricle; *LA,* left atrium; *LPA,* left pulmonary artery; *PA,* pulmonary artery; *RA,* right atrium; *TA,* truncus arteriosus; *RPA,* right pulmonary artery; *RV,* right ventricle. (From Park MK. *Park's Pediatric Cardiology for Practitioners.* 6th ed. Philadelphia: Elsevier; 2014.)

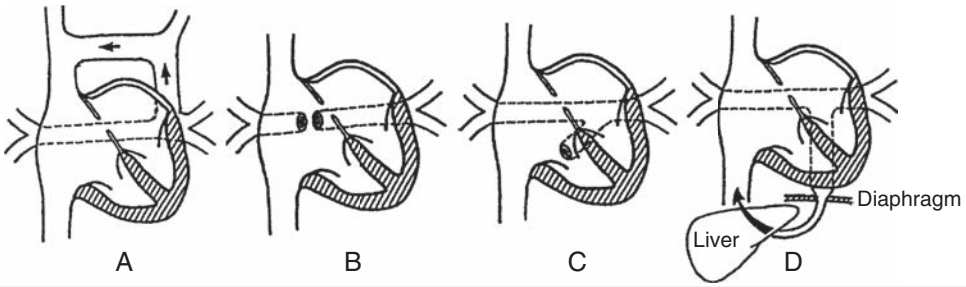


Fig. 8.15 Types of total anomalous pulmonary venous return (TAPVR). (A) Supracardiac TAPVR. (B) Cardiac TAPVR with the veins returning directly to the right atrium. (C) Cardiac TAPVR with the veins returning to the coronary sinus. (D) Infracardiac TAPVR. (From Park MK. *Park's Pediatric Cardiology for Practitioners.* 6th ed. Philadelphia: Elsevier; 2014.)

- Truncus arteriosus
  - A common arterial trunk gives rise to the aorta and pulmonary arteries arise. A VSD is always present (Fig. 8.14).
  - Truncus type is defined by the manner in which the pulmonary arteries arise:
    - Type 1: a main pulmonary artery arises from the truncus and bifurcates into right and left pulmonary arteries.
    - Type 2: the right and left pulmonary arteries arise from separate origins from the truncus but in close proximity to each other.
    - Type 3: the right and left pulmonary arteries arise from separate origins from the truncus at a distance from each other.
  - The truncal valve is often dysfunctional, with varying degrees of stenosis and insufficiency commonly seen.
  - Murmur is dependent on the type and degree of dysfunction of the truncal valve.
    - It can be a systolic ejection murmur with stenosis or a regurgitant diastolic murmur with truncal insufficiency.
    - Both murmurs will be present with a valve that is both stenotic and regurgitant.
  - It is associated with 22q11 deletion syndrome and a right-sided aortic arch.
  - Infants are typically minimally cyanotic, with few symptoms initially.
  - As the pulmonary vascular resistance falls, the infants develop significant congestive heart failure, which can be difficult to control medically.
  - Surgical repair in the first weeks of life is typically performed to include ventricular septal defect closure and moving the pulmonary arteries from a truncus to a right ventricular to pulmonary artery conduit. Truncal valve repair is sometimes required in the neonatal period.
  - Truncal valve dysfunction is often the primary determinant of the long-term prognosis.
- Total anomalous pulmonary venous return (TAPVR)
  - All pulmonary veins return to a systemic vein or the right atrium, resulting in complete mixing, with all systemic output passing from right to left across the patent foramen ovale (Fig. 8.15).
  - Supracardiac TAPVR results from the pulmonary venous return ascending through a vertical vein to the innominate vein, so that all pulmonary venous flow returns to the heart via the superior vena cava to the right atrium.
  - Cardiac TAPVR results from the pulmonary venous return entering the coronary sinus, which then empties into systemic veins or directly into the right atrium.
  - Infracardiac TAPVR results from the pulmonary venous return descending through the diaphragm and joining the hepatic veins and/or inferior vena cava (IVC) before returning to the right atrium.
    - Infracardiac TAPVR is frequently obstructed

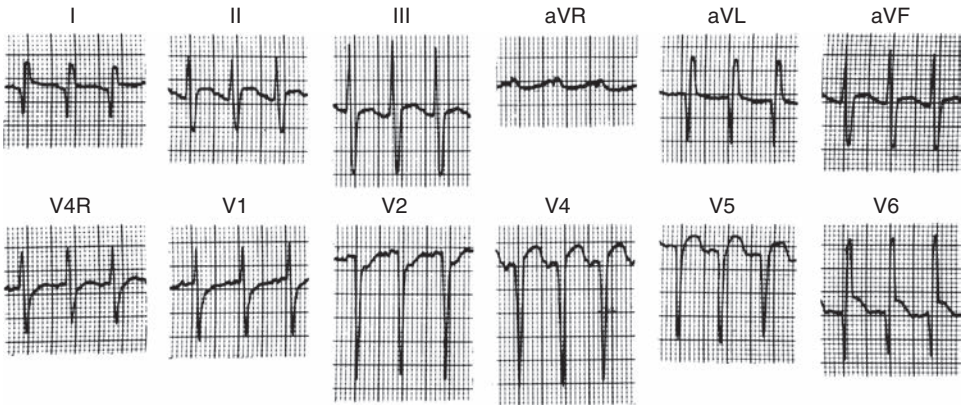


Fig. 8.16 Electrocardiogram in an infant with anomalous left coronary artery from the pulmonary artery. (From Park MK. *Park's Pediatric Cardiology for Practitioners*. 6th ed. Philadelphia: Elsevier; 2014.)

- The presentation of TAPVR depends on the degree of obstruction to pulmonary venous return:
  - Infants with TAPVR and unobstructed veins are minimally cyanotic initially and present with progressive congestive heart failure due to right ventricular volume overload and pulmonary overcirculation.
  - Infants with obstructed TAPVR present with a more marked degrees of cyanosis. Obstruction of the pulmonary veins creates pulmonary edema, which can be severe. Profound cyanosis with a white-out on the chest x-ray can result.
- Treatment is surgical anastomosis of the pulmonary veins to the left atrium in the first weeks of life, but this may need to be done urgently in the case of obstructed TAPVR.

Double-Outlet Right Ventricle

- Complex and highly variable group of lesions characterized by a ventricular septal defect with both the aorta and pulmonary artery arising from the right ventricle
- Outflow tract obstruction on the right or left is commonly seen

l-Transposition of the Great Arteries

- This is also called congenitally corrected transposition.
- A morphologic left ventricle is on the right and morphologic right ventricle is on the left, so that the aorta arises from the morphologic right ventricle, and the pulmonary artery arises from the morphologic right ventricle.
- Physiologically, this allows deoxygenated blood from the right atrium to go through the morphologic left ventricle to the pulmonary artery to the lungs appropriately. Also, oxygenated blood from the left atrium goes through the morphologic right ventricle to the aorta appropriately.
- This is often associated with additional defects, such as ventricular septal defects and outflow tract obstruction.

Arterial Vascular Lesions

- Anomalous left coronary artery off the pulmonary artery
  - The left main coronary artery arises from some aspect of the pulmonary artery instead of the aortic root.
  - These are typically asymptomatic at birth due to the elevated pulmonary artery pressures in the first weeks of life. As the pulmonary artery pressure drops, the coronary perfusion pressure decreases, leading to ischemia.
  - Infants present with irritability, pallor, diaphoresis, and poor feeding, followed by tachypnea.
  - The examination often reveals a gallop and the holosystolic murmur of mitral insufficiency.
  - The ECG typically shows deep Q waves in leads I and aVL. Q waves are common in V5 and V6. T wave inversion is also commonly seen in I, aVL, V5, and V6, as well as ST depression (Fig. 8.16).
  - The chest x-ray demonstrates cardiomegaly.
  - Diagnosis is often made by echocardiography, but cardiac catheterization may be needed to confirm the diagnosis.
  - Inotropic support is used to support the infant, but urgent surgical reimplantation of the left main into the aortic root is the mainstay of treatment.

Suggested Readings

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VanOvermeire B, Smets K, Lecoutere D, et al. A comparison of ibuprofen and indomethacin for closure of patent ductus arteriosus. *N Engl J Med*. 2000;343:674–681.

Questions

1. A 1-week-old infant with tetralogy of Fallot is undergoing a rule-out sepsis evaluation. The infant's baseline saturations are 98%, with a 2/6 systolic ejection murmur along the left sternal border. During the blood draw, the infant's saturations drop to 60% and the infant becomes visibly cyanotic. On auscultation, the lung sounds remain clear, but the murmur is no longer audible. What interventions should be performed?
   a. Intubation with 100% O_2
   b. STAT echocardiogram
   c. Arterial blood gas
   d. Morphine and phenylephrine administration

2. A newborn infant was found to have interrupted aortic arch type B, with truncus arteriosus. What other features is the infant likely to have?
   a. Epicanthal folds with a single palmar crease
   b. Elfin facies
   c. Broad thumbs and toes
   d. Absent thymus on chest x-ray and hypocalcemia

9 Cardiopulmonary Dysfunction

KIMBERLY VERA

Neonatal Cardiomyopathies

Cardiomyopathies are a wide spectrum of disorders characterized by myocardial dysfunction in the absence of structural heart disease. Cardiac dysfunction often involves both systolic and diastolic components. The Frank-Starling curve graphically represents how increasing preload increases cardiac output in normal hearts. In hearts with decreased contractility, this curve is shifted downward and to the right. Pharmacologic treatments of cardiomyopathies attempt to shift the curve back upward and to the left (Fig. 9.1).

- Clinical manifestations include poor feeding, hepatomegaly, tachypnea, gallop rhythm, and murmur from valvar dysfunction. Signs of inadequate cardiac output can occur, including tachycardia, narrowed pulse pressure, diminished pulses, and oliguria.
- The chest x-ray typically reveals cardiomegaly and pulmonary edema.
- Cardiomyopathies can be divided into dilated cardiomyopathies and hypertrophic cardiomyopathies, with some causative factors resulting in both dilation and hypertrophy.
- Dilated cardiomyopathies are characterized by decreased ventricular wall motion and ventricular enlargement.
  - Dilated cardiomyopathies can have numerous causes, including hypoxia (birth asphyxia), infection (myocarditis), incessant tachyarrhythmias, and primary disorders of energy production (Box 9.1).
  - Treatment is often driven by the exact cause, but supportive measures are common to most forms of dilated cardiomyopathies.
    - Correction of electrolyte abnormalities and acid-base status
    - Careful management of fluid status with fluid and diuretics to allow for enough volume to optimize cardiac output while minimizing pulmonary edema
    - Intravenous inotropic agents to augment cardiac output
    - Extracorporeal membrane oxygenation—can be used in patients refractory to management in cases where the cause is thought to be reversible or as a bridge to cardiac transplantation
    - Oral agents—can be used in patients who do not need intravenous support
      - Spironolactone, angiotensin-converting enzyme (ACE) inhibitors, and beta-adrenergic receptor blockers such as carvedilol and digoxin often used

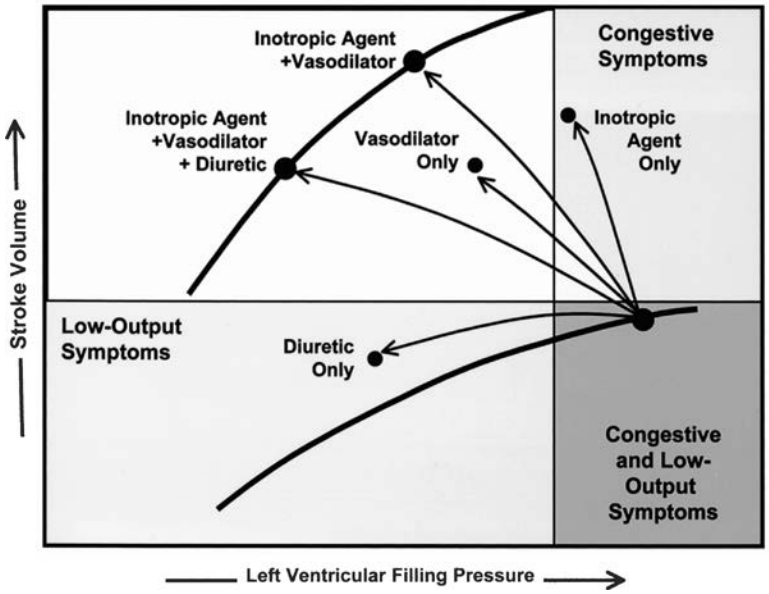

Fig. 9.1 Frank-Starling curve. The *upper line* is the curve in a heart with normal contractility. Decreased contractility shifts the line downward and to the right. Various treatment modalities shown can shift the curve back upward and leftward. (From Park MK. *Park's Pediatric Cardiology for Practitioners.* 6th ed. Philadelphia: Elsevier; 2014.)

Box 9.1 Causes of Dilated Cardiomyopathies

Infectious
Viral
Bacterial sepsis
Myocardial ischemia, birth asphyxia
Reversible electrolyte abnormalities
Hypoglycemia
Hypocalcemia
Hypophosphatemia
Incessant tachyarrhythmias
Genetic isolated cardiomyopathies
Familial dilated cardiomyopathy
Arrhythmogenic right ventricular dysplasia
Noncompaction of the left ventricle
Neuromuscular diseases
Duchenne muscular dystrophy
Becker muscular dystrophy
Friedreich ataxia

Metabolic Disorders

Carnitine deficiency syndromes
Disorders of pyruvate metabolism
Disorders of oxidative phosphorylation
Kearns-Sayre syndrome
Barth syndrome
Infiltrative storage disease
Glycogen storage diseases
Mucopolysaccharidosis
Hurler syndrome
Amino acid and organic acid disorders
Propionic acidemia

- Cardiac transplantation can be considered for infants and children who appear to have an otherwise fatal course.
- Neonatal myocarditis is a form of dilated cardiomyopathy that can be acquired perinatally or postnatally.
  - The most common causes are echovirus and type B coxsackievirus.
  - Beyond supportive measures discussed above, treatment can include immunoglobulin, interferon, and steroids.

- Hypertrophic cardiomyopathy is characterized by inappropriate thickening of the ventricular walls with diastolic dysfunction. Systolic function can be normal, hyperdynamic, or depressed.
  - Thickened ventricular walls can produce ventricular outflow stenosis and result in an outflow tract murmur.
  - The electrocardiogram (ECG) can show diffusely increased QRS voltages as well as repolarization abnormalities.
    - Short PR interval is found in Pompe disease.
  - Hypertrophic cardiomyopathies also have a wide range of causes, including genetic diseases such as infiltrative storage diseases and primary metabolic disorders of energy production (Box 9.2).
  - Treatment of most hypertrophic cardiomyopathies is supportive and targeted at the primary cause.
    - Inotropes are often not helpful because they can worsen the outflow tract obstruction.

Box 9.2 Causes of Hypertrophic Cardiomyopathies

Endocrine Disorders

Maternal diabetes mellitus
Pheochromocytoma
Hyperthyroidism
In utero sympathomimetic exposure
Genetic isolated cardiomyopathies
Contractile protein mutation
Genetic syndromes
Noonan syndrome
Cardiofacial cutaneous syndrome
LEOPARD syndrome
Neurofibromatosis
Beckwith-Wiedemann syndrome
Neuromuscular diseases
Friedreich ataxia

Metabolic Disorders

Carnitine deficiency disorders
Disorders of pyruvate metabolism
Disorders of oxidative phosphorylation
Kearns-Sayre syndrome
Barth syndrome
Infiltrative storage disorders
Glycogen storage disorders
Pompe disease
Mucopolysaccharidosis
Hurler syndrome
Hunter syndrome
Sanfilippo syndrome
Fabry disease
Gaucher disease
Tyrosinemia

  - Infants of diabetic mothers can develop a transient hypertrophic cardiomyopathy, primarily of the ventricular septum.
    - Left ventricular outflow tract obstruction can occur and can range from mild to severe.
    - It results from hyperinsulinemia produced by transplacental passage of a high maternal glucose load.
    - Hypertrophy slowly regresses over time postnatally.
  - The most common hypertrophic cardiomyopathies are genetic disorders of one of the cardiac contractile proteins, most commonly of the myosin heavy chain.
    - Neonatal echocardiogram can be normal, but hypertrophy can develop later in childhood or adulthood.
    - Those presenting at birth have a poor prognosis.

Cardiac Tumors

The most common type of cardiac tumor is a rhabdomyoma, which is strongly associated with tuberous sclerosis.

- Often occurs with multiple tumors throughout heart
- Natural history is to regress over months to years
- Can rarely create hemodynamic compromise if the tumors block inflow or outflow of the heart
- Possible development of serious arrhythmias

Systemic Blood Pressure Regulation

Blood pressure is the product of systemic blood flow and systemic vascular resistance. In neonates, systemic vascular resistance is a larger determinant of blood pressure than blood flow.

- The measurement of the blood pressure in severely ill or preterm neonates is preferentially done with an intraarterial catheter.
  - Complications include thrombosis and infections.
- Hypotension is a decrease in blood pressure so that tissue oxygen delivery does not meet tissue oxygen demand.
  - Hypotension in neonates can be defined as a mean blood pressure of <30 mm Hg, mean blood pressure below the patient's gestational age in weeks, or blood pressure where there is evidence of circulatory compromise.
  - Autoregulation occurs with hypotension so that vital organ vascular beds, especially the brain, dilate, and fewer vital arterial beds constrict to maintain oxygen delivery to vital organs.
    - Autoregulation is impaired in preterm neonates so that blood pressure more clearly mirrors cerebral blood flow.
    - Factors that impair autoregulation include birth asphyxia, acidosis, infection, hypoglycemia, tissue hypoxia or ischemia, and sudden alterations in arterial carbon dioxide tension.
  - Hypotension in neonates can be have numerous causes (Box 9.3).
    - Very preterm infants frequently develop hypotension because the immature left ventricle is unable to mount the dramatic increase in output needed to adapt to the sudden increase in systemic vascular resistance with the removal of the low-resistance placental circuit.
  - Hypotension is manifested clinically by tachycardia, prolonged capillary refill time, acidosis, elevation of the serum lactate level, and decreased urinary output.
    - NIRS (near-infrared spectroscopy) can be used to detect changes in tissue oxygenation of the cerebral and renal vascular beds. Hypotension will result in downtrends of the NIRS.
  - Treatment of hypotension should be targeted at the cause.
    - Volume administration with isotonic saline at 10–20 mL/kg can be used.
      - Hypovolemia is a relatively rare cause of hypotension in neonates, apart from the relative hypovolemia caused by vasodilation in sepsis.
      - Aggressive volume resuscitation should be avoided because it increases morbidity and mortality.
      - Blood transfusion should be carried out if hypovolemia is secondary to blood loss.
    - Inotropic support
      - Dopamine is most commonly used to treat hypotension in preterm neonates, but dobutamine and epinephrine can also be used.
    - Steroids
      - Hydrocortisone can be used in inotropic-resistant hypotension.
      - In critically ill infants, the cardiovascular system can develop desensitization to catecholamines. Steroid administration attenuates this response and decreases the need for inotropes.
      - Concurrent administration of hydrocortisone with indomethacin in the first postnatal week increases the risk of gastrointestinal perforation.
    - Maintenance of normal pH and calcium levels also helps maintain the cardiovascular sensitivity to catecholamines.
- Hypertension is defined as blood pressure greater than the 95th percentile.
  - There are numerous causes of neonatal hypertension, but the most common causes of neonatal hypertension are renal parenchymal disease and renal vascular disease (Box 9.4).
  - History of an umbilical arterial catheter is a risk factor for developing hypertension.
    - Thromboembolic evens occur at the time of placement secondary to endothelial injury. The resultant decrease in kidney perfusion results in sodium and water retention.
  - Chronic lung disease is a significant risk factor for hypertension; however, the mechanism is unknown.
  - Signs and symptoms can include tachypnea, tremor, lethargy, feeding difficulties, seizures, apnea, hypertonicity, hypertensive retinopathy, cerebral edema, and intracranial hemorrhage.
    - The severity of the blood pressure elevation is not correlated to the presence or severity of signs and symptoms.
    - Hypertension is frequently asymptomatic.
    - Infants can develop congestive heart failure symptoms if left ventricular function is decreased due hypertension.
  - Evaluation of neonatal hypertension
    - Obtain a history of any prenatal exposures or procedures, such as prior umbilical artery catheters.
    - Review current medications.
    - Take four extremity blood pressure readings.
    - A full examination should include palpation for flank masses and auscultation for an epigastric bruit.

Box 9.3 Causes of Hypotension

Inflammatory response
Sepsis
Necrotizing enterocolitis
Asphyxia
Major surgery
Myocardial dysfunction
Closure of the ductus in a systemically dependent, ductal dependent congenital heart lesion
Coarctation
Aortic stenosis
Hypoplastic left heart syndrome
Use of afterload reduction agents
Milrinone
Prostaglandin E2

Box 9.4 Causes of Neonatal Hypertension

Renal

Acute renal failure
Polycystic kidney disease
Renal cortical and medullary necrosis
Hypoplastic kidney
Pyelonephritis
Obstructive uropathy
Nephrolithiasis

Vascular

Renal artery thrombosis
Aortic thrombus
Coarctation of the aorta
Renal vein thrombosis
Renal artery thrombosis
Idiopathic arterial calcification

Endocrine

Pheochromocytoma
Neuroblastoma
Hyperthyroidism
Adrenal disorders

Iatrogenic

Corticosteroids
Theophylline
Pancuronium
Phenylephrine eye drops

Other

Bronchopulmonary dysplasia
Patent ductus arteriosus
Increased intracranial pressure
Fluid overload

- An epigastric bruit can be present with renal artery stenosis.
- Blood work should include electrolyte, creatinine, and blood urea nitrogen levels.
- Urinalysis—ultrasound imaging of the genitourinary tract can detect renal vein thrombosis, renal artery stenosis, and renal parenchymal abnormalities.
- Echocardiography can detect left ventricular hypertrophy and decreased left ventricular and rule out coarctation of the aorta.

- Treatment
  - Asymptomatic infants with blood pressures between the 95th and 99th percentiles and no end-organ dysfunction can be observed.
  - Infants with blood pressure readings greater than the 99th percentile or with end-organ involvement should be treated.
  - Five classes of antihypertensives used in the neonatal population are diuretics, beta blockers, ACE inhibitors, calcium channel blockers, and direct peripheral vasodilators (Table 9.1).
    - ACE inhibitors are very effective in neonates because of the high renal vascular resistance, but they should not be used until renal vascular disease is ruled out.

Table 9.1 Oral Antihypertensives

Drug	Dose	Notes
Captopril (ACE inhibitor)	0.05–0.5 mg/kg/day tid	Monitor creatinine and potassium
Hydrochlorothiazide (thiazide diuretic)	2–4 mg/kg/day bid	Monitor electrolytes
Hydralazine (vasodilator)	0.75–7.5 mg/kg tid or qid	Tachycardia, fluid retention, lupus-like syndrome
Minoxidil (vasodilator)	0.1–0.2 mg/kg/dose bid or tid	Most potent vasodilator
Amlodipine (calcium channel blocker)	0.1–0.3 mg/kg/dose bid	Useful for chronic hypertension
Propranolol (beta blocker)	1–8 mg/kg/day tid	Can cause bronchospasm and hypoglycemia; avoid in bronchopulmonary dysplasia

Table 9.2 IV Antihypertensives

Drug	Dose	Notes
Nicardipine (calcium channel blocker)	0.5–3 mcg/kg/min	Tachycardia
Esmolol (beta blocker)	100–300 mcg/kg/min	Very short half-life
Hydralazine (vasodilator)	0.15–0.6 mg/kg	Tachycardia
Nitroprusside (vasodilator)	0.5–10 mcg/kg/min	Thiocyanate toxicity when used for >72 hr or in renal failure

- IV antihypertensives should be used in a neonatal hypertensive crisis with continuous blood pressure monitoring via an arterial line (Table 9.2).
  - Nicardipine is the drug of choice in a neonatal hypertensive crisis.

Suggested Readings

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Question

1. A term infant undergoes echocardiography after birth due to a murmur. Numerous small cardiac tumors are identified throughout the heart. Which genetic disease is likely?
   a. Down syndrome
   b. Williams syndrome
   c. Tuberous sclerosis
   d. Hunter syndrome

10 Electrocardiography, Electrophysiology, and Dysrhythmias

KIMBERLY VERA

A normal electrocardiogram (EKG) reflects normal transit times through the conduction system. Abnormalities on an EKG can not only reflect an abnormality in conduction and rhythm but can also reflect an anatomic defect in the heart.

- Normal intervals (Fig. 10.1)
  - The PR interval measures the time of conduction from the sinoatrial node through the AV node and includes the depolarization time of the atria.
    - Measured from the onset of the P wave to the onset of the QRS complex
  - QRS duration measures the time of depolarization of the ventricles.
    - Measured from the onset to termination of the QRS complex
  - The QT interval measures the time of ventricular depolarization and repolarization.
    - Measured from the onset of the QRS complex to the end of the T wave
    - QT interval must be corrected for heart rate producing the QTc interval
    - Bazett formula most often used: QTc = QT/(√RR interval)
  - RR interval measures the time from one QRS complex to the next.
- Normal waveforms
  - The P wave represents depolarization of the atria.
    - The normal P wave axis is 0 to +90 degrees so that a normal P wave axis is seen with a positive P wave in I and aVF.

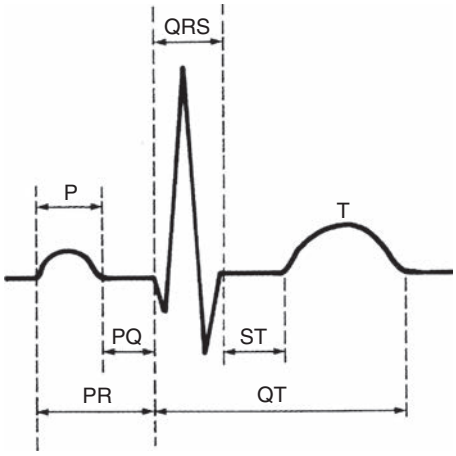

Fig. 10.1 Normal intervals on an EKG. (From Park MK. *Park's Pediatric Cardiology for Practitioners.* 6th ed. Philadelphia: Elsevier; 2014.)

  - QRS represents depolarization of the ventricles.
    - The QRS axis represents the mean vector of the ventricular depolarization (Fig. 10.2).
    - Newborns have a right axis deviation when compared to adults, with up to +180 degrees considered normal (Fig. 10.3).
    - An abnormal QRS axis is seen with ventricular hypertrophy, bundle branch block, and ventricular conduction disturbances.
  - Q waves are produced by depolarization of the ventricular septum.
    - These are common in leads I, II, III, and aVF and nearly always present in V5 and V6,
  - T waves represent the ventricular repolarization process.

Normal sinus rhythm originates from the sinoatrial node, which is influenced by many factors, including the autonomic nervous system, catecholamines, temperature, and blood pressure. Impulses from the sinoatrial node proceed through the atrioventricular node, where the impulse is slowed to allow atrial contraction to complete prior to ventricular contraction. Conduction then passes through the His bundle and into the bundle branches to initiate ventricular contraction.

- Sinus arrhythmia is phasic variation in heart rate with respiration.
  - Most common cause of an irregular heart rate
  - Occurs more frequently at lower heart rates so that it is often seen in sleeping infants or infants with high vagal tone
- Sinus bradycardia is defined as a heart rate originating from the sinus node with rates of less than 80 beats/min while awake or less than 60 beats/min while asleep.
  - The most common cause of sinus bradycardia is increased vagal tone.
  - Increased vagal tone is seen with gastric distention, upper airway obstruction, increased intracranial pressure, pharyngeal stimulation, and Valsalva.
  - Other causes of sinus bradycardia include hypoxia, hypothyroidism, drug therapy, hypothermia, and long QT syndrome.
- Atrioventricular (AV) block represents a slowing or complete blockage of conduction at the atrioventricular node and can be described as first-, second-, or third-degree block.
- First-degree block describes a prolonged PR interval.
  - The PR interval should be 160 milliseconds or less on the first day of life and 140 milliseconds or less after the first day of life.

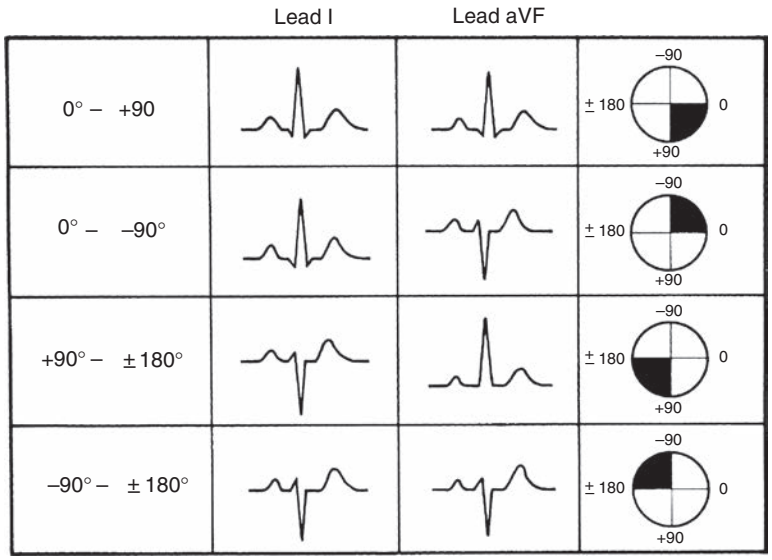

Fig. 10.2 Method of finding the QRS axis. (From Park MK. *Park's Pediatric Cardiology for Practitioners.* 6th ed. Philadelphia: Elsevier; 2014.)

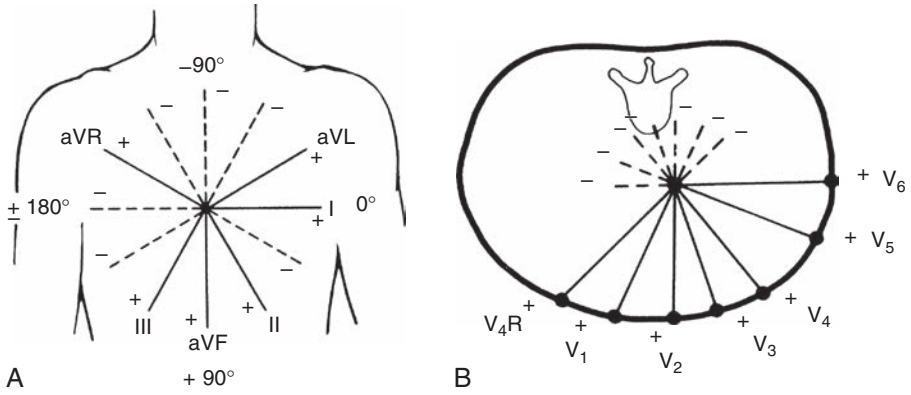

Fig. 10.3 Hexaxial reference system for EKGs. (A) frontal projection of vector loop. (B) Horizontal projection. A+B constitute EKG. (From Park MK. *Park's Pediatric Cardiology for Practitioners.* 6th ed. Philadelphia: Elsevier; 2014.)

- Causes of first-degree block include medication, especially digoxin, and surgical trauma from cardiac surgery.
- Treatment is not necessary.

- Second-degree AV block is an intermittent loss of AV conduction and is further classified into Mobitz type I and Mobitz type II (Fig. 10.4).
  - Mobitz type I block, or Wenckebach, is a gradual prolongation of the PR interval, followed by a P wave with no following QRS complex.
    - Grouped QRS complexes are often seen in Mobitz type I block.
    - Wenckebach is often seen during sleep and in infants with high vagal tone.
    - No treatment is necessary.
  - Mobitz type II is intermittent loss of P wave conduction, without prior PR prolongation.
    - If every other P wave is conducted, the grade is described as 2:1 block.
    - High-grade block is when more than one consecutive P wave fails to conduct, such as 3:1 block.
    - High-grade block may progress to complete AV block.

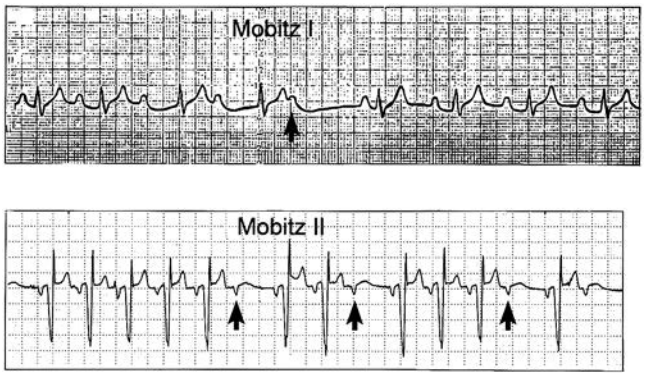

Fig. 10.4 Second-degree atrioventricular block. Arrows demonstrate P waves that are not followed by a QRS complex. (From Keane JF. *Nadas' Pediatric Cardiology.* 2nd ed. Philadelphia: Saunders; 2006.)

    - Mobitz type II can be seen in infants born to mothers with connective tissue disease, infants with congenital heart disease with L-looped ventricles, and infants who have had cardiac surgery.
    - A pacemaker may be needed, especially if a wide QRS is present.

- Third-degree AV block or complete heart block occurs when no atrial impulses are conducted to the ventricle.
  - The P waves are completely disassociated from the QRS complexes.
  - QRS complexes can be narrow or wide, depending on whether the escape rhythm originates near the AV node (narrow) or distal to the bundle of His (wide).
  - Atrial rates are normal for age and vary normally with stimuli. The ventricular rates are regular, with minimal variability, with typical rates of 60–80 beats/min.
  - The most common cause of complete AV block is SSA/Ro and SSB/La antibodies, which cross the placenta in mothers with connective tissue disease.
  - Onset is typically in fetal life.
  - Mothers often have no signs or symptoms of connective tissue disease so that their disease is unknown.
  - Neonates with congenital heart block are often asymptomatic due to increased stroke volume.
    - Congestive heart failure symptoms can be present at birth or develop postnatally.
  - Isoproterenol can be used to increase the ventricular rate in symptomatic infants
  - Infants can be born with or develop signs of inadequate cardiac output, necessitating emergent transvenous and transcutaneous pacing.
  - Permanent pacemaker placement is indicated for congestive heart failure, cardiomegaly, ventricular dysfunction, premature ventricular contractions, prolonged QTc interval, and a wide ventricular escape complex.
  - Complete heart block can also occur in infants with complex congenital heart disease, such as those with congenitally corrected transposition and left atrial isomerism heterotaxy, as well as infants post cardiac surgery.
- Sinus tachycardia is notable for fast heart rates, up to 240 beats/min in a neonate with a normal P wave axis.
  - Sinus tachycardia will have some variability in rates.
  - Common causes of sinus tachycardia include hypovolemia, fever, hypoxia, anemia, inadequate sedation, and pain.
  - Treatment should be directed at the underlying cause of the sinus tachycardia.
- Premature atrial contractions occur when an ectopic atrial focus depolarizes earlier than the sinus node, creating an early P wave on the EKG (Fig. 10.5).
  - The early P wave may be a different morphology than the sinus P waves and may be buried in the preceding T wave.
  - The premature P way be followed by a normal narrow QRS complex or a wide QRS complex. A wide QRS complex is produced when the early P wave is conducted aberrantly because a bundle branch is still refractory from the prior ventricular depolarization.
  - Very early premature atrial contractions can be blocked because the AV node is still refractory from the prior ventricular depolarization.
  - Frequent blocked premature atrial contractions can cause bradycardia.
  - Premature atrial contractions are common and usually have no specific etiology, but intracardiac lines, caffeine, isoproterenol, dopamine, and epinephrine can cause them iatrogenically.

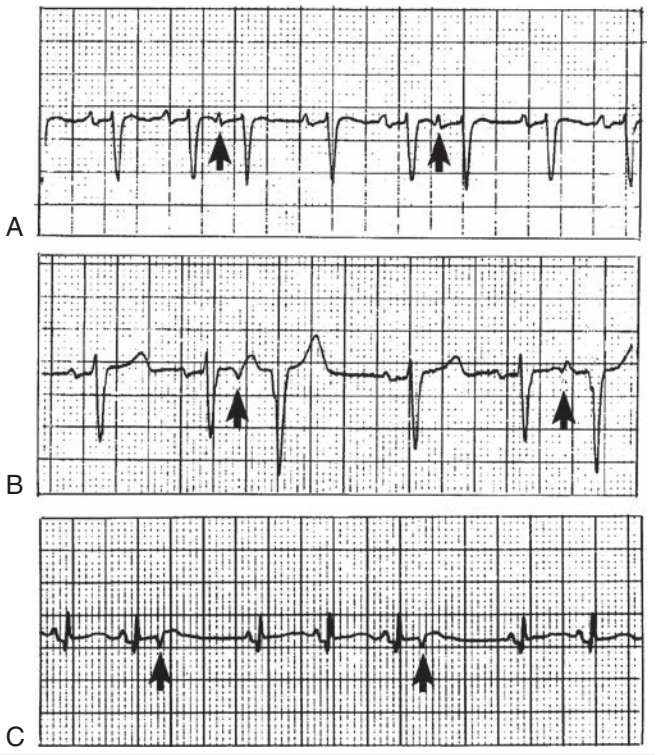

Fig. 10.5 Variations of premature atrial contractions (PACs). (A) PAC with a normal QRS complex. (B) PAC with a widened QRS complex. (C) PAC with no subsequent QRS complex (blocked PAC). (From Keane JF. *Nadas' Pediatric Cardiology.* 2nd ed. Philadelphia: Saunders; 2006.)

  - Electrolyte disturbances, cardiac tumors, and myocarditis are rare causes of premature atrial contractions.
  - Even frequent premature atrial contractions do not cause symptoms and do not require treatment.
  - Premature atrial contractions usually resolve spontaneously by the third month of life.
- Supraventricular tachycardia (SVT) is the most common arrhythmia in infants and children.
- Accessory mediated tachycardia
  - This account for 75% of SVT in infants.
  - Accessory pathways are anomalous tissue bands that connect the atria to the ventricle, which allow conduction between the atria and ventricle outside of the AV node.
  - In Wolff-Parkinson-White syndrome, the accessory pathway conducts antegrade (from the atrial to the ventricle) during sinus rhythm, creating preexcitation, or a delta wave, on the EKG. This occurs because the normal conduction through the AV node is slowed, but the conduction across the accessory pathway is not allowing some of the ventricle to depolarize early (Fig. 10.6).
    - Up to one-third of patients with Wolff-Parkinson-White syndrome have only intermittent preexcitation on the EKG.
  - Concealed accessory pathways can only conduct retrograde (from the ventricle to the atria), so that the baseline EKG is normal.
    - This is the mechanism in more than half of infants with reentrant SVT.

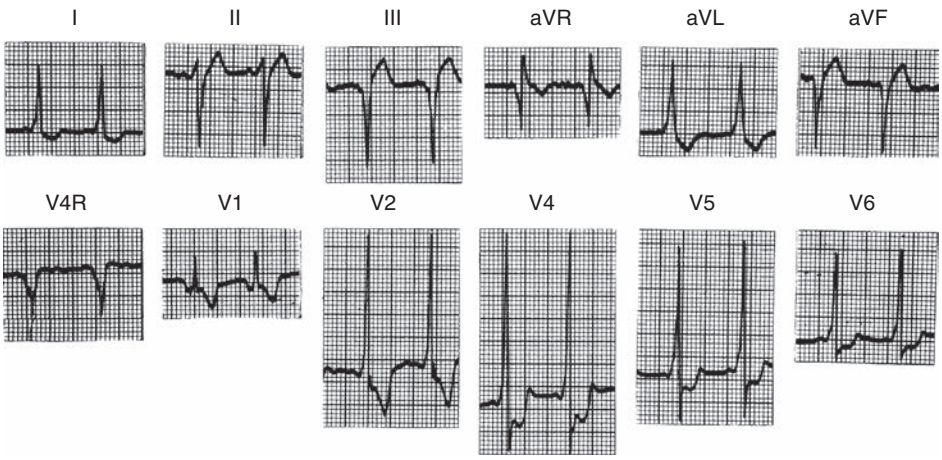

Fig. 10.6 EKG demonstrating delta waves. (From Park MK. *Park's Pediatric Cardiology for Practitioners.* 6th ed. Philadelphia: Elsevier; 2014.)

- Orthodromic reciprocating tachycardia occurs when an impulse, often a premature atrial contraction, is conducted through the AV node and then is conducted retrograde from the ventricle back to the atria. This impulse then goes back down the AV node, creating a self-perpetuating circuit.
- Accessory mediated SVT generally has rates of greater than 250 beats/min, with very minimal variability.
- Onset and termination of the tachycardia are abrupt.
- During tachycardia, the QRS complexes are typically narrow, and P waves are often not visible.
- Infants typically tolerate these rates for 36–72 hours before signs of congestive heart failure develop.
- Accessory mediated SVT can be acutely terminated by measures that cause temporary block of the AV node.
  - Vagal maneuvers are first-line treatment to break an episode of hemodynamically stable SVT.
  - Ice slurry to the patient's forehead, eyes, and nose bridge for 10–20 seconds is performed and may be repeated several times.
  - Adenosine administration at 0.1 mg/kg, pushed rapidly via a three-way stopcock, should be performed if vagal maneuvers fail. A short period of asystole should be seen after administration. The dose may be repeated with 0.2 mg/kg if the short asystolic period is not seen with the lower dose.
  - In the rare infant with hemodynamically unstable SVT, synchronized DC cardioversion should be performed as the first intervention. The initial energy dose of 0.5 J/kg may be increased to 1–2 J/kg if there is no response.
- Prophylactic antiarrhythmic treatment is often indicated because the recurrence rate of neonatal SVT is high.
  - Beta blockers are often used in this capacity.
  - Digoxin maybe used as prophylaxis as well, but this drug is contraindicated in patients with pre-excitation.
- Permanent junctional reciprocating tachycardia
  - This occurs with a concealed accessory pathway that conducts slowly in a retrograde fashion.

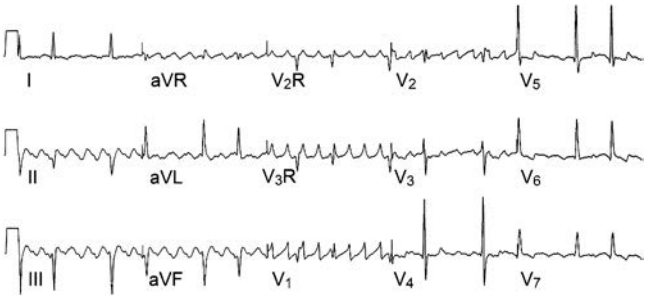

Fig. 10.7 Atrial flutter. (From Keane JF. *Nadas' Pediatric Cardiology.* 2nd ed. Philadelphia: Saunders; 2006.)

  - Heart rates are generally slower than typical SVT, with rates of 180–200 beats/min, with more rate variability.
  - It tends to be more resistant to typical SVT antiarrhythmic therapy and may require ablation.
- Atrial flutter
  - A reentrant circuit forms within the atria only, leading to very rapid atrial rates of 375–500 beats/min.
  - AV block is common at these high rates, leading to variable ventricular response rates. Frequently the ventricular response rates are 2:1 or 3:1.
  - Typically, the EKG will show flutter waves, which appear sawtooth-like (Fig. 10.7).
  - This can be difficult to see on a baseline EKG but the flutter waves are easy to see after the administration of adenosine.
  - Adenosine is helpful in the diagnosis but will not terminate the rhythm because this arrhythmia is not dependent on the AV node.
  - Atrial flutter can be terminated by DC cardioversion or overdrive pacing via a transesophageal lead.
  - Recurrence of atrial flutter in a structurally normal heart is rare so prophylactic treatment is typically not required.
- Ectopic atrial tachycardia
  - This is automatic tachycardia caused by atrial cells, which depolarize independently and more rapidly than the sinus node.

- P wave morphology is different from the sinus P waves.
- The onset and termination of tachycardia are gradual.
- Infants are typically asymptomatic initially but can develop congestive heart failure symptoms after several days. A dilated cardiomyopathy can develop if the infant goes untreated for weeks to months.
- Adenosine does not terminate the rhythm but can transiently slow the rate, allowing for mechanism delineation.
- Treatment is focused on rate control and often involves the use of beta blockers.
- Ectopic atrial tachycardia often resolves spontaneously, but refractory cases can be treated with ablation.

- Premature ventricular contraction (PVC; Fig. 10.8)
  - This is an early depolarization of the ventricle, not preceded by a P wave.
  - The QRS complex is typically wider than the sinus QRS complex.
  - Uniform PVCs have the same QRS morphology; multiform PVCs have multiple QRS morphologies.
  - Often the cause is idiopathic, but infants with PVCs should be evaluated for metabolic abnormalities, myocarditis, cardiac tumors, and structural heart disease.

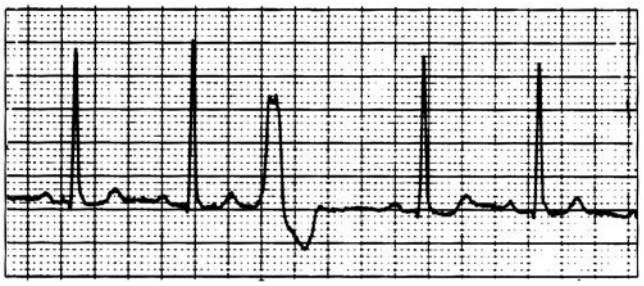

Fig. 10.8 Premature ventricular contraction. (From Keane JF. *Nadas' Pediatric Cardiology.* 2nd ed. Philadelphia: Saunders; 2006.)

  - Multiform PVCs are much more likely to represent significant underlying pathology.
  - No treatment is needed for idiopathic PVCs, and they often resolve in the first few months of life.
- Ventricular tachycardia is a wide complex rhythm that often results from reentry within the ventricle.
  - The rates should be at least 20% greater than the sinus rate.
    - Wide complex rhythm at less than 20% of the sinus rate is an accelerated idioventricular rhythm.
  - Nonsustained ventricular tachycardia lasts less than 30 seconds, and sustained ventricular tachycardia lasts longer than 30 seconds.
  - P wave complexes are disassociated from the ventricular complexes.
  - Torsades de pointes is a type of ventricular tachycardia in which the QRS complexes continually change but spiral around the baseline (Fig. 10.9).
  - Causes include electrolyte and metabolic abnormalities, myocarditis, drug toxicity, myocardial tumors, and myocardial ischemia.
  - Sustained ventricular tachycardia is a critical emergency requiring prompt treatment because infants are often hemodynamically compromised.
    - Patients in shock should undergo DC cardioversion at 1–2 J/kg. The energy can be doubled for a second shock if the first shock is unsuccessful.
    - If the patient is responsive with reasonable vital signs, amiodarone (5 mg/kg) or procainamide (15 mg/kg) can be given.
- Magnesium sulfate is used in torsades de pointes.
- Electrolyte abnormalities can be reflected in the EKG.
- Hypocalcemia prolongs the QTc, whereas hypercalcemia shortens the QTc (Fig. 10.10).
- Hypokalemia can produce a U wave, prolonged QTc, flat or biphasic T waves, and depressed ST segments (Fig. 10.11).
- Hyperkalemia is first seen on the EKG with peaked T waves. The QRS then becomes prolonged, followed by the PR interval. The p waves then disappear, and the QRS complexes become biphasic, like a sine wave (see Fig. 10.11).

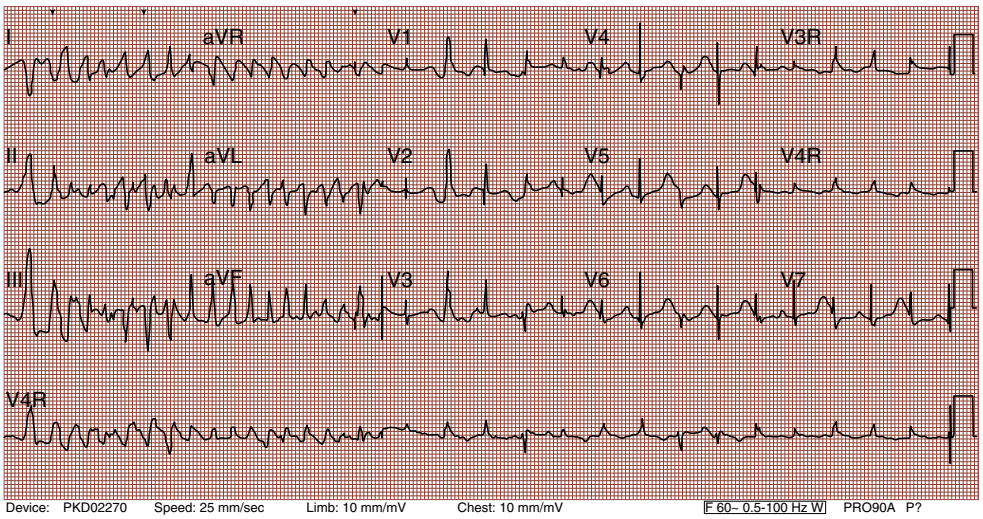

Fig. 10.9 Torsades de pointes. (From Gleason CA. *Avery's Diseases of the Newborn.* 9th ed. Philadelphia: Elsevier; 2012.)

Fig. 10.10 Electrocardiographic changes in hypocalcemia and hypercalcemia. (From Park MK. *Park's Pediatric Cardiology for Practitioners.* 6th ed. Philadelphia: Elsevier; 2014.)

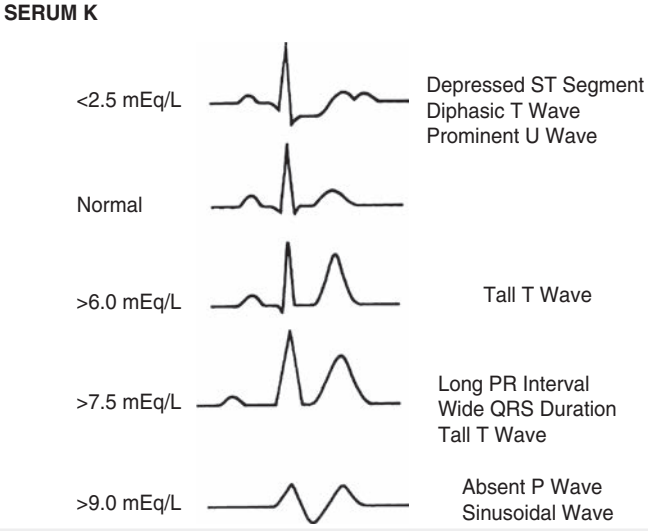

Fig. 10.11 Electrocardiographic changes in hypokalemia and hyperkalemia. (From Park MK. *Park's Pediatric Cardiology for Practitioners.* 6th ed. Philadelphia: Elsevier; 2014.)

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Questions

1. An infant was born at full term to a 29-year-old woman with lupus by cesarean section due to persistent fetal bradycardia. The newborn appears vigorous, with normal capillary refill, blood pressure of 80/55 mm Hg, and 2+ femoral pulses. The heart rate, however, is 65 beats/min, with a narrow QRS complex not associated with p waves. What is the best course of action?
   a. Begin isoproterenol
   b. Begin cardiopulmonary resuscitation
   c. Monitor closely on telemetry
   d. Use transcutaneous pacing

2. A 3-day-old infant suddenly develops tachycardia to 240 beats/min. Adenosine is administered, which slows the ventricular rate briefly to 140 beats/min, revealing a sawtooth-like pattern between the QRS complexes. Transesophageal pacing is used to terminate the tachycardia. Which drug is best to use as prophylaxis to prevent future tachycardia?
   a. Propranolol
   b. No prophylactic therapy needed
   c. Digoxin
   d. Amiodarone

11 Pharmacologic Therapy of Heart Disease

KIMBERLY VERA

- Digoxin is a cardiac glycoside used as an inotropic agent.
  - Its primary mechanism of action is inhibition of sarcolemmal Na^+-K^+ ATPase activity, resulting in increased intracellular sodium. The increased intracellular sodium affects the sodium-calcium exchange, leading to increased intracellular calcium. The increased calcium available to the contractile proteins increases contractility.
    - Secondary effects of digoxin include slowing of cardiac conduction and heart rate.
  - Digoxin is primarily given orally and depends on renal excretion.
  - Dosage must be altered in infants with renal impairment.
  - Serum digoxin levels can be measured but are generally used in cases of suspected toxicity and not for routine monitoring.
  - The primary indication for digoxin use is for patients in heart failure with poor systolic cardiac function.
    - Digoxin is also used as an antiarrhythmic.
  - Toxicity is manifested by poor feeding, vomiting, atrioventricular block, and cardiac arrhythmias.
    - Prolongation of the PR interval is an expected consequence of usage and is not considered a sign of toxicity.
    - Hypokalemia can promote digoxin toxicity so diuretics should be used with care in conjunction with digoxin use.
    - Amiodarone reduces the elimination of digoxin so concurrent use should be done with a decreased dose of digoxin.
    - Digoxin toxicity is treated with normalization of potassium levels, antiarrhythmic therapy for arrhythmias, cardiac pacing for atrioventricular block, and Fab antibody fragments for severe toxicity.
- Adrenergic agonists mediate their effects via specific receptors (Table 11.1).
  - Beta-1 receptors in the myocardium mediate increases in heart rate, contractility, and increased cardiac conduction.
  - Beta-2 receptors in the lung mediate bronchodilation and pulmonary vasodilation.
  - Beta-2 receptors in skeletal muscle cause vasodilation.
  - Alpha-adrenergic receptors in the vasculature mediate vasoconstriction.
  - Dopaminergic receptors in the renal and splanchnic vascular beds mediate vasodilation.
- All adrenergic agents require close and continuous hemodynamic monitoring to titrate the dose appropriately.
- Adrenergic agents should be administered through a central venous catheter because extravasation from a peripheral IV can cause significant tissue damage.
- Dopamine acts primarily via stimulation of the cardiac beta-1 receptors.
  - Dopamine also promotes the release of norepinephrine within the myocardium, causing additional stimulation of the beta-1 receptors.
  - At high doses, dopamine stimulates alpha-1 adrenergic receptors, causing vasoconstriction.
  - At low to moderate doses, dopamine stimulates dopaminergic receptors in the renal vasculature, promoting renal vasodilation.
  - The indication for dopamine is to increase cardiac output in an infant with poor systolic cardiac function.
  - Low to moderate doses may have the advantageous effect of increasing urinary output due to the renal vasodilatory affect.
  - High doses of dopamine can lead to gangrene from severe vasoconstriction, tachycardia, and arrhythmias.
  - Dopamine clearance is delayed in the presence of liver or renal dysfunction.
  - Dopamine is inactivated when given with sodium bicarbonate.
- Dobutamine acts via both beta-adrenergic receptors and alpha-adrenergic receptors.
  - At typical doses, the primary response is via the beta-1 receptors, resulting in an increase in contractility, with minimal effect on heart rate and pulmonary vascular resistance.
  - As the dose of dobutamine increases, the heart rate and myocardial oxygen demand increase.
  - The primary use is in infants with heart failure due to poor systolic ventricular function.
- Epinephrine is an endogenous catecholamine, with very potent effects on both alpha- and beta-adrenergic receptors.
  - At low doses, beta-1 effects are predominant, with increased heart rate, blood pressure, and contractility.

Table 11.1 Receptors Stimulated by Adrenergic Drugs

Drug	Predominant Receptors Effected
Dopamine	Beta-1, DA1
Dobutamine	Beta-1
Epinephrine	Beta-1, beta-2, alpha-1
Isoproterenol	Beta-1, beta-2

DA1, Dopamine receptor 1.

- As the dose increases to moderate, the beta-2 receptor effect is seen, with a mild decrease in the diastolic blood pressure.
- At high doses, the alpha-adrenergic effects are predominant, leading to significant vasoconstriction.
- Epinephrine is indicated for infants with low cardiac output who have not adequately responded to dopamine or dobutamine.
- Epinephrine increases myocardial oxygen demand and can lead to ventricular arrhythmias, myocardial ischemia, and tissue ischemia.

- Isoproterenol is a synthetic catecholamine with effects on both beta-1 and beta-2 receptors.
  - Isoproterenol increases cardiac contractility and heart rate via beta-1 effects and promotes systemic vasodilation via beta-2 effects.
  - The beta-2 effect also makes this drug a potent pulmonary vasodilator.
  - The primary indication for isoproterenol is bradycardia due to either sinus node dysfunction or atrioventricular block.
  - The major side effects of isoproterenol are tachycardia and arrhythmias.
- Cardiac indications for diuretics in infants include congestive heart failure and fluid overload in a postoperative cardiac patient.
- Furosemide is a loop diuretic, which acts via inhibition of chloride-sodium-potassium cotransport in the thick ascending limb of the loop of Henle. The reduction of absorption of chloride, sodium, and potassium leads to the increased excretion of free water.
  - This drug is renally excreted, and the dose must be adjusted in those with renal impairment and in premature infants with immature kidneys.
    - The half-life of furosemide is 20 hours in preterm infants and 8 hours in term infants.
  - Adverse effects include dehydration, electrolyte derangements, and ototoxicity.
    - Hypokalemia is particularly common and frequently requires potassium supplementation.
    - A hypochloremic metabolic alkalosis can develop and can be treated with chloride supplementation.
    - The ototoxicity risk is increased in patients with renal dysfunction and with co-administration with other ototoxic agents.
- Hydrochlorothiazide and chlorothiazide are similar thiazide diuretics that act by inhibiting sodium and chloride transport in the distal convoluted tubule.
  - Adverse effects include hypokalemia, hyperuricemia, and hypercalcemia.
- Spironolactone is a potassium-sparing diuretic that inhibits aldosterone in the distal tubule.
  - Spironolactone is a relatively weak diuretic, so it is often used in combination with other diuretics to lessen the hypokalemic effect of most diuretics.
  - The primary adverse effect is hyperkalemia.
- Prostaglandin E1 (PGE1) is used to maintain the patency of the ductus arteriosus or dilate a closed or closing ductus arteriosus in an infant with ductal-dependent congenital heart disease.
  - It must be infused continuously, given its short half-life.
  - Intravenous access is preferred, but PGE1 can be given through an umbilical arterial line.
  - PGE1 dilates both systemic and pulmonary venous vasculature.
  - Side effects include hypotension, apnea, fever, irritability, edema, and cutaneous flushing.
- Fetal exposure to numerous maternal drugs (Table 11.2) and maternal diseases can result in fetal heart disease.

Table 11.2 Maternal Drugs Associated With Fetal Cardiac Abnormalities

Drug	Cardiac Lesion
Carbamazepine	ASD, PDA
Cocaine	ASD, VSD, congenital heart block, TGA
Coumadin	VSD
Cyclophosphamide	TOF
Daunorubicin	TOF
Ethanol	VSD, ASD, DORV, PA, dextrocardia, PDA, TOF
Methotrexate	Dextrocardia
Lithium	Ebstein anomaly
Phenytoin	VSD, pulmonary stenosis, aortic stenosis, coarctation of the aorta
Retinoic acid	VSD, HLHS, TGA, TOF
Thalidomide	TOF, truncus arteriosus, septal defects
Trimethadione	TGA, TOF, HLHS
Valproic acid	TOF, VSD, aortic stenosis, PDA
Vitamin D	Supravalvar aortic stenosis, pulmonary stenosis

ASD, Atrial septal defect; *DORV,* double-outlet right ventricle; *HLHS,* hypoplastic left heart syndrome; *PA,* pulmonary atresia; *PDA,* patent ductus arteriosus; *TGA,* transposition of the great arteries; *TOF,* tetralogy of Fallot; *VSD,* ventricular septal defect.

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Questions

1. An infant with a large ventricular septal defect and congestive heart failure is being medically managed with digoxin, enalapril, and furosemide (Lasix). Spironolactone was added yesterday due to persistent hypokalemia. Overnight, the infant developed Mobitz II heart block. This is a toxicity of which medication?
   a. Spironolactone
   b. Digoxin
   c. Enalapril
   d. Lasix

2. A 10-day-old infant is being treated for sepsis with antibiotics and dopamine. The infant is requiring escalating doses of dopamine. All the interventions below can increase the infant's response to the current dose of dopamine, except for one. Which intervention does not increase an infant's sensitivity to catecholamines?
   a. Beginning steroid administration
   b. Normalizing pH
   c. Normalizing serum calcium levels
   d. Normalizing potassium levels

SECTION 4

Respiratory

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12 Embryology and Physiology

ECHEZONA T. MADUEKWE

Development of the Human Lung

- Proper prenatal lung development to a functional stage is critical to survival after delivery.
- Development of the lung can be divided into two major phases: structural development (lung growth), and functional development (lung maturation).
- Lung growth starts with the formation of the conducting airways and continues after birth with the increase in the alveolar number.
- Delivery before the completion of both the structural and functional development of the lungs will result in respiratory insufficiency of the newborn.

Structural Development

The morphologic changes can be divided into five stages: ***e***mbryonic stage, ***p***seudoglandular stage, ***c***analicular stage, ***s***accular stage, and ***a***lveolar stage. These can be remembered with a mnemonic: Every Person Can Study Alone.

See Fig. 12.1.

EMBRYONIC STAGE

- Developmental period: 4-7 weeks' gestation.
  - Lung buds – originate as outgrowths from ventral wall of the foregut (4 weeks)
  - Formation of major bronchopulmonary segments
  - Airway development under control by retinoic acid signaling → induce TBX_4 expression in endoderm, HOX, and FGF genes
  - Vitamin A deficiency implicated in pulmonary agenesis and stenosis of the trachea
  - Vascular development of the primitive arteries and veins is mediated by the vascular endothelial growth factor (VEGF) and extracellular matrix (fibronectin, laminin, type IV collagen).
  - Pulmonary arteries are from the sixth pair of aortic arches.
  - Pulmonary vein is from outgrowths of the left atrium.

PSEUDOGLANDULAR STAGE

- Developmental period: 7-17 weeks' gestation.
- Tubular branching (15–20 generations) continues down to the level of the terminal bronchioles.
- Early branching is regulated by the insulin-like growth factor.
  - Cellular differentiation (ciliated, goblet, basal) starts from proximal to distal under the control of FGF-10 and FGF-7.
  - Disruption of FGF results in blockage of dichotomous branching of the conducting airways.
  - Excess FGF-7 leads to poor differentiation, which histologically resembles congenital pulmonary adenomatoid malformation.
- The lining cell is the columnar epithelium, but the more distal structures are lined with the cuboidal epithelium.
- Vasculogenesis (formation of new blood vessels) starts in the mesenchyme surrounding the terminal buds.
- Removal of the mesenchyme impairs branching morphogenesis.

CANALICULAR STAGE

- Developmental period: 17-26 weeks' gestation.
- Respiratory bronchioles and alveolar ducts form a few terminal sacs toward the end of the stage.
- Angiogenesis starts (formation of new vessels from preexisting vessels): prominent capillary meshwork within the mesenchyme promotes the ability to exchange gas, and an blood-air barrier forms.
- Canalization of the lung capillaries and surfactant synthesis begins.
- Thyroid transcription factor-1 (TTF-1) increases the expression of surfactant protein.
- Absence of TTF-1 leads to impaired lung morphogenesis.
- Lining cell is simple cuboidal epithelium; later, lamellar bodies form.
- Primitive cuboidal cells differentiate into types I and II cells under the control of TTF-1, FOXa1, FOXa2, and GATA6.

SACCULAR STAGE

- Developmental period: 27-36 weeks' gestation.
- Terminal sacs or primitive alveoli form.
- Sacs are separated from each other by primary septa, indicating the start of alveolarization.
- Lining cells are types I and II pneumocytes (type II makes surfactant).
- The capillary network becomes closer together; walls between the sacs contain a double-capillary network.

ALVEOLAR STAGE

- Developmental period: 36 weeks' gestation to childhood.
- The terminal sacs are partitioned by secondary septae (adult alveoli).

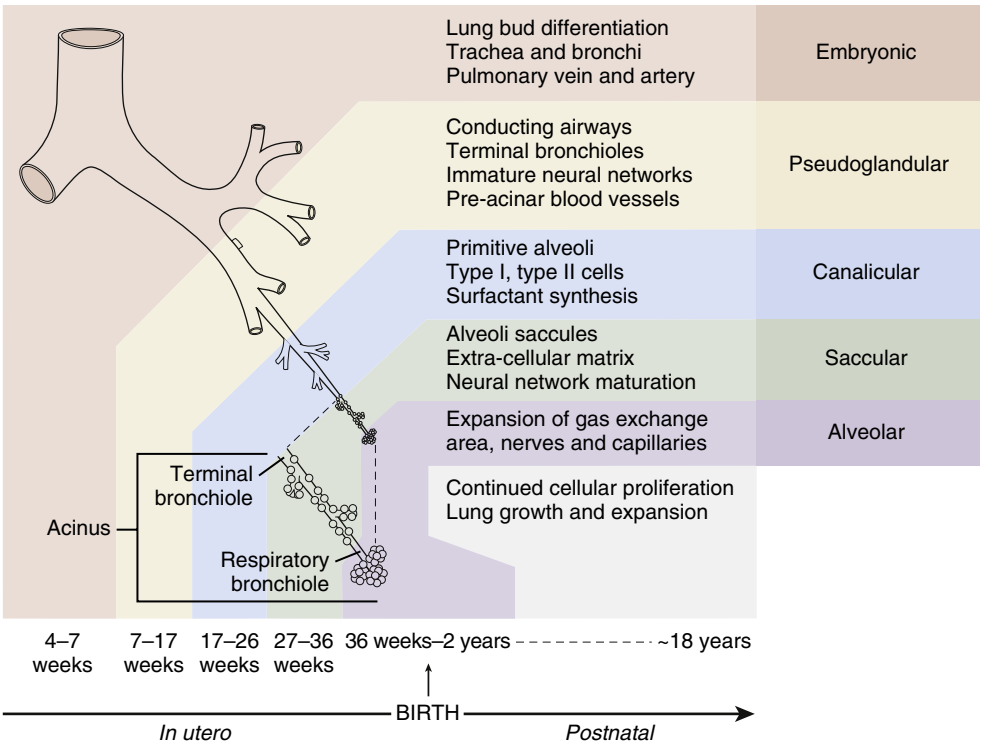

Fig. 12.1 Principal stages of lung development in humans. (From Kajeckar R. Environmental factors and developmental outcomes in the lung. *Pharmacol Ther.* 2007;114:129–145.)

Table 12.1 Clinical Implications of Abnormal Morphologic Development

Embryologic Stage	Pseudoglandular Stage	Canalicular Stage	Saccular Stage	Alveolar Stage
Atresias or fistula (esophageal, laryngeal, tracheal) Bronchogenic cysts Pulmonary sequestration Pulmonary aplasia Pulmonary agenesis	Pulmonary sequestration Pulmonary hypoplasia Pulmonary lymphangiectasia Congenital pulmonary airway malformation Congenital diaphragmatic hernia Lung cysts	Alveolar capillary dysplasia Surfactant deficiency Pulmonary hypoplasia[a] Renal dysplasia	Alveolar capillary dysplasia Surfactant deficiency Pulmonary hypoplasia Acinar dysplasia	Surfactant deficiency Pulmonary hypertension Lobar emphysema

[a]Second-degree oligohydramnios or premature rupture of the membranes (PROM).

- There is an increase in the number of alveoli (up to 500 million in adult).
- There is an increase in lung volume and surface area.
- Lining cells are types I and II pneumocytes.
- New double-capillary layers are formed, followed by remodeling to form the mature single layer (blood-air barrier).

See Table 12.1.

Physical Influences on Lung Growth

- Lung fluid and amniotic fluid are required for proper development of the lung.

FETAL RESPIRATION AND FETAL LUNG FLUID

- Fetal lung is not involved in respiratory gas exchange; lung filled with fluid
- Fetal breathing movements (FBM) important for lung growth, development of respiratory muscles and neural regulation
- Principal muscles are diaphragm and glottis
- Larynx: major site of fetal lung fluid (FLF) regulation by regulation of efflux
  - FLF is a product of active chloride (Cl^-) secretion and bicarbonate resorption in the respiratory epithelium.
  - FLF absorption is mediated by ENaC and Na-K-ATPase.
  - FLF maintains air spaces in a distended state, limiting amniotic fluid entry.
- FBM episodic in nature, with apnea sensitivity to hypoxia
- Net flow usually out of the lungs while maintaining a stable chemical environment, preventing entry of amniotic fluid or meconium
- Fetal lung fluid dynamics and composition (Table 12.2)
  - FLF composition is different from that of fetal plasma or amniotic fluid: high Cl^-, low bicarbonate (HCO_3), minimal protein
  - Late in gestation, K^+ concentration increases
  - FLF secreted as result of active transport of Cl^- ion (Na-K-2Cl transporter) → electrical potential difference~ −4 mV across pulmonary epithelium

Table 12.2 Composition of Human Fetal Lung Fluid Compared With Other Body Fluids

Component	Lung Fluid	Interstitial Fluid	Plasma	Amniotic Fluid
Sodium (mEq/L)	150	147	150	113
Potassium (mEq/L)	6.3	4.8	4.8	7.6
Chloride (mEq/L)	157[a]	107	107	87
Bicarbonate (mEq/L)	3[a]	25	24	19
pH	6.27[a]	7.31	7.34	7.02
Protein (g/dL)	0.03[a]	3.27	4.09	0.10

[a]Bicarbonate, protein, and pH are less in lung fluid, but chloride level is higher in lung fluid.
Adapted from Gleason CS, Devaskar SU. *Avery's Diseases of the Newborn.* 9th ed. Philadelphia: Elsevier; 2012:577.

- Electrochemical difference results in the flow of fluid from pulmonary microcirculation → interstitium → terminal sacs
- Pulmonary epithelium restricts movement of protein (tiny openings), endothelial membrane permits passage of proteins
- As a result, lung lymph liquid protein content is 100× greater than FLF
- FLF volume in air spaces is ~20-30mL/kg with flow rate averaging 4-6 mL/kg/hour

See Table 12.2.

Fetal Lung Fluid Clearance

- Fetal lung fluid changes during labor
  - 35% cleared antepartum
    - Decreased Cl^- secretion → decreased FLF secretion
    - Increased Na^+ transport from the alveolar space
    - Increased lymphatic oncotic pressure
  - 30% cleared intrapartum
    - Active Na^+ absorption mediated by ENaC channels
    - Epinephrine concentrations high during labor, reverse flux from secretion to absorption
  - 35% cleared postpartum
    - Increase transpulmonary pressure (lung distention)
    - Increased lymphatic oncotic pressure (low fetal alveolar protein)
- Mediators of fetal lung fluid clearance

See Table 12.3.

Table 12.3 Mediators of Fetal Lung Fluid (FLF) Clearance

Hormones Involved in Na^+ Uptake and FLF Clearance	Channel Inhibitors	Channels	Function of Inhibitors
Epinephrine	Amiloride	ENaC	Blocks fluid clearance
Glucocorticoids	Glucocorticoids	ENaC	ENaC upregulation
Vasopressin	Bumetanide	Na-K-2Cl	Impairs lung fluid clearance/liquid absorption
Aldosterone	Ouabain	Na-K-ATPase	Reduction in fluid clearance

- Abnormal development
- Abnormalities of chest wall, congenital diaphragmatic hernia (CDH), oligohydramnios → lung hypoplasia
- Ablation of phrenic nerve → abolition of FBM → lung hypoplasia (laryngeal, tracheal)
- Fetal pleural effusions → lung hypoplasia
- Laryngeal atresia → increased FLF → increased lung volume, surface area, and alveolar numbers
- Inadequate lung epithelial Na^+ transport (ENaC function) in term newborn → transient tachypnea of newborn
- Cesarean section → decreased clearance of lung fluid at time of birth → transient tachypnea of newborn
- Increased risk of respiratory distress syndrome in preterm infants with deficient ENaC expression in their respiratory epithelium

Functional Development

Lung maturation and the achievement of functionality are mainly biochemical processes and are controlled by hormones. The production of surfactant (biochemical maturation) seems to be independent of lung growth.

SURFACTANT

- Crucial for maintaining the functional integrity of alveoli
  - Produced by type II cells and stored in the lamellar bodies
  - Mainly composed of 80% phospholipids, 10% neutral lipids (cholesterol), 10% proteins

Surfactant Lipids

- Phosphatidylcholine (lecithin) is the most abundant phospholipid → 70% of total lipids (unsaturated, ~25%; saturated, ~45%)
- Phosphatidylglycerol accounts for 5%; important for even spreading of surfactant monolayer on alveolar surfaces

Surfactant Proteins

- The protein part of surfactant has four types, SP-A, SP-B, SP-C, and SP-D.
  - SP-B and SP-C are the principal proteins and are hydrophobic.
  - SP-B is involved in surface tension reduction, tubular myelin formation, and type II cell functions.
  - SP-C is involved in surface tension reduction and film stability.
  - SP-A and SP-D are hydrophilic; their mRNA is detected earlier than 20–24 weeks.
  - SP-A is required for tubular myelin formation and plays a role in host defense but has little or no surface-active properties.
  - SP-D is not located in lamellar bodies in type II cells and is involved in surface lipid homeostasis, host defense, and antioxidation.
- ABCA3 protein transports phospholipids into lamellar bodies for surfactant formation and appears to be involved in the formation of lamellar bodies.

Hormones Involved in Surfactant Production

- Glucocorticoids stimulate lung maturation → cortisol
- Cortisol induces fetal lung fibroblast → fibroblast pneumocyte factor
- Fibroblast pneumocyte factor stimulates surfactant production
- Thyroid hormones are also required for the development of the surfactant system

Abnormal Development

- SP-B deficiency
  - Autosomal recessive inheritance, most common surfactant protein deficiency
  - Histology—pulmonary alveolar proteinosis, no lamellar bodies, no tubular myelin
  - Unsustained response to exogenous surfactant—ultimate treatment is lung transplantation
  - SP-B polymorphism associated with respiratory distress syndrome (RDS) and bronchopulmonary dysplasia (BPD)
- SP-C deficiency
  - Autosomal dominant inheritance; presents as chronic lung disease in infancy or interstitial (fibrotic) lung disease
- ABCA3 deficiency
  - Autosomal recessive inheritance
  - Reduction or absence of protein function
  - Decreased transport of surfactant phospholipids
  - Impaired lamellar body formation—dense lamellar bodies or eccentrically placed electron-dense inclusions
  - Presents in neonatal period like RDS due to abnormal processing of SP-B and SP-C

Surface Tension and Surfactant

See Fig. 12.2.

- Surface tension is defined as a cohesive force of attraction experienced by molecules present at a gas-liquid interface.
- Surfactant forms a film between the two media, stabilizing their interactions with a resultant reduction in surface tension, preventing alveolar collapse and increasing pulmonary compliance.

Surfactant, Surface Tension, and the Laplace Law

See Fig. 12.3.

- The relationship between surface tension (T), distending pressure (P), and radius of the alveoli obeys the Laplace law: P = 2T/r.
- The surface tension therefore increases with an increase in the radius of the alveoli, and vice versa.
- Insufficient surfactant at the alveolar air-liquid interface increases surface tension and decreases lung compliance.
- Smaller surfactant-deficient alveoli develop more deflating pressure and may get emptied into the larger alveoli.
- Emptying of the smaller alveoli into the larger alveoli is prevented by the presence of surfactant.
- Physiologic effects of surfactant deficiency on lung mechanics include decreased lung compliance, decreased lung volume, and increased intrapulmonary shunting and hypoxemia.

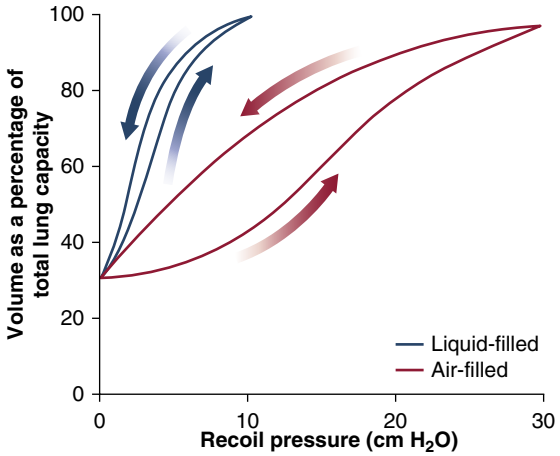

Fig. 12.2 Effect of surface tension on recoil force. Pressure-volume curves obtained on inflation and deflation of a normal air-filled lung and the same lung when filled with saline. The horizontal difference between the curves reflects the effect of surface tension, which is greater on inspiration than expiration and abolished when the lung is liquid filled. (Modified from Culver BH, ed. The Respiratory System. Seattle, University of Washington Publication Services, 2006; data from Bachofen H, Hildebrandt J, Bachofen M. Pressure-volume curves of air- and liquid-filled excised lungs—surface tension in situ. *J Appl Physiol.*1970;29:422–431.)

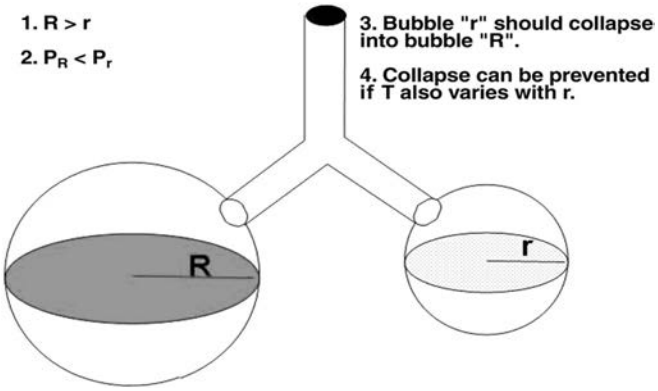

Fig. 12.3 Law of Laplace as it applies to bubbles of equal radius. P_r, distending pressure of small alveolus; P_R, distending pressure of big alveolus; *r*, radius of the small alveolus; *R*, Radius of the big alveolus; *T*, Surface tension. (From Prange HD. Laplace's law and the alveolus: a misconception of anatomy and a misconception of physics. *Adv Physiol Educ.* 2003;27:34–40.)

LUNG VOLUMES

See Fig. 12.4.

- The lung has no innate resting volume (collapses completely if separated from the chest wall).
- Movement of air in and out of the lungs during respiration results in lung volume changes and can be measured with a spirometer.
- Functional residual capacity (FRC) is the volume of gas that remains in the lung at the end of a passive expiration: expiratory reserve volume (ERV) + RV = 20–30 mL/kg.

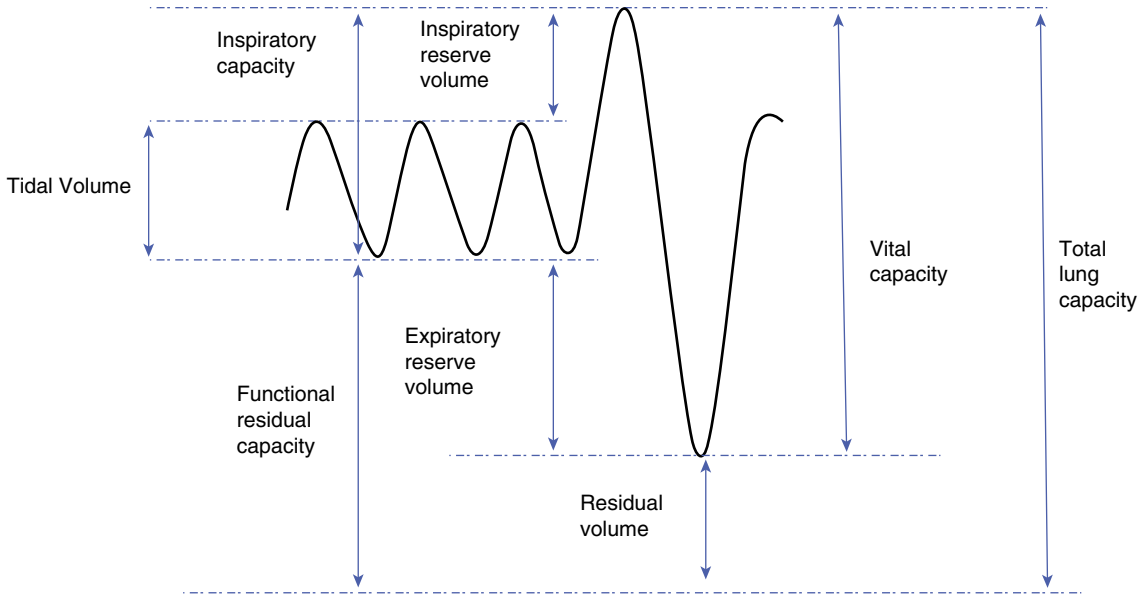

Fig. 12.4 Lung volume. (From Davis RP. Neonatal pulmonary physiology. *Semin Pediatr Surg.* 2013;22:179–184.)

- Residual volume (RV) is the volume of gas that remains in the lung after maximal expiration.

NOTE: FRC and RV can only be measured through helium spirometry or plethysmography, not ordinary spirometry.

Mechanics of Respiration

Basic Information

- Air flows from a region of higher pressure to a region of lower pressure (Boyle's law).
- Normal breathing starts with active contraction of inspiratory muscles, resulting in:
  - Enlargement of the thoracic cavity
  - Lowering of intrathoracic and intrapleural pressures
  - Enlargement of the bronchi, bronchioles, and alveoli
  - Lowering the alveolar pressure below the atmospheric pressure
- Inspiration muscles: diaphragm (most important), external intercostal muscles, and accessory muscles provide the forces required to overcome elastic recoil and frictional resistance.
- Expiration occurs due to elastic recoil of the pulmonary and thoracic tissues stretched during inspiration.
- Expiration muscles are the abdominal muscles (most important) and internal intercostal muscles.

See Table 12.4.

Resistance (R): the resistance to air flowing through the respiratory system can be calculated as follows:

$$R = \text{change in pressure (in cm } H_2O)/(\text{change in flow (in L/sec)}) = \Delta P/\Delta Q$$

- Flow (Q) mechanics depend on Poiseuille's law:

Table 12.4 Comparison of Lung Mechanics Between Neonates and Adults

Parameter	Neonate	Adult
Respiratory rate (RR)	Increased (40–60)	15
Tidal volume (TV)	4–6	Increased (5–8)
Minute ventilation (TV × RR)	Increased	
Dead space	Similar (1.5–3)	Similar (1–2)
Lung compliance (mL/cm H_2O/kg)	1–2	Increased (3)
Chest compliance (mL/cm H_2O/kg)	Increased (5–10)	3
Alveolar ventilation ([TV – dead space] × RR)	Increased	
Oxygen consumption	Increased	
Resistance (cm H_2O/L/sec)	Increased (50–150)	2–3
Time constant	Very short (0.12–0.5 sec)	Long
Residual volume (RV)	Increased	
Functional residual capacity (FRC)	Similar	Similar
Total lung capacity (TLC)		Increased
Inspiratory capacity (IC)		Increased
Vital capacity (VC)		Increased

$$Q = \Pi Pr^4/(8\eta l)$$

where flow is related to viscosity (η), pressure gradient (P), length (l), and radius to the power of 4.

  - Reduction in the radius by one-half results in a 16-fold increase in resistance.
- Airway resistance is affected by (1) diameter, (2) velocity of airflow, and (3) physical properties of the inspired gas.
- Lung tissue resistance is the resistance within the lung tissues generated during inflation and deflation.

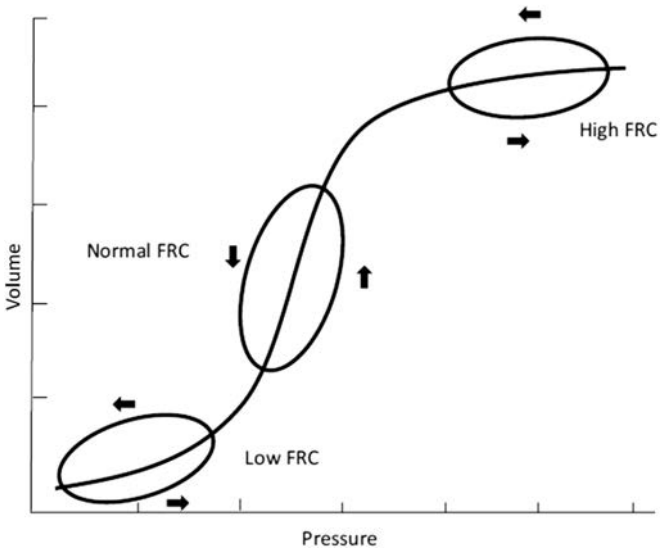

Fig. 12.5 Static compliance curve showing the relationship between changes in volume over pressure with superimposed dynamic flow volume loops. The bottom of the loop is consistent with positive end-expiratory pressure (PEEP) level, the top with peak airway pressure (PIP). *FRC,* Functional residual capacity. (From Davis RP. Neonatal pulmonary physiology. *Semin Pediatr Surg.* 2013;22:179–184.)

Table 12.5 Factors Affecting Static Compliance and Dynamic Compliance

A

Parameter	Compliance
Static Compliance	
Increased functional residual capacity Age Body size Posture	Increased
Decreased lung volume Lobar, lung resection Collapse or consolidation Diffuse atelectasis	Decreased
Increased lung elasticity Emphysema	Increased

B

Dynamic Compliance	
Increased airway resistance Emphysema (due to prolonged time constants)	Decreased
Increased respiratory frequency Slower alveoli fail to fill	Decreased

- Tissue resistance is high in neonates due to a low ratio of lung volume to lung weight and relative pulmonary interstitial fluid.
- Chest wall resistance contributes to total resistance but is unlikely to increase with lung disease. It is decreased in premature infants (less muscular rib cage).
- Total resistance is the sum of airway resistance and tissue (lung + chest) resistance (R = chest wall [~25%] + airway [~55%] + lung tissue [~20%]).
- Gas flow
  - Gas flow pattern is dependent on the airway type—laminar flow (small airways) and turbulent flow (branching airways and large airways).
  - Laminar flow—gas molecules travel in a straight line, with faster moving molecules near the center.
  - Turbulent flow occurs at high rates of gas flow with chaotic movements.

COMPLIANCE

See Fig. 12.5.

Compliance of the lung—or expansibility of the lung—is defined as the change in the volume of the lung per unit change in pressure and can be static or dynamic.

$$\text{Compliance} = \text{change in volume (in mL)} / (\text{change in pressure [in cm } H_2O])$$

- Static lung compliance is defined as the relationship between the change in lung volume and change in transpulmonary pressure (airway − intrapleural pressure change) measured with no air flow.
  - The value decreases as lung volume increases (limitations of nonelastic components of the chest wall and lung).
  - It reflects the elastic properties of the lung.
  - The pressure-volume curve does not reach zero volume (due to trapping of gas in the small airways).
  - Neonates have greater chest wall compliance than adults due to:
    - The cartilaginous material of the chest wall compared to an adult's rigid or calcified chest wall.
    - The rib cage is not well stabilized by the intercostal muscles in infants when the diaphragm contracts.
  - After correction for volume, premature infants have more lung compliance compared to term infants
- Dynamic lung compliance is measured during spontaneous breathing, but airflow is zero at the point of flow reversal during the normal respiratory cycle.
  - It reflects both elastic and resistive components and is measured from the end of expiration to the end of inspiration for a given volume.
  - Dynamic and static compliance have about the same value in normal lungs at low and moderate frequencies.
  - Dynamic compliance is less than static compliance at higher frequencies in normal lungs, and also less than static compliance at normal frequencies in abnormal lungs (due to incomplete filling of the alveoli at the available time).
  - Decreased dynamic compliance is seen in conditions with prolonged time constant (e.g., emphysema) and increased respiratory frequency (failure of filling slower alveoli).

See Table 12.5.

- Pressure-volume (P-V) relationships (see Figs. 12.2 and 12.5):
  - Static pressure-volume curves represent the relationship between pressure and volume during passive inspiration and expiration.
  - Dynamic pressure volume curves estimate the work of breathing (area contained in the loop) and can be measured during spontaneous breathing.

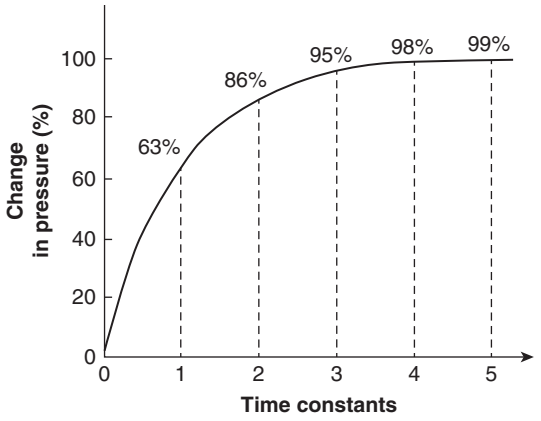

Fig. 12.6 Percentage change in pressure in relation to time constants allowed for equilibration. (From Waldemar A. Conventional mechanical ventilation: traditional and new strategies. *Pediatr Rev.* 1999;20:e117–e126.)

- The slope of the line between the start of inspiration and expiration = compliance.
- Curve shift down and to the right (decreased compliance) occurs in interstitial lung disease, pulmonary fibrosis, postabdominal surgery, and RDS.
- Curve shift up and to the left (increased compliance) is seen in BPD, emphysema, and chronic obstructive pulmonary disorders.

- Time constant (Fig. 12.6)
  - This is defined as resistance × compliance and characterizes the time necessary for alveolar pressure to deplete 63% of its volume:

$$\text{Time constant (TC)} = \text{resistance} \times \text{compliance}$$

  - It takes three to five TCs for a relative complete inspiratory or expiratory phase.
  - 1TC = 63% emptying, 2TC = 86% emptying, 3TC = 95% emptying, 4TC = 98% emptying, and 5TC = 99% emptying.
  - The TC will be shorter if C (compliance) is decreased (RDS), but longer if C (compliance) is high (large for gestational age [LGA] baby, with normal lungs) or if R is high (chronic lung disease).
  - Infants have shorter TCs compared to adults (lung empties faster; they breathe faster).
  - A condition with short TCs is RDS (low compliance).
  - Conditions with long TCs include LGA baby with normal lungs (high compliance), BPD, chronic lung disease (high resistance). The ventilation strategy should match the time constant (e.g., low rate, higher tidal volumes in BPD patients).
- Hysteresis
  - The volume differences in the deflation and inflation arms of the PV curve is called *hysteresis*; it is caused by higher tension present in the lungs before inflation. As a result, higher pressure is required to inflate the lungs.
- Work of breathing (Fig. 12.7)
  - The work required by the respiratory muscles to overcome the mechanical impedance to respiration (work of breathing [kg cm] = pressure × volume).
  - The work of breathing is directly proportional to the airway resistance and inversely related to lung-chest compliance.

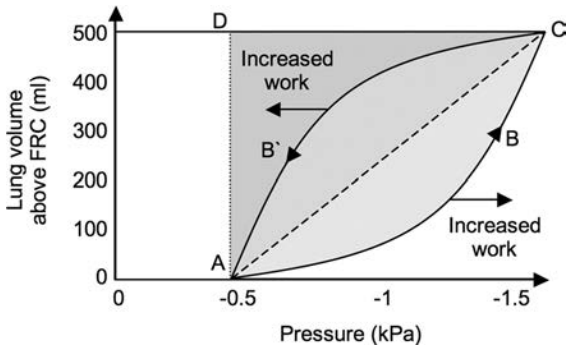

Fig. 12.7 The effect of airway and tissue resistance on the pressure-volume relationship within the chest. *ABC,* Traced line on inspiration; area *ABCA,* work done to overcome viscous resistance and friction on inspiration; area *ACDA,* work done to overcome elastic tissue resistance area; *CB′A,* traced line on expiration; area *CB′AC,* work done on expiration against airway resistance; *FRC,* functional residual capacity. (From Cross M. Respiratory physiology. In: Cross ME, Plunkett EVE, eds. *Physics, Pharmacology and Physiology for Anesthetists: Key Concepts for the FRCA.* 2nd ed. New York: Cambridge University Press, 2014:153.)

Pulmonary Function

Dead Space

- Defined as the volume occupied by gas which does not participate in gaseous exchange in the lungs—three components
- Anatomic dead space- gas the never reaches the alveoli
- Factors affecting the anatomic dead space: ETT size, ETT length, flow sensors, suction apparatus, acquired tracheostomy
- Alveolar dead space-gas reaches alveoli with no capillary flow, or with inadequate flow. Factors affecting alveolar dead space: hyperinflation, heterogeneous inflation, decreased pulmonary blood flow
- Physiologic dead space = anatomic DS + alveolar DS. Total volume not participating in gas exchange
- It can be calculated by the Bohr equation:

$$Vd/Vt = PaCO_2 - Peco_2/(Paco_2)$$

where Vd = dead space volume, Vt = tidal volume, $Paco_2$ = carbon dioxide in the arterial blood, and $Peco_2$ = partial pressure of carbon dioxide in the expired air.

Pulmonary Edema

- Definition: increase in extravascular pulmonary water content
- Occurs when transudation or exudation is greater than lymphatic drainage
- Causes
  - Increased capillary pressure (edema protein < normal pulmonary lymph): overtransfusion, vasopressors, left ventricular (LV) failure, left-to-right shunt, anemia
  - Increased alveolar-capillary permeability (edema protein very close to that of plasma): direct injury, indirect injury (like sepsis)
  - Decreased lymphatic obstruction: infection, tumor
  - Decreased plasma oncotic pressure (seldom the primary cause of edema but common in very ill patients)

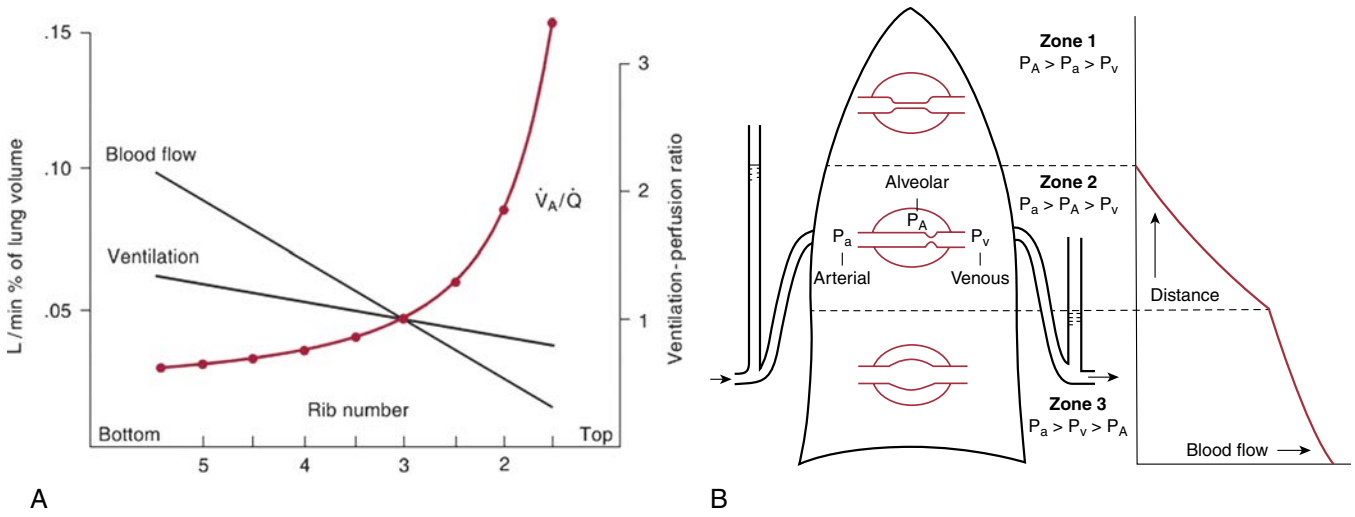

Fig. 12.8 Distribution of ventilation and perfusion in an upright lung. (A) Ventilation- perfusion ratio decreases down the lung . (B) Model to explain uneven distribution of blood flow in lung bases (From West JB, Luks AM. *West's Respiratory Physiology: The Essentials.* 10th ed. Philadelphia: Wolters Kluwer Health; 2015.)

- Miscellaneous—neurogenic (cerebral lesions), reexpansion (secondary to increased permeability), high altitude
- Effects on lung function
  - A venous admixture or shunt → increased PAO_2 - PaO_2 gradient and arterial hypoxemia.
  - $Paco_2$ may be normal or subnormal in mild to moderate edema due to hypoxia-induced increased respiratory drive.
  - Hypercapnia secondary to interference with gas exchange can occur when a high Fio_2 is used to treat severe edema.

VENTILATION-PERFUSION RELATIONSHIPS

Three Processes for Gas Exchange

- *Ventilation:* exchange of air between lungs and the atmosphere (oxygen for carbon dioxide)
- *Diffusion:* spontaneous movement of gases (between the gas in the alveoli and the blood in the lung capillaries)
- *Perfusion:* passage of fluid through the circulatory system (process of pumping blood through the lungs by the cardiovascular system)
- *Ventilation-perfusion ratio:* the ratio between the amount of air getting to the alveoli (alveolar ventilation = V in mL/min) and the amount of blood going to the lungs (cardiac output = Q in mL/min)
  - V/Q = alveolar ventilation/(cardiac output)
  - V/Q ratio can be decreased by decreasing the ventilation or increasing the perfusion → decrease in arterial O_2 level (Pao_2) and increasing the arterial CO_2 (carbon dioxide).
  - V/Q ratio can be increased by either increasing ventilation or decreasing perfusion → increase in pulmonary alveolar O_2 (PAo_2) and, as a result, an increase in Pao_2 (also a decrease in $PAco_2$ and $Paco_2$)
  - V/Q ratio can be changed physiologically or pathologically.

Changing V/Q Ratio Physiologically

See Fig. 12.8.

- Blood flow to different parts of the lung is dependent on gravity.
- Upper zone (zone 1):
  - Alveolar pressure (PA) is greater than both arterial (Pa) and venous (Pv) capillary pressures (PA > Pa > Pv).
  - It has the lowest pulmonary artery pressure → lowest perfusion.
  - The highest ventilation-perfusion ratio occurs at rest.
- Middle zone (zone II):
  - Perfusion and gas exchange are influenced by pressure differences between arterial and alveolar pressures (Pa > PA > Pv), with a normal V/Q ratio.
- The lower zone (zone III):
  - Alveolar pressure is lower than both arterial and venous pressures (Pa > Pv > PA) and ventilation is reduced → intrapulmonary shunting.
  - It has the highest pulmonary arterial pressure → highest perfusion, but lowest V/Q ratio at rest.

Changing V/Q Ratio Pathologically

- Various pathologies will change blood delivery and/or ventilation to alter the V/Q ratio.
- This can add to the alteration in blood gases produced directly by the pathology.
- Any increase in alveolar dead space will increase V/Q ratio mismatch (see dead space discussion above).
- Any increase in physiologic shunting or anatomic shunting will decrease the V/Q ratio.
- Compensatory mechanisms include hypoxic vasoconstriction and bronchoconstriction.

INTRAPLEURAL PRESSURES AND CARDIOVASCULAR FUNCTION

- Changes in the intrapleural pressure caused by spontaneous mechanical ventilation can independently affect atrial filling (preload), impedance to ventricular emptying (afterload), heart rate, and myocardial contractility.

- Spontaneous inspiration → negative pleural pressure. Reduced intrathoracic pressure is transmitted to the right atrium.
- Systemic venous return depends on the pressure gradient between the extrathoracic veins and the right atrium pressure. Spontaneous inspiration increases this gradient → accelerated venous return → increase in right ventricular preload and stroke volume.
- Right ventricular preload and cardiac output decrease with more positive intrathoracic pressure.
- Changes in the intrathoracic pressure also has effects on the left ventricle. The thoracic aorta is within the thorax, so it is subject to changes in the pleural pressure.
- The transmural pressure of the aorta is the difference between the pressure in the vessel and the pleural pressure.
- During spontaneous (negative pressure) inspiration, there is a decrease pleural pressure > decrease intravascular aortic pressure → increase in transmural pressure → increased LV afterload and reduction in LV stroke volume.
- In acute airway obstruction, inspiratory pleural pressure is already negative, and LV afterload is greatly elevated. A minimal further negative in intrathoracic pressure → acute increase in afterload → pulmonary edema.

Gas Exchange

- Carbon dioxide (CO_2) elimination
  - Dependent on alveolar minute ventilation, adequate pulmonary blood flow (V/Q matching), and effective diffusion across alveolar-capillary membrane
  - Minute ventilation affected by resistance, compliance, and time constants
- Factors affecting diffusion
  - Fick's equation of diffusion

$$dQ/dt = k \times A \times dC/dl$$

$$dQ/dt = \text{rate of diffusion} = \text{diffusion per unit time (mL/min)}$$

where K = diffusion coefficient, A = area available for diffusion, dC = molecule concentration difference across membrane, and dl = length of the diffusion pathway.

- $Paco_2$ determined by $PAco_2$ = CO_2 production/(alveolar ventilation)
- Alveolar minute ventilation (MV_{alv}) = tidal volume (TV_{alv} [in mL]) × respiratory rate (RR; per minute)

Implications of Increasing CO_2

- TV_{alv} falling—increased airway resistance, decreased lung compliance, air trapping, instrumental dead space (ETT)
- CO_2 production rising—sepsis, fever, cold stress
- Physiologic dead space rising—chronic lung disease, overinflation
  - Benefits of increased CO_2 (hypercapnia): ensures maximal spontaneous respiratory drive, decreased complication of hypocarbia, protective effect on the lung, decreased lung injury from decreased RR and tidal volume; also ensures use of decreased minute ventilation

Oxygen Delivery to the Tissues

- Oxygen (O_2) is essential for aerobic metabolism, but there is no oxygen storage system in the tissues.
- A continuous tissue oxygen supply is dependent on metabolic requirements.
- Tissues O_2 delivery therefore depends on:
  - O_2 tension in the arterial blood—adequate pulmonary blood flow, adequate lung function, appropriate V/Q matching
    - V/Q is relatively well matched in the middle zone.
  - Sufficient oxygen-carrying capacity
  - Adequate circulation and tissue perfusion

Control of Gas Exchange—Oxygenation

- Arterial oxygen tension (Pao_2) is determined by:
  - Inspired oxygen concentration and barometric pressure
  - Alveolar ventilation
  - Diffusion of oxygen from alveoli to pulmonary capillaries
  - Distribution and matching of alveolar ventilation and perfusion
  - Control of oxygenation, therefore, depends on:
    - Oxygenation of blood in the pulmonary vein, which is a function of alveolar oxygen pressure (PAo_2), diffusion from the alveolus to the red blood cells (RBCs), right → left intrapulmonary shunting, optimal V/Q matching
    - Can still occur independent of ventilation
- Outcome of acute hypoxemic respiratory failure can be predicted using the oxygenation index (OI):

$$OI = (Fio_2 \times MAP \times 100)/Pao_2$$

where Fio_2 = fraction of inspired oxygen, MAP = mean airway pressure, and Pao_2 = postductal arterial oxygen pressure.

Arterial Hypoxemia

- Results from failure of oxygen uptake in the lungs:
  - Alveolar hypoventilation—respiratory depression, obstructive airway disease, respiratory muscle weakness
  - Impaired oxygen diffusion from the alveoli to the pulmonary capillaries—pulmonary edema
  - V/Q mismatch—pneumothorax, alveolar collapse, pulmonary vasodilators, obstructive airway disease
  - Severity of disease condition assessed by the ratio of arterial oxygen (a) to alveolar oxygen (A) → a/A = Pao_2/PAo_2
  - Normal ratio ≅ 0.9; with severe V/Q mismatch, a/A ratio ≅ <0.2

Oxygen Tension–Based Indices

- Evaluates oxygen saturation of blood in the lungs
- Arterial oxygen tension (Pao_2)
  - Good indicator of oxygenation status
  - Relates to the diffusion properties and lung perfusion
- Pao_2 misleading in the following situations:
  - Hypothermia
  - Carbon monoxide
  - Peripheral shunting
  - Low hemoglobin
  - Decreased cardiac output

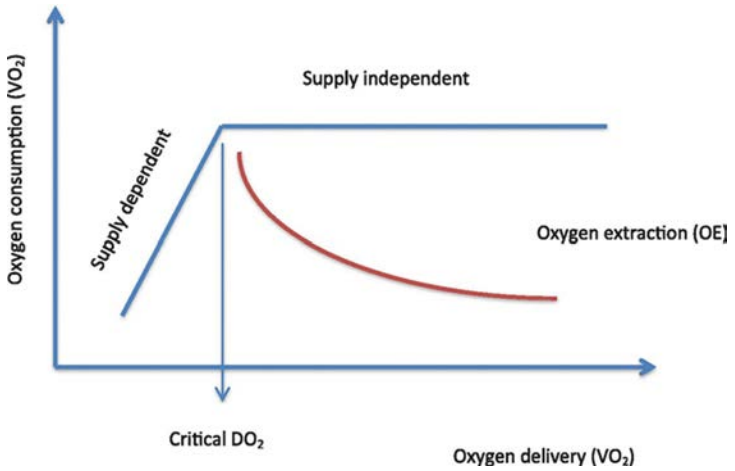

Fig. 12.9 Relationship among oxygen delivery, consumption, and extraction. (From Andersen CC. A theoretical and practical approach to defining "adequate oxygenation" in the preterm newborn. *Pediatrics.* 2017;139(4).)

- Alveolar-arterial oxygen tension difference (A-a gradient)
  - PAo_2 (alveolar oxygen pressure) provides the driving pressure for diffusion into the pulmonary capillary blood (main determinant of Pao_2 [arterial oxygen pressure])
  - $PAo_2 - Pao_2$ (A-a) gradient—describes efficiency of oxygen uptake from alveolar gas to arterial blood in the lungs
  - Alveolar gas equation:

$$PAo_2 = Fio_2 \times (PB - PH_2O) - (Paco_2/R)$$

where Fio_2 = fraction of inspired oxygen; PB = atmospheric pressure; PH_2O = water vapor pressures at 37°C; $Paco_2$ = arterial carbon dioxide pressure; R = respiratory quotient (ratio of carbon dioxide eliminated divided by the oxygen consumed) → value that is typically 0.8

  - $P(A\text{-}a)o_2$ increases indicate problem with transfer of oxygen from alveolus into blood:
    - Oxygen diffusion disorders
    - Decreased V/Q ratios
    - Right → left cardiac shunting
- Oxygen delivery and consumption (Fig. 12.9)
  - Adequacy of tissues oxygenation depends on the rate of O_2 delivered to the tissues (Do_2) and the rate of O_2 consumed by the tissues (Vo_2)
  - Delivery
    - Do_2: volume of O_2 delivered to the systemic vascular bed per minute (the product of cardiac output [CO] and arterial oxygen concentration [Cao_2])
    - $Do_2 = CO \times Cao_2 \times 10$
    - Arterial oxygen content (Cao_2) calculation = oxygen bound to hemoglobin (Hgb) + oxygen dissolved in plasma
    - $Cao_2 = (Hgb\ [g/dL] \times 1.34\ [mL\ of\ O_2/g\ Hgb] \times Sao_2) + (Pao_2 \times 0.003\ [mL\ of\ O_2/dL/mm\ Hg])$
    - Do_2 decreased in low Hgb, low CO, low Sao_2, low Pao_2, and vice versa
  - Consumption
    - $Vo_2 = CO \times (Cao_2 - CVo_2) \times 10$
    - CVo_2 = venous O_2 content

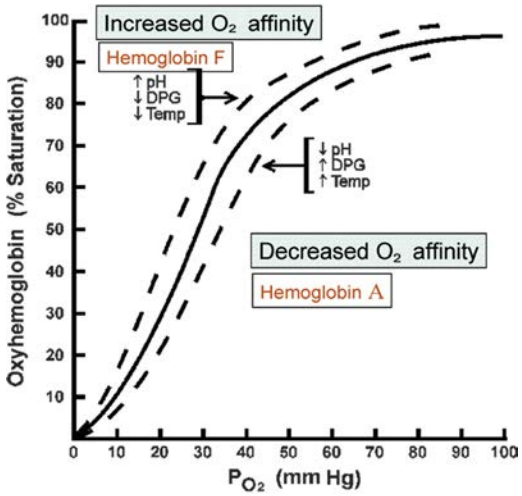

Fig. 12.10 Oxygen dissociation curve. (From Weindling MA. The definition of hypotension in very low birth weight infants during immediate neonatal period. *NeoReviews.* 2007;8:e32–e43.)

    - CVo_2 increased in seizures, hyperthermia, body size; decreased in peripheral shunting, cyanide poisoning, hypothermia

Factors That Affect Oxygen Affinity

See Fig. 12.10.

- pH
- Temperature
- 2,3-Diphosphoglycerate (2,3-DPG) Pco_2
- Fetal hemoglobin
- Carboxyhemoglobin/methemoglobin → shift to left
- Sulfhemoglobin → shift to right

Effect of Altitude on Hemoglobin Affinity for Oxygen

See Fig. 12.11.

- At moderate altitude → right shift of the oxygen dissociation curve due to increased 2,3-DPG
- At extreme altitude

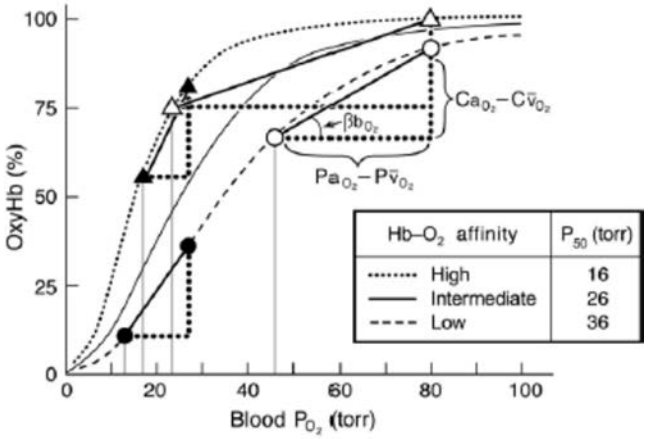

Fig. 12.11 Hemoglobin-oxygen affinity under conditions of moderate and severe hypoxia. (From Storz JF. Mechanisms of hemoglobin adaption to high-altitude hypoxia. *High Alt Med Biol.* 2008;9(2):148–157.)

- Hypoxia → stimulation of peripheral chemoreceptors → hyperventilation → respiratory alkalosis → left shift of the oxygen dissociation curve

Haldane Versus the Bohr Effect

- Haldane effect is a phenomenon where an increase in arterial Po_2 reduces the affinity of the hemoglobin to CO_2
- It describes how oxygen concentrations determine hemoglobin's affinity for carbon dioxide.
- High O_2 concentrations enhance the unloading of CO_2.
- Low O_2 concentrations promote loading of CO_2 onto hemoglobin.
  - *H*emoglobins
  - *A*ffinity
  - *LD*ane—carbon dioxide
- Bohr effect describes how carbon dioxide and H^+ affect the affinity of the hemoglobin for oxygen.
- High CO_2 and H^+ concentrations decrease the affinity of the hemoglobin for O_2, and vice versa.
  - *B*
  - *O*xygen
  - *H*ydrogen
  - *R*eleased in tissue

Pulmonary Function Testing

This is used in the evaluation of lung volumes, airway function, and gas exchange and includes:

- Spirometry
- Lung volume measurements
- Diffusing capacity for carbon monoxide
- Arterial blood gases

Pulmonary function test values are derived from current neonatal ventilators with capabilities for measuring lung mechanics and ventilator parameters. Underreading the tidal volume and inaccuracy in compliance and resistance measurements are some limitations.

- Airway function
  - Simple spirometry—forced vital capacity (FVC), forced expiratory volume in 1 second (FEV_1), ratio of the two volumes (FEV_1/FVC), maximal voluntary ventilation, maximal inspiratory-expiratory pressures, and airway resistance
- Lung volumes and ventilation
  - Functional residual capacity, total lung capacity, residual volume, minute ventilation, alveolar ventilation, dead space
- Blood gases and gas exchange tests
  - Blood gas analysis, capnography—measurement of carbon dioxide (CO_2) concentration in an exhaled breath to determine the end-tidal CO_2 displayed graphically or as a numeric read out (capnometry), and pulse oximetry, which provides continuous information on peripheral oxygen saturation and heart rate (limited by lack of data accuracy during hypoxemia, hyperoxemia, peripheral hypoperfusion, body movements, and the need for regular calibrations)
- Diffusing capacity tests
  - Measurement of diffusing capacity; also known as the transfer factor
- Cardiopulmonary exercise tests
  - Allow causes for a reduced exercise tolerance to be identified
- Spirometry
  - The most frequently used measure of lung function
  - Measure of volume against time
  - Flow volumes—produced when air movement in and out of the lungs occurs during maximal inspiratory effort followed by maximal expiratory effort
  - Limitations
    - Spirometry can detect obstructive abnormalities but may not be sensitive to restrictive abnormalities.
    - Test results can show lung function abnormalities, but they are not disease-specific.
    - A reduction of vital capacity indicates respiratory disease but cannot differentiate between restrictive and obstructive.
- Lung volumes and ventilation
  - Whole-body plethysmography used to measure static lung volumes
  - Not practical in the neonatal intensive care unit (NICU)
  - Other techniques mainly used in the NICU include nitrogen washout, helium dilution
  - Measures total lung capacity, functional residual capacity, and residual volume

Diffusing Capacity Test

- Gives information about the size and integrity of the alveolar blood membrane
- Measures the diffusing of gas across the alveolar membrane determined by surface area, integrity of the alveolar membrane, and pulmonary vascular bed
- Measured using carbon monoxide gas (DLCO), and corrected for the patient's hemoglobin (DLCOc)
- Abnormal diffusing capacity
  - Low total lung capacity (TLC)—intrapulmonary restrictive defect; interstitial lung disease, pulmonary edema, pulmonary vascular disease (e.g., persistent pulmonary hypertension of the newborn [PPHN])
  - High TLC—emphysema
  - Pulmonary emboli should be considered in patient with isolated reduction in DLCOc in absence of any other respiratory cause

- Limitations of diffusing capacity test
  - Surface area in which the diffusion occurs
  - Capillary blood volume
  - Hemoglobin concentration
  - Properties of the lung parenchyma (e.g., alveolar-capillary membrane thickness)

Blood gas interpretation

- pH, $Paco_2$, Pao_2, HCO_3, base excess or base deficit
  - pH < 7.35 indicates acidosis, pH > 7.45 indicates alkalosis; if acidosis, what is value of $Paco_2$ and HCO_3? If $Paco_2$ elevated, acidosis is respiratory
  - Pco_2 abnormal = respiratory problem; Pco_2 < 35 mm Hg = respiratory alkalosis (hyperventilation); Pco_2 > 45 mm Hg = respiratory acidosis (insufficient ventilation)
  - HCO_3—kidneys responsible for excretion of HCO_3; HCO_3 < 22 = metabolic acidosis, HCO_3 > 26 = metabolic alkalosis, base excess (BE) or base deficit (BD); BE > 4 = metabolic alkalosis, BD < 4 = metabolic acidosis
- Check for compensation
  - Assess pH—normal pH + abnormal $Paco_2$ + abnormal HCO_3 = complete compensation
  - pH < 7.35 = acidosis with partial compensation; pH = 7.35–7.40, consider acidosis as primary cause prior to full compensation
  - pH > 7.45 = alkalosis with partial compensation; pH = 7.41–7.45, consider alkalosis as primary cause prior to full compensation
- Check oxygenation (Pao_2)—reliable only if arterial
  - $Pao_2 \cong$ 40–50 mm Hg = mild hypoxemia
  - $Pao_2 \cong$ 30–40 mm Hg = moderate hypoxemia
  - $Pao_2 \cong$ <30 mm Hg = severe hypoxemia
- Overall assessment:

Analyze the primary disorder, oxygenation, and degree of compensation.

- Limitations of blood gas sampling
  - Sampling errors cause alteration in blood gas values.
  - Arterial blood samplings are most reliable for pH, $Paco_2$, and Pao_2.
  - Capillary blood samples are not accurate for Pao_2.
  - The most common sampling errors are dilutions with heparin → lower $Paco_2$ and lower pH and alter Pao_2.
  - Therapeutic cooling → falsely high Pao_2, falsely low pH and $Paco_2$, unless corrected for temperature.
  - Air bubbles → increased Pao_2, lower $Paco_2$, and increased pH.

Suggested Readings

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13 Respiratory Distress Syndrome

WILLIAM MANISCALCO

BASIC INFORMATION

- Respiratory distress syndrome (RDS) is the most common cause of respiratory disease in premature newborns.
  - Over 50% of babies born at less than 29 weeks' gestation will have RDS.
  - Maternal prenatal corticosteroids mitigate the risk of RDS if the pregnancy is between 23 and 34 weeks' gestation and delivery between 24 hours and 7 days after steroid therapy.
  - Maternal diabetes, male sex, and perinatal asphyxia increase the risk of RDS.
- RDS results from a developmental deficiency of pulmonary surfactant, a complex phospholipid/protein mixture that lowers alveolar surface tension.
  - According to the law of Laplace ($P = 2T/r$), as the radius of an alveolus decreases during expiration, an alveolus lacking surfactant will require increased pressure to maintain patency.
  - During expiration, alveoli that lack surfactant collapse, resulting in decreased functional residual capacity, generalized atelectasis, and ventilation-perfusion mismatching. Clinically, positive end expiratory pressure (PEEP) mitigates some of these effects.
  - During inspiration, surfactant deficient lungs have decreased compliance and need increased negative intrathoracic pressure or increased positive pressure to open collapsed alveoli (Fig. 13.1) (Gleason and Juulevaskar, 2018, Fig. 46.5).
  - Shear stress from high inspiratory pressure results in alveolar damage, inflammation, and protein leakage, which can inactivate endogenous surfactant.
- Surfactant is synthesized, packaged into lamellar bodies, and secreted as tubular myelin by alveolar type II cells.
  - Hydrophobic surfactant-associated proteins (SP-B and SP-C) are essential for tubular myelin to spread and form a monolayer on the alveolar surface.
  - The major surface active phospholipid is dipalmitoylphosphatidylcholine, but other minor phospholipids have important roles.
  - Alveolar surfactant is taken up into type II cells, reprocessed, and resecreted.

CLINICAL PRESENTATION

- Prematurity is the essential setting to develop RDS; respiratory symptoms in term patients are unlikely to be RDS, but late preterm infants are still at some risk.
- Typical symptoms include tachypnea, retractions, grunting, and hypoxia.
  - Timing of symptoms is dependent on the degree of prematurity: extremely premature infants may be symptomatic at birth, whereas more mature infants may develop symptoms over the first several hours as endogenous surfactant stores are depleted or inactivated.
  - Retractions reflect increased negative intrathoracic pressure during inspiration, and grunting may prevent alveolar collapse by maintaining positive intrathoracic pressure during expiration.
- Auscultation shows faint breath sounds and fine rales.
- Persistent increased work of breathing may lead to apnea and hypotension.

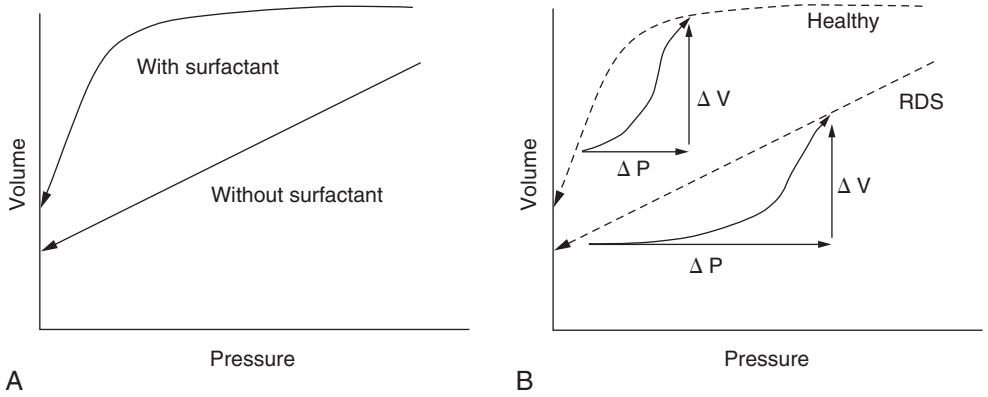

Fig. 13.1 Effects of surfactant on lung pressure volume curves. Expiratory (A) and inspiratory (B, inserts)) pressure volume curves for surfactant sufficient and deficient lungs. In both cases, the pressure required to achieve any lung volume is greater in the surfactant deficient lung. (From Gleason, CA and Juul, SE, Avery's Diseases of the Newborn, 10th ed, 2018.)

- Endogenous surfactant is generally produced in the first 3–4 days of life, mitigating RDS symptoms in some patients.

DIAGNOSIS AND EVALUATION

- A diagnosis of RDS is supported by the clinical setting (prematurity), timing of symptoms (onset in the first few hours of life), and consistent chest x-ray.
  - The chest x-ray has poor lung volumes (diaphragm < 8 ribs), diffuse, homogeneous "ground-glass" appearance, and air bronchograms (Fig. 13.2) (from Gleason and Juul, 2018, Fig. 46.11).
  - Hypoxemia that is responsive to supplemental oxygen supports the diagnosis of RDS rather than cyanotic congenital heart disease.
- Alternative diagnoses include sepsis, transient tachypnea of the newborn, cyanotic congenital heart disease, pneumothorax, and pulmonary hypoplasia.
  - Early onset sepsis, particularly Group B streptococcal sepsis, may closely mimic the timing, symptoms, and chest x-ray of RDS.
  - Distinguishing RDS from cyanotic heart disease may require an echocardiogram.
- Initial evaluation should include an AP chest x-ray (consider a decubitus view if a pneumothorax is suspected). Other components of the initial evaluation may include arterial blood gases, complete blood count (including a differential), blood cultures, and blood glucose.

TREATMENT

- Treatment of RDS rests on three major pillars: maintenance of lung volumes, surfactant replacement, and supportive therapy.
- As summarized by the American Academy of Pediatrics (AAP, 2014), systematic reviews show use of nasal continuous positive airway pressure (nCPAP) shortly after birth, which likely prevents alveolar collapse, is associated with improved survival, reduced need for mechanical ventilation, and decreased bronchopulmonary dysplasia, compared to intubation and surfactant administration.
  - This approach is effective even in extremely premature infants.
  - Patients requiring resuscitation or with poor initial respiratory drive may not be candidates for early nCPAP and may require initial intubation and surfactant.
    - If intubation is required, administration of surfactant followed by rapid extubation (INSURE) is preferable to prolonged ventilation.
  - Developmental outcome may be similar for patients successfully treated with nCPAP and those receiving intubation and surfactant.
- Failure of early nCPAP is common and may reach approximately 50% in patients between 25 and 28 weeks' gestation.
  - A widely accepted definition of nCPAP failure requiring intubation is lacking, but a rising fraction of inspired oxygen (Fio_2) that crosses a threshold of 0.3–0.4 may be considered.
  - These patients may benefit from intubation, surfactant, and rapid extubation, particularly if maternal corticosteroids were not used.
  - nCPAP failure is associated with a substantial increase in mortality and morbidity, including bronchopulmonary dysplasia (BPD).
- Additional approaches such as nasal intermittent ventilation, bubble nCPAP, early caffeine administration, and less invasive surfactant administration need more study.
- Mechanical ventilation for RDS is addressed in Chapter 17.
- Natural surfactants derived from animal sources appear superior to synthetic surfactants.
  - Natural surfactants retain surfactant proteins B and C but not A and D.
  - Currently available natural surfactants seem equally efficacious.
- For patients who are not eligible for early nCPAP or who fail early nCPAP, surfactant administration within 30 minutes of birth (giving time for resuscitation and stabilization) or shortly after failure is superior to delayed, selective surfactant administration.
  - Most patients require only one dose of surfactant, but indications for subsequent doses include rising Fio_2 above 0.3–0.4.
  - Surfactant administration >72 hours of life may not be efficacious.
  - Complications associated with surfactant administration include those due to intubation and positive pressure, occlusion of the endotracheal tube, and delivery of surfactant to the right main stem bronchus.
- Supportive care for patients with RDS includes maintaining a neutral thermal environment; judicious fluid management; careful monitoring of arterial blood gases and continuous oxygen saturation; and attention to nutritional requirements, likely through providing early parenteral nutrition.
  - Fluid management (addressed in Section 7) is important to prevent fluid overload, which may contribute to Patent Ductus Arteriosis (PDA), and hypovolemia due to increased insensible water loss.

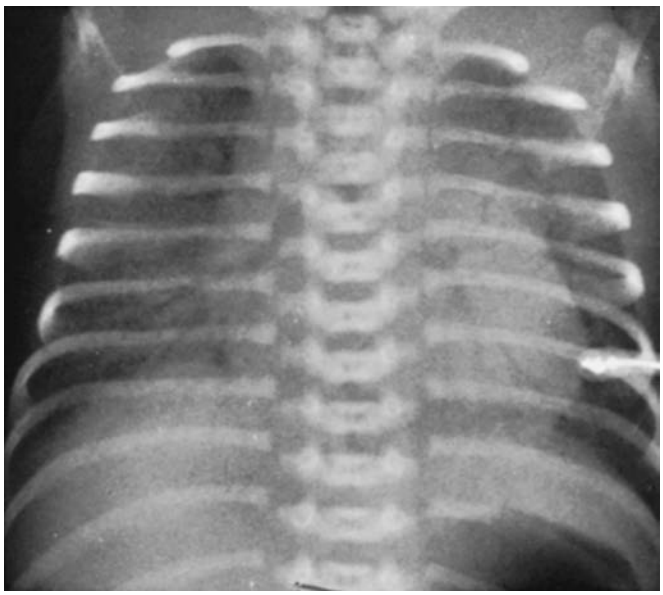

Fig. 13.2 Chest x-ray of respiratory distress syndrome (RDS). The chest radiograph of a patient with RDS shows decreased lung volume, air bronchograms and a diffuse reticulaogranular appearance. (From Gleason CA and Juul SE. Avery's Diseases of the Newborn, 10th ed, 2018, Fig. 46.11.)

- Careful monitoring of blood gases will avoid hyperoxia, hypoxia, and overventilation, which are associated with lung injury and increased mortality.
- Data are lacking on the management of hypotension in patients with RDS, particularly those with good peripheral perfusion.
- Because of difficulty distinguishing between RDS and early onset sepsis, antibiotics are routinely prescribed for premature patients with respiratory symptoms.

- Complications of RDS include air leaks, such as interstitial emphysema, and chronic lung injury or BPD.
  - Despite improvements in RDS prevention and management, the incidence of BPD remains high in very premature infants, possibly due to increased survival.

Transient Tachypnea of the Newborn

BASIC INFORMATION

- Results from delayed clearance of fetal lung fluid
- Increased risk with C/S, IDM, precipitous delivery
- Can be difficult to differentiate from more serious pathophysiology such as RDS or pneumonia

CLINICAL PRESENTATION

- Tachypnea present at birth, slowly improves over 2–3 days
- At risk for aspiration with feeds due to tachypnea

DIAGNOSIS AND EVALUATION

- Typically clinical diagnosis unless significant tachypnea
- O_2 saturation is normal or slightly decreased
- The chest radiograph is hyperinflated, pulmonary edema

TREATMENT

- Supportive
- Supplemental oxygen occasionally needed to avoid hypoxia
- Consider NG feeds if respiratory rate >70 breaths per minute (bpm) or IVF if >80 bpm to avoid aspiration until tachypnea resolves
- If symptoms persist or worsen, assess for infectious, cardiac, or other serious pulmonary etiology

Bronchopulmonary Dysplasia

BASIC INFORMATION

- Bronchopulmonary dysplasia (BPD) is a chronic lung disease of premature infants that results from the confluence of lung immaturity with the injurious side effects of respiratory interventions necessary to support premature infants.
- The incidence of BPD is inversely related to gestational age and has not changed appreciably since the advent of surfactant therapy, perhaps due to increased survival of more immature infants.
  - The incidence varies among institutions and with various BPD definitions.
  - A genetic predisposition is suspected, but candidate genes have not been identified.
- Patients who develop BPD are generally in the late canalicular to early saccular stage of lung development (22–32 weeks), which is characterized by:
  - expansion of distal respiratory surfaces area; extensive microvascularization of respiratory units; reduced interstitial space; and apposition of the distal capillaries to the respiratory epithelium;
  - surfactant deficiency, which results in increased surface tension. postnatal alveolar collapse, poor compliance, and need for mechanical ventilation;
  - deficiency of antioxidant enzymes (superoxide dismutase, catalase, etc.) and nonenzymatic antioxidant defenses;
  - immature mechanisms to remove alveolar fluid;
  - immature immunologic responses to prenatal and postnatal infections;
  - poor respiratory drive and a compliant chest wall, resulting in the need for positive pressure, including mechanical ventilation, even with minimal RDS.
- The wide variation in individual occurrence of BPD has not been explained.
- The pathophysiology of BPD is complex (see Gleason and Juul, 2018, Fig. 48.1), involving the intrinsic immaturity of the premature lung and several extrinsic factors, including relative hyperoxia, barotrauma/volutrauma, infection, inflammation, and pulmonary edema.
  - Reactive oxygen species (ROS) produced by cellular metabolism of oxygen may overwhelm detoxifying mechanisms, resulting in damage to cell protein, lipids, and nucleic acids.
  - Increased oxidized lipids and proteins are found in the blood of patients who are treated with oxygen in the delivery room or who develop BPD.
  - Elevated oxygen use in resuscitation and longer term cumulative oxygen exposure predict BPD. Interpretation of these studies is complicated by varying definitions of BPD, combined outcomes of BPD and death, and varying methods to measure oxygen exposure.
  - Studies of oxygen saturation suggest higher targets are associated with increased lung disease. However, appropriate oxygen saturations for premature infants are not known. The increased mortality at low saturations must be balanced with increased oxidant injury at higher saturations.
- Mechanical ventilation, particularly resulting in hyperinflation, is associated with BPD.
  - Premature infants with hypocarbia have a higher incidence of BPD.
  - Mechanical ventilation is associated with air leaks (pneumothorax, pulmonary interstitial emphysema, etc.), which may contribute to BPD.
  - Mechanical ventilation resulting in hyperinflation, particularly in the presence of atelectasis, damages the pulmonary epithelium and endothelium, increases capillary leakage, and augments inflammation in experimental animals.
  - Institutions with less invasive approaches to respiratory support have a lower incidence of BPD.

- The trend toward less invasive early respiratory support has been associated with a decrease in the incidence of severe BPD.
- Infection, especially postnatal sepsis/pneumonia, increases the risk for BPD.
  - Respiratory colonization with *Ureaplasma* sp. is associated with BPD, but the role of specific antimicrobial therapy is not known.
  - Postnatal sepsis/pneumonia is strongly associated with an increased risk for BPD.
  - A prenatal inflammatory response to maternal chorioamnionitis may be mechanistically linked to BPD, but meta-analyses fail to show a strong correlation.
- The definition of BPD has evolved as less mature infants survived, surfactant therapy became available, and the pathology has transformed from fibrosis to impaired alveolar and vascular development.
  - The current definition of BPD depends on gestational age, use of oxygen and positive pressure, and the postnatal age (see Gleason and Juul, 2018, Table 48.1).

CLINICAL PRESENTATION

- The current definition of BPD depends on respiratory support at 36 weeks or 56 days, but the typical clinical presentation occurs much sooner. Clinical characteristics include:
  - A premature infant, generally <32 weeks, who required supplemental oxygen and mechanical ventilation to treat the initial lung immaturity or surfactant deficiency.
  - Infants requiring minimal respiratory support, including only nCPAP, may develop BPD. Patients treated with early nCPAP have a lower incidence of death or BPD, but ~50% fail nCPAP and require intubation and surfactant.
  - Increased work of breathing and need for supplemental oxygen that lasts beyond 1–2 weeks of life and that do not resolve or may worsen.
  - Highly variable chest x-ray, ranging from diffuse haziness to areas of hyperinflation, atelectasis, and increased interstitial markings in more severe cases.

DIAGNOSIS AND EVALUATION

- BPD must be distinguished from a PDA or sepsis/pneumonia, which may present as worsening respiratory status in the first several weeks of life.

TREATMENT

- Treatment and prevention modalities include pharmacologic, respiratory, and supportive measures. Many current therapies lack a strong evidence-based rationale.
  - Caffeine initiated within the first 48–72 hours of life is associated with a reduced risk for BPD, possibly through effects on minute ventilation and CO_2 sensitivity.
  - Vitamin A supplementation reduces the risk of BPD when administered during the first month of life. The benefit, however, is small.
  - Systemic dexamethasone reduces the risk of BPD in mechanically ventilated infants. Infants treated with pharmacologic doses at less than one week of life have increased risk of cerebral palsy and GI perforations. Dexamethasone treatment after one week of life is associated with smaller brain volumes in adolescence. The AAP recommends that high dose dexamethasone not be used routinely to prevent BPD. Investigations into various dexamethasone treatment regimens, different glucocorticoids, and improved patient selection may clarify the balance between the risks and benefits of glucocorticoid therapy.
  - Inhaled glucocorticoids may have a role in preventing BPD, but data on long-term risks are lacking.
  - Diuretics, particularly furosemide and thiazides, are frequently used in established BPD. Evidence suggests short-term improvements in pulmonary mechanics or oxygenation, but salutary long-term effects on BPD have not been proven.
  - Beta-2 agonist bronchodilators may provide short-term benefits to ventilated infants with BPD, but evidence for a long-term effect is lacking.
- The application of respiratory support to treat BPD is covered in Chapter 17.
- Pulmonary hypertension (PH) is common in BPD and presents management challenges.
  - Depending on the severity of BPD and echocardiogram criteria, 5%–29% of patients with BPD have PH.
  - The etiology of PH is complex, involving hyperoxia, hypoxia, and other prenatal and postnatal factors that disrupt normal vascular development.
  - PH is a relative late finding in BPD, occurring after ~6 weeks, and is a predictor of mortality.
  - No controlled trials of PH prevention or treatment modalities are definitive, but careful attention to preventing hypoxia, hypercarbia, and use of vasodilators in selected patients may be useful.
- Supportive therapies that may affect BPD include fluid and nutrition management and treatment of a PDA.
  - Pulmonary edema may increase the risk of BPD, but the data regarding restrictive fluid management to prevent or ameliorate established BPD are mixed. Fluid restriction that diminishes nutritional intake may be counterproductive.
  - Poor postnatal growth is common in patients with BPD. Energy requirements in BPD may be 20%–25% greater than normal, requiring high caloric density feeding to achieve acceptable growth.
  - Patients with PDAs are at increased risk for BPD, possibly due to pulmonary edema and decreased lung compliance. Please see Section 3 for therapy of PDA.
- Patients with BPD are at risk for the following postdischarge outcomes:
  - Increased mortality, particularly in the presence of pulmonary hypertension or respiratory infections such as respiratory syncytial virus (RSV);
  - Persistent respiratory dysfunction, including airway hypersensitivity;
  - Poor postdischarge growth, although confounding variable may contribute;
  - Impaired cognitive and motor function, cerebral palsy, deafness, and blindness that correlate with the severity of BPD.

Suggested Readings

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Questions

1. Surfactant proteins B and C are essential components for surfactant replacement because they:
   a. Increase surfactant spreading at the air-liquid interface.
   b. Coat bacteria and viruses to increase innate immunity.
   c. Detoxify oxygen radicals and reduce injury to alveolar type II cells.
   d. All of the above.

2. Which of the following recommendations about postnatal glucocorticoid use in BPD are contained in the 2010 AAP policy statement?
   a. Therapy with high-dose dexamethasone cannot be recommended.
   b. There is insufficient evidence to make a recommendation regarding treatment with low-dose dexamethasone.
   c. Early hydrocortisone treatment may be beneficial in a specific population of patients; however, there is insufficient evidence to recommend its use for all infants at risk of BPD.
   d. All of the above.

14 Aspiration, Pneumonia, and Persistent Pulmonary Hypertension

NARAYAN PRABHU IYER and DEEPAK KUMAR

Meconium Aspiration

1. Background
   a. Meconium aspiration syndrome (MAS) is the occurrence of respiratory disease, otherwise unexplained, following aspiration of meconium-stained amniotic fluid (MSAF).
   b. MSAF occurs with 8%–25% live births of which 2%–10% develop MAS.
   c. Meconium first appears in fetal intestines between 10–16 weeks' gestation and consists of water, gastrointestinal secretions, cellular debris, bile, mucus, blood, lanugo, and vernix.
   d. Meconium passage is rare between 20–34 weeks' gestation; the incidence of MSAF increases after 38 weeks and reaches peak (30%) at 42 weeks' gestation.
   e. Increased amounts of motilin and parasympathetic innervation are thought to be the reasons behind increased incidence of MSAF in postterm infants compared to the rare passage of meconium in preterm infants.
   f. Fetal hypoxia, with the resultant intestinal ischemia, can induce intestinal hyperperistalsis and relaxation of anal sphincter leading to in utero passage of meconium.
   g. Most MSAF are not associated with fetal hypoxia, are not depressed at birth, and do not develop MAS. But in the presence of fetal hypoxia (i.e., reduced/abnormal fetal heart tones) there is greater risk of developing MAS and poor perinatal outcome. The risk of poor neonatal outcome in the presence of abnormal fetal heart tones is, however, similar in infants born with MSAF compared with infants born with clear AF. Therefore presence of abnormal fetal heart tones is a better predictor of poor outcomes than the presence of MSAF.
   h. Pathophysiology
      1) Lung abnormalities of MAS are related to airway obstruction, reduced lung compliance (due to surfactant inactivation), and parenchymal lung damage (due to inflammation induced by meconium).
      2) Airway obstruction is often partial, causing a ball valve mechanism which in turn leads to increased expiratory resistance and increased functional residual capacity (air trapping).
      3) Chronic in utero hypoxemia, which is typically associated with MSAF and MAS, is also associated with pulmonary vascular remodeling and persistent pulmonary hypertension (PPHN).
2. Clinical features
   a. MAS has a wide spectrum, ranging from mild respiratory disease to severe respiratory failure requiring extracorporeal membranous oxygenation (ECMO).
   b. Infants with MAS have respiratory distress and in severe cases, show signs of air trapping such as barrel chest and prolonged expiratory phase. Thick meconium and extensive staining of meconium is associated with more severe MAS.
   c. PPHN is also associated with severe MAS.
   d. Symptoms of pneumonitis peak over 1–3 days after birth and resolve over the next 1–2 weeks.
3. Diagnosis and evaluation
   a. Chest x-ray
      1) Infants with MAS, especially when associated with thick MSAF, have coarse, heterogeneous patchy infiltrates on chest x-ray.
      2) Areas of hyperaeration are also seen.
      3) Increased incidence of pneumothorax, pneumomediastinum, and sometimes pleural effusion.
      4) Severity of chest x-ray findings may not correlate with clinical severity.
   b. Evaluation of PPHN using cardiac echocardiogram.
4. Treatment
   a. Prevention
      1) Early intervention when fetal hypoxia is noted.
      2) Reducing post-term (≥41 weeks) deliveries.
      3) Intrapartum amnioinfusion not associated with improved outcomes in clinical studies.
      4) Oral and nasopharyngeal suction at the time of delivery, prior to the first breath, does not reduce MAS incidence or severity.
      5) Routine tracheal intubation and suction after delivery is not recommended. As in all infants, airway suction and clearance remain part of basic resuscitation when respiration is not established following stimulation.
   b. Supportive treatment
      1) Management of temperature, electrolyte imbalance, acidosis, hypotension, reduced cardiac function, coagulopathy, and renal dysfunction—which are all associated with fetal hypoxia-ischemia.
      2) Hypothermia for moderate to severe hypoxic ischemic encephalopathy.
      3) Correction of hypoxia using mechanical ventilation. Prolonged expiratory time and heavy sedation

are often required. High frequency ventilation plus inhaled nitric oxide have greater efficacy together than when used alone in MAS.
4) Exogenous surfactant decreases the need for ECMO if given early.
5) Treatment of MAS-associated PPHN (discussed later in this chapter).
6) ECMO: in severe, refractory respiratory failure, ECMO is the final rescue treatment. Survival rate in infants with MAS who require ECMO is >95%.

Aspiration Pneumonia (Excluding Meconium Aspiration)

1. Background
   a. Perinatal aspiration: due to aspiration of amniotic fluid (including infected amniotic fluid), maternal blood, and vernix.
   b. Postnatal aspiration: preterm infants with swallowing difficulties or displaced nasogastric tube, severe gastroesophageal reflux disease (GERD), laryngeal clefts, esophageal atresia with tracheoesophageal fistula.
2. Clinical features
   a. Perinatal aspiration presents with respiratory distress soon after birth and can be indistinguishable from meconium aspiration syndrome.
      1) Aspiration of maternal blood can be confused for pulmonary hemorrhage. Compared to infant with aspirated maternal blood, infants with pulmonary hemorrhage often have significant hemodynamic instability and coagulopathy.
   b. Postnatal aspiration presents with desaturation, apnea, bradycardia, and respiratory distress.
3. Diagnosis and evaluation
   a. History of antepartum hemorrhage and presence of meconium are some historical clues to the diagnosis in perinatal aspiration.
   b. Infants with postnatal aspiration, especially if recurrent, often require extensive work-up for GERD, airway anomalies, dysphagia evaluation, and neurologic evaluation.
4. Treatment
   a. Antibiotics.
   b. Respiratory support as indicated.

Neonatal Pneumonia

1. Background
   a. Pneumonia remains a major cause of morbidity and mortality, especially in the developing countries.
   b. Incidence: 1% in term infants; 10% in preterm infants; autopsy reports suggest pneumonia as a cause in 20%–60% of stillbirths and liveborn neonatal deaths combined.
   c. Pneumonia classified as early if presenting within 3 days after birth or late if presenting after 3 days.
   d. Congenital pneumonia is a subset of early pneumonia and can be acquired transplacentally (hematogenous spread) or through infected amniotic fluid (ascending infection from birth canal).
   e. Ventilator-associated pneumonia (VAP) is a common cause of postnatal pneumonia.
   f. Causes
      1) Transplacental: most commonly due to viral agents: CMV, rubella, varicella-zoster, HSV, HIV, enterovirus, and influenza. *Listeria monocytogenes, Mycobacterium tuberculosis,* and *Treponema pallidum* are the bacterial agents causing congenital pneumonia.
      2) Perinatal (congenital, nontransplacental): Group B streptococcus (GBS); gram-negative organisms account for the majority (*Escherichia coli*, *Klebsiella*, *Haemophilus*, *Pseudomonas*, *Bacteroides*, *Proteus*, *Citrobacter*, and *Serratia*); *Chlamydia trachomatis.*
      3) Postnatal: *Staphylococcus aureus*, GBS, and gram-negative bacteria (*Klebsiella*, *Pseudomonas*, *Serratia*, *Acinetobacter*, etc.). CMV can be acquired postnatally through breast milk or contaminated blood. RSV, influenza, parainfluenza, adenovirus, and enteroviruses are important viral causes.
2. Clinical features
   a. There is often a history of maternal fever, skin rash (especially mothers with secondary syphilis), and joint swelling in infants with transplacentally acquired infection.
   b. Infants with listeriosis are often born with preterm labor and greenish brown discoloration of the amniotic fluid. Their mothers may have a history of ingesting food contaminated with listeria including unpasteurized milk, raw sprouts, cold and uncooked hot dogs, soft cheeses, and smoked seafood.
   c. Perinatally acquired disease presents with respiratory distress and/or signs of sepsis at birth or within the first two days after birth.
      1) *Ureaplasma urealyticum* in preterm infants is associated with chronic lung disease.
      2) *Chlamydia trachomatis* pneumonia usually presents as staccato cough, apnea, upper respiratory symptoms, often with antecedent conjunctivitis, between 2–8 weeks after birth.
   d. Postnatally acquired pneumonia is most often seen in infants on invasive mechanical ventilation (IMV).
      1) HSV pneumonia is most often due to HSV type II.
      2) Viral agents such as RSV and influenza are associated with fever, respiratory distress, and sometimes apnea.
      3) Fungal disease is usually seen in the context of disseminated disease and is more often seen in very low birth weight infants (VLBW) with prolonged antibiotic use, prolonged use of IMV, presence of central line, intravenous nutrition, and postnatal use of corticosteroids.
      4) Suppurative pneumonia: *S. aureus*, *Klebsiella*, *Pseudomonas*, *E. coli*, and fungi can cause suppurative pneumonia which is characterized by necrosis of lung parenchyma, microabscess formation, and formation of multiple air-filled pneumatoceles.

3. Diagnosis and evaluation
   a. History of maternal illness is often beneficial in transplacentally and perinatally acquired pneumonia.
   b. Chest x-ray is usually nonspecific.
      1) Interstitial pneumonitis is seen with viral infections, listeria, mycoplasma and chlamydia. Pneumonia due to chlamydia is also associated with radiologic signs of hyperinflation.
      2) Congenital syphilis leads to pneumonia alba, a pathologic description for pale, firm, and enlarged lungs seen in autopsy. Chest x-ray often shows nodular and band-like opacities bilaterally.
      3) Most bacterial pneumonias have a nonspecific lobar appearance.
      4) Suppurative pneumonia is associated with pneumatoceles, usually thin-walled, and rarely with signs of empyema and lung abscess.
      5) Tracheal aspirates are usually diagnostic, although it is often difficult to distinguish active infection from colonization. The Centers for Disease Control and Prevention (CDC) definition of VAP has evolved over the past few years, and newer terminology of ventilator-associated events (VAE) is now in use in adults.
      6) Viral panels on nasopharyngeal swabs in infants with signs of upper respiratory symptoms/history of contacts.
      7) High index of suspicion is often required for the diagnosis of postnatal CMV and HSV. These require culture or polymerase chain reaction (PCR) analysis.
4. Treatment
   a. Initially broad-spectrum antibiotics.
   b. Influenza pneumonia requires early initiation of oseltamivir, often with antibiotics against secondary bacterial infections.
   c. Management of specific agents: HSV, CMV, *Mycoplasma*, *Ureaplasma*, *Listeria*, *Chlamydia*, and fungi is available.

Persistent Pulmonary Hypertension (PPHN)

1. Background
   a. Persistent elevation of the pulmonary arterial pressures (or pulmonary vascular resistance [PVR]) during the transition from in utero circulation to postnatal circulation.
   b. Normally, there are four phases to transition of PVR:
      1) In utero phase: PVR is higher than systemic vascular resistance. Oxygenated blood from placenta preferentially flows from inferior vena cava to right atrium, left atrium, left ventricle, aorta, and head and neck vessels. Venous return from head and neck flows through superior vena cava and preferentially goes to right ventricle, pulmonary artery, ductus arteriosus (DA), and descending aorta supplying left upper extremity and lower half of the body.
      2) Immediate phase: happens in the first minutes after birth when lungs are distended with fresh air which is accompanied by a rapid reduction in PVR. Shear stress to pulmonary arteries and oxygenation induces endothelial cell nitric oxide synthase (eNOS) which in turn leads to release of nitric oxide (NO). Oxygen and NO lead to further reduction in PVR. NO acts by inducing cyclic guanosine monophosphate (cGMP) which in turn activates protein kinase that decreases intracellular calcium leading to smooth muscle relaxation.
      3) Fast phase: lasts 12–24 hours after birth. NO and prostaglandin I2 (PGI2) cause progressive reductions in PVR, which falls rapidly.
      4) Final phase: lasts for, on average, 6–8 weeks up to several months and is characterized by pulmonary vascular remodeling.
   c. Causes of PPHN
      1) Pulmonary vasoconstriction postnatally, but normal pulmonary vascular development: acute perinatal hypoxia, meconium aspiration syndrome (MAS), sepsis, respiratory distress syndrome (RDS), hypothermia. Increased PVR is transitory and reversible, and prognosis is generally good.
      2) Fixed decreased pulmonary arteriolar diameter: chronic hypoxia, in utero closure of DA, chronic pulmonary venous hypertension (as in total anomalous pulmonary venous return [TAPVR]), and sometimes idiopathic disease process can stimulate thickening of smooth muscle layer in the intraacinar and alveolar arteries. Prognosis is poor.
      3) Decreased cross-sectional area of pulmonary vascular bed: hypoplasia of alveoli and associated vasculature as in congenital diaphragmatic hernia (CDH), lung hypoplasia (idiopathic or associated with renal problems), thoracic dystrophies, or oligohydramnios due to prolonged rupture of membranes). Poor prognosis.
      4) Functional obstruction of pulmonary blood flow: polycythemia, hyperfibrinogenemia. Usually good prognosis.
2. Clinical features
   a. Respiratory distress and labile hypoxemia, often disproportionate to pulmonary parenchymal disease.
   b. Right ventricular heave, single or closely split and loud S2, low-pitched systolic murmur.
3. Diagnosis and evaluation
   a. Preductal oxygen saturations are higher than the postductal oxygen saturation when shunting at ductal level. This is also reflected in the arterial partial pressure of oxygen (Pa_{O_2}) difference between pre- and postductal blood samples.
   b. Hyperoxia test: exposure to 100% oxygen for 5–10 minutes results in increase in Pa_{O_2} to >100 in PPHN but not so in cyanotic heart lesions.
   c. Echocardiography: rules out cyanotic heart lesions and demonstrates increased right ventricular pressures, deviation of interventricular septum to the left, right to left shunting across PDA, and intracardiac shunt across foramen ovale.
   d. Chest x-ray may reveal opacities and hyperinflation in MAS or lobar opacities in pneumonia.

4. Treatment
   a. Supportive: correct shock, polycythemia, hypoglycemia, hypothermia, metabolic acidosis, and hypotension.
   b. High ambient oxygen while avoiding hyperoxemia, and optimal mechanical ventilation. High mean airway pressures can increase the resistance inside pulmonary vasculature and worsen pulmonary arterial hypertension. While respiratory alkalosis can counter the effects of metabolic acidosis, the resultant low carbon dioxide can cause reduced cerebral blood flow and the strategy of hyperventilation is, therefore, to be avoided.
   c. Specific pulmonary vasodilators:
      1) Inhaled nitric oxide (iNO): at doses <40 parts per million (ppm), iNO specifically dilates pulmonary vasculature. It preferentially vasodilates ventilated alveolar vessels, thus reducing ventilation perfusion mismatch. Combination of high-frequency ventilation and iNO have additive effects. iNO reduces the need for ECMO.
      2) Phosphodiesterase inhibitors inhibit the degradation of cGMP or cyclic adenosine monophosphate (cAMP) and reduce intracellular calcium and PVR. Sildenafil inhibits PDE5 and milrinone PDE3.
      3) Endothelin receptor antagonists (bosentan) block the action of endothelin 1, a potent vasoconstrictor.
   d. ECMO
      1) For infants who have failed medical management, including the use of pulmonary vasodilators, ECMO is offered. Success of ECMO depends on the underlying cause of PPHN and has an overall survival rate of >80%.
   e. Outcome
      1) Prematurity, acidosis, and hypoxia prior to ECMO and need for ECMO >7 days are independently associated with poor prognosis and higher mortality.
      2) Long-term sequelae include chronic lung disease (25%), major neurologic abnormalities (13%), and poor growth. Infants with CDH have worse prognosis than more reversible causes of PPHN such as MAS.

Suggested Readings

El Shahed AI, Dargaville PA, Ohlsson A, Soll R. Surfactant for meconium aspiration syndrome in term and late preterm infants. *Cochrane Database Syst Rev*. 2014;12:CD002054.

Lakshminrusimha S, Konduri GG, Steinhorn RH. Considerations in the management of hypoxemic respiratory failure and persistent pulmonary hypertension in term and late preterm neonates. *J Perinatol*. 2016;36(Suppl 2):S12–19.

Wyckoff MH, et al. Part 13: Neonatal Resuscitation: 2015 American Heart Association Guidelines Update for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. *Circulation*. 2015;132(18 Suppl 2):S543–S560.

Questions

1. A 41-week-old infant is born after induction of labor. There was thick particulate meconium at delivery. The neonatal resuscitation team that received the infant did initial resuscitation by stimulating the infant, and when there was no respiratory effort, initiated positive pressure ventilation (PPV). The infant eventually required endotracheal intubation and admission to the NICU. A chest x-ray revealed coarse bilateral opacities. Which of the following strategies is recommended in the further management of this infant?
   a. Lung lavage with dilute surfactant
   b. Exogenous surfactant at standard doses
   c. Respiratory alkalosis using high ventilator rates
   d. Routine use of muscle relaxants

2. A preterm infant born at 26 weeks' gestation is now 3 days old and you are considering initiating trophic enteral feeds. Mom is known to be seropositive for cytomegalovirus (CMV) and she asks you about the risk of transmission of CMV through breast milk and the risk of pneumonia due to CMV. What is your response?
   a. CMV is eliminated by freeze-thawing process.
   b. CMV only rarely causes pneumonia, postnatally.
   c. CMV can cause interstitial pneumonia in preterm infants but can be eliminated by short-term pasteurization.
   d. Provide preterm formula as the risk of pneumonia is very high.

15 Pleural Disorders and Additional Causes of Respiratory Distress

NARAYAN PRABHU IYER and DEEPAK KUMAR

Extrapulmonary Lesions Causing Respiratory Distress

CONGENITAL DIAPHRAGMATIC HERNIA (CDH)

1. Background
   a. Due to failure of the development of the posterolateral portion of the diaphragm, which results in persistence of pleuroperitoneal canal or foramen of Bochdalek.
   b. Abdominal viscera can slide through the pleuroperitoneal canal and occupy the chest cavity, compress developing lung tissue, and lead to ipsilateral pulmonary hypoplasia.
   c. The hypoplastic lung lacks all three components: alveoli, normal bronchiolar branching pattern, and pulmonary vascular structures. Remaining pulmonary arteries show muscular hypertrophy and postnatal pulmonary hypertension.
2. Clinical features
   a. Varying degrees of respiratory distress and failure and pulmonary hypertension.
   b. Smaller lesions could be asymptomatic at birth and are often diagnosed incidentally.
3. Diagnosis and evaluation
   a. Prenatal diagnosis is usually possible with demonstration of herniated abdominal viscera and mediastinal shift.
   b. Prenatal prognostic measures have been described to risk stratify fetuses with CDH. These include the lung-to-head ratio (LHR) and volumetric analyses of lung. Different predictive thresholds for LHR have been proposed, and an LHR of <0.85 has been associated with 100% mortality.
   c. Postnatal evaluation for other congenital and genetic abnormalities is also performed.
4. Treatment
   a. Immediate intubation and nasogastric tube decompression of stomach and bowels.
   b. Initial aim is to mitigate pulmonary hypertensive crisis and support gas exchange.
   c. "Gentle ventilation" in the form of permissive hypercarbia is practiced in order to minimize lung injury.
   d. Extracorporeal membrane oxygenation (ECMO) is required in some infants with CDH, if the standard therapy fails. See Chapter 17.
   e. Surgical repair is delayed until pulmonary hypertension improves.
   f. Survival for isolated CDH varies from 70%–90% and is lower (50%) for infants who require ECMO.

EVENTRATION OF THE DIAPHRAGM

1. Background
   a. May be congenital or acquired.
   b. Acquired causes include operative trauma and birth trauma.
2. Clinical features
   a. Respiratory distress, occasionally requiring mechanical ventilation.
3. Diagnosis
   a. Chest x-ray.
   b. Fluoroscopy showing paradoxical movement of the diaphragm.
   c. Ultrasound of chest showing lack of movement of hemidiaphragm (preferred initial diagnostic test).
4. Treatment
   a. Plication of diaphragm with nonabsorbable sutures to create a taut diaphragm.

SPINAL CORD INJURY INCLUDING CORD TRANSECTION

1. Background
   a. Spinal cord injury in the form of phrenic nerve injury and partial or complete spinal cord transection are rare causes of respiratory distress.
2. Clinical features
   a. Respiratory distress, usually unilaterally, usually on the right side, and often associated with brachial plexus palsy.
   b. Bilateral phrenic nerve injury and complete spinal cord transection are usually associated with respiratory failure and poor respiratory effort requiring mechanical ventilation.
3. Diagnosis
   a. Fluoroscopic examination of the chest shows paradoxical movement of the diaphragm in unilateral phrenic nerve palsy.
   b. Ultrasound of the diaphragm can be diagnostic but sometimes phrenic nerve conduction studies are required.

4. Treatment
   a. Noninvasive and occasionally invasive mechanical ventilation is required to support the infants.
   b. Phrenic nerve injury can improve over time, but many infants require diaphragm plication. Early demonstration of improvement and early plication is associated with better outcomes.

Airway Obstruction Causing Respiratory Distress

CERVICAL VASCULAR ANOMALIES

1. Background
   a. Lymphatic malformations are the most common cervical vascular malformations noticed in the newborn period.
   b. They generally represent sequestered lymphatic channels that failed to communicate with larger lymphatics or draining veins.
2. Clinical features
   a. Nearly half present prenatally or at birth while the rest become evident during the first decade of life.
   b. The cysts can be macrocystic, microcystic, or mixed in morphology.
   c. Lymphatic malformations shrink over time, but most do not and some increase in size with intracystic hemorrhage or infection.
3. Diagnosis
   a. Prenatal or postnatal ultrasound.
   b. MRI of neck to describe extent of the malformation and its effect on surrounding tissues.
4. Treatment
   a. Massive malformations require tracheotomy.
   b. Macrocystic lesions are amenable to sclerotherapy with OK432, doxycycline, sirolimus, and ethanol. Microcystic lesions may respond to bleomycin.
   c. Surgical excision: often there is recurrence and multiple surgeries are required.

PYRIFORM APERATURE STENOSIS

1. Background
   a. Rare; due to overgrowth of medial nasal process of maxilla.
   b. Pyriform aperture is the narrowest region of nasal passage, and even small decreases in cross-sectional areas can cause significant respiratory distress.
2. Clinical features
   a. Mild nasal congestion to apnea and severe respiratory distress.
   b. Can be associated with midline maxillary incisor and other midline abnormalities.
3. Diagnosis
   a. Nasal endoscopy.
   b. CT scan.
4. Treatment
   a. Nasal decongestion.
   b. Surgical excision.

CHOANAL ATRESIA

1. Background
   a. Congenital absence of communication between the posterior nasal cavity and the nasopharynx.
   b. Most commonly caused by a bony plate at the posteriors nasal choana.
2. Clinical features
   a. Females are affected more and unilateral disease is more common than bilateral disease.
   b. Respiratory distress especially during feeding.
   c. Unilateral disease can present as persistent rhinorrhea.
   d. More than half, especially with bilateral disease, have associated abnormalities such as the CHARGE syndrome (Coloboma, Heart defect, choanal Atresia, Retarded growth, Genitourinary and Ear anomalies).
3. Diagnosis
   a. CT scan.
4. Treatment
   a. Surgery to open posterior choanae.

GLOSSOPTOSIS (RELATIVE MACROGLOSSIA)

1. Background
   a. Seen most commonly with Pierre Robin sequence (PRS).
   b. PRS represents a sequence of events beginning with arrest of mandibular development and micrognathia. The tongue rests higher in the oral cavity and prevents fusion of palatal shelves.
2. Clinical features
   a. Micrognathia, glossoptosis, and U-shaped cleft palate.
   b. Presents with respiratory distress that is more severe in supine position and worsens during sleep.
   c. Often associated with syndromes: most common being Stickler syndrome.
3. Diagnosis
   a. Clinical exam.
   b. 3-D reconstruction of face may be required to better assess the micrognathia.
4. Treatment
   a. Wait and watch: airway obstruction generally improves by the time baby has doubled his or her weight.
   b. Tracheotomy.
   c. Mandibular distraction osteogenesis in selected patients.

MACROGLOSSIA

1. Background
   a. Tongue can be enlarged uniformly or can be focal.
   b. Can be isolated or associated with Beckwith-Wiedemann syndrome and trisomy 21.
2. Clinical features
   a. Respiratory distress and feeding difficulty.
   b. When associated with Beckwith-Wiedemann syndrome, findings include increased fetal and infantile growth, abdominal wall defects, visceromegaly, hypoglycemia, and embryonal malignancies.

3. Treatment
   a. Tongue reduction.
   b. Tracheotomy.

LARYNGOMALACIA

1. Background
   a. It is the most common cause of stridor in infants.
   b. There is inspiratory collapse of supraglottic structures, especially mucosa overlying the arytenoid cartilage and aryepiglottic folds.
2. Clinical features
   a. Inspiratory stridor in the first few days after birth.
   b. Feeding difficulties, aspiration.
   c. Symptoms worsen with agitation and prone positioning and improve with supine positioning.
3. Diagnosis
   a. Flexible fibro-optic laryngoscopy.
4. Treatment
   a. Most can be managed conservatively as the symptoms resolve by 12–24 months.
   b. Supraglottoplasty to remove redundant supraglottic mucosa.
   c. Tracheotomy.

VOCAL CORD PARALYSIS

1. Background
   a. Second most common cause of stridor in infants.
   b. Can be unilateral or bilateral; acquired or congenital.
   c. Unilateral is usually iatrogenic: due to cardiothoracic surgery and incidental trauma during endotracheal intubation. Can also be due to intrathoracic lesions causing compression of recurrent laryngeal nerve and birth trauma.
   d. Bilateral paralysis could be caused by Chiari malformation or other causes of brainstem compression.
2. Clinical features
   a. Unilateral presents with stridor, weak cry, and feeding difficulties.
   b. Bilateral: prominent stridor; although can be asymptomatic due to paramedian position of both cords.
3. Diagnosis
   a. Flexible laryngoscopy.
   b. MRI brain/spine to exclude Chiari malformation in bilateral paralysis.
4. Treatment
   a. Unilateral paralysis: spontaneous recovery; rarely medialization procedures.
   b. Bilateral paralysis: treatment of underlying cause; 50% require tracheotomy.

LARYNGEAL CLEFT

1. Background
   a. Due to inadequate development of tracheoesophageal septum.
   b. Laryngotracheal apparatus communicates with esophagus to varying degrees (Types 1 to 4).
2. Clinical features
   a. Aspiration, cough, respiratory distress, stridor.
   b. More than half are associated with other abnormalities.
3. Diagnosis
   a. Flexible laryngoscopy.
4. Treatment
   a. Types 2 to 4 require surgical correction.

SUBGLOTTIC STENOSIS

1. Background
   a. Third most common cause of stridor in children.
   b. Can be acquired or congenital.
   c. Congenital results from fibrous bands or due to cartilaginous deformities.
   d. Acquired results from trauma, especially traumatic and prolonged intubation.
2. Clinical features
   a. Stridor and respiratory distress.
   b. Congenital stenosis is prone to present as recurrent stridor and is often less severe than acquired ones.
3. Diagnosis
   a. Flexible laryngoscopy and tracheobronchoscopy.
4. Treatment
   a. Conservative for congenital and less severe forms.
   b. Higher grade stenosis can be managed by balloon dilatation, airway reconstruction, or tracheotomy.

SUBGLOTTIC HEMANGIOMA

1. Background
   a. Hemangioma is a common tumor of infancy; subglottic site is unusual.
2. Clinical features
   a. Asymptomatic during the first few weeks.
   b. Tumor enters proliferative phase after few weeks and tumor growth leads to stridor and respiratory distress.
   c. Symptoms worse in supine position.
   d. Cutaneous hemangioma is present in 50% of cases and has a "beard-like" distribution.
3. Diagnosis
   a. Direct laryngoscopy.
   b. MRI/CT scan of neck.
4. Treatment
   a. Watchful waiting not acceptable.
   b. Propranolol.
   c. IV corticosteroids for symptomatic infants; given along with propranolol.
   d. Surgical excision.
   e. Tracheotomy.

TRACHEAL STENOSIS

1. Background
   a. Most cases are congenital in origin. Can be acquired secondary to endotracheal intubation.
   b. Complete tracheal rings are important congenital causes.
   c. About 50% are associated with pulmonary sling.
2. Clinical features
   a. Respiratory distress, expiratory stridor.
   b. Cough, feeding and wheezing.
   c. Recurrent respiratory infections.

3. Diagnosis
   a. Endoscopy.
   b. MRI and CT of chest.
4. Treatment
   a. Steroids, bronchodilators.
   b. Physiotherapy.
   c. Surgical intervention: resection with end-to-end anastomosis; slide tracheoplasty.
   d. Balloon dilatation.

TRACHEOMALACIA

1. Background
   a. Cartilaginous: membranous ratio is normally horseshoe shaped (4.5:1). In tracheomalacia, there is less cartilage and resultant collapse of trachea.
2. Clinical features
   a. Respiratory distress, chronic cough, wheezing.
   b. Recurrent pneumonia.
   c. Apnea.
3. Diagnosis
   a. Bronchoscopy under spontaneous ventilation.
4. Treatment
   a. CPAP.
   b. Tracheotomy or aortopexy.

VASCULAR COMPRESSION (VASCULAR RING)

1. Background
   a. The most common symptomatic anomaly is due to an anomalous innominate artery.
2. Clinical features
   a. Chronic cough, dyspnea, stridor, wheezing.
   b. Reflex apnea.
   c. Occasionally, dysphagia.
3. Diagnosis
   a. Bronchoscopy.
   b. Symptomatic cases requiring surgery: MRA and CT angiography.
4. Treatment: aortopexy.

Miscellaneous Lesions Causing Respiratory Distress

CONGENITAL LOBAR EMPHYSEMA (CLE)

1. Background
   a. Emphysematous enlargement, usually of one lobe, caused by air entry into the affected lobe with blockage of expiration and air trapping.
   b. Causes include bronchial stenosis, bronchomalacia, intraluminal obstruction, or extraluminal compression by mass such as bronchogenic cyst.
2. Clinical features
   a. Usually affects left upper lobe followed by right middle lobe.
   b. Air trapping results in emphysematous lobar expansion which can cause compression of adjacent lung and mediastinal displacement.
   c. Lobar hyperexpansion and adjacent lung collapse can be life-threatening.
3. Diagnosis and evaluation:
   a. Chest x-ray shows characteristic finding of unilateral lobar hyperinflation with compression, atelectasis of adjacent lung, and mediastinal shift.
   b. CT of chest or MRI of chest may reveal any underlying cause for CLE.
   c. Echocardiography may reveal any vascular structures compressing the bronchi.
4. Treatment
   a. If asymptomatic or mildly symptomatic: observation can be tried.
   b. Surgical resection: thoracotomy and lobectomy are indicated for progressive respiratory distress and or persistent/recurrent pneumonia.

CONGENITAL PULMONARY AIRWAY MALFORMATION (CPAM)

1. Background
   a. Group of lesions characterized by abnormal airway branching morphogenesis of the lower respiratory tract.
   b. Most common congenital lung lesion.
   c. CPAM are hamartomatous lesions that are cystic or adenomatous in nature (thus the previous terminology of congenital cystic adenomatous malformation [CCAM]) and contain epithelial elements from trachea, bronchial, and alveolar tissues.
2. Clinical features
   a. Large lesions can present as hydrops in utero.
   b. Postnatally, CPAM could be asymptomatic or cause respiratory distress.
   c. Usually affects a single lobe, most commonly the left lower lobe.
   d. There are five types of CPAM:
      1) Type 0: rarest form, originating from tracheobronchial epithelium and presenting as small cysts.
      2) Type 1: most common type, comprising 60%–70% of all CPAMs. It originates from distal bronchi and bronchioles and presents as 2–10 cm large cysts, thin-walled, affecting one lobe.
      3) Type 2: consist of 15%–20% of CPAMs. They consist of terminal bronchiolar epithelium and present as 0.5cm–2 cm cysts that blend with normal tissue. Up to 60% of patients have other abnormalities such as esophageal atresia, intestinal atresia, and renal agenesis.
      4) Type 3: consist of 5%–10% of CPAMs. They are often large and can involve multiple lobes. They have acinar origin and can be cystic and solid or entirely solid. This type of CPAM is not associated with malignancy.
      5) Type 4: comprise 5%–10% of CPAMs and consist of large cysts derived from alveolar lining cells. They carry the highest premalignant potential.
3. Diagnosis
   a. Can be diagnosed on prenatal ultrasound.
   b. Cyst volume ratio (CVR): cyst volume divided by head circumference, measure on prenatal ultrasounds, can be used to predict outcome. CVR >1.6 are associated with higher risk of hydrops.

c. Chest x-ray and CT chest with contrast are used for diagnosis. Contrast is used to identify any systemic feeder vessels. Lesions with systemic feeding vessels are called bronchopulmonary sequestration.

4. Treatment
   a. Fetuses with high-risk lesions (defined by size and CVR) can be managed with maternal steroids and, if needed, fetal resection of lesion. Large cystic lesions can be managed with in utero thoracoamniotic shunts.
   b. Postnatally, surgical resection is recommended due to risk of infection and malignancy.
   c. Best time for surgery is between 2–6 months of age, although, symptomatic lesions may require more emergent resection.

Pleural Disorders Causing Respiratory Distress

PLEURAL EFFUSION

1. Background
   a. Pleural fluid:
      1) Produced by visceral pleura
      2) Absorbed by lymphatics of parietal pleura
   b. Types of pleural effusion:
      1) Congenital
      2) Acquired
   c. Congenital pleural effusion:
      1) Hydrops fetalis: abnormal fetal fluid collection in a minimum of two anatomic locations. Usually bilateral pleural effusions. Causes include chromosomal abnormalities, congenital heart disease, immune and nonimmune anemia, metabolic problems, and infections (herpes simplex, parvovirus).
      2) Congenital chylothorax: accumulation of chyle in the pleural space. Congenital chylothorax is due to abnormal development of the lymphatic system. Causes include chromosomal anomalies such as trisomy 21, Turner syndrome, and other genetic abnormalities.
   d. Acquired pleural effusion:
      1) Iatrogenic effusions as complications of thoracic surgery (most common cause of acquired pleural effusion), central venous catheter leak.
      2) Pneumonia.
      3) Hypoalbuminemia (nephrotic syndrome).
      4) Superior vena cava syndrome.

2. Clinical features
   a. Congenital pleural effusions:
      1) Are usually seen antenatally.
      2) Large fetal bilateral pleural effusions may cause immediate respiratory distress at birth.
      3) Associated pulmonary hypoplasia results in need for prolonged assisted ventilation.
   b. In acquired effusions, symptoms depend on the size of the pleural effusions, with moderate to severe effusions causing respiratory failure.

3. Diagnosis
   a. Antenatal: fetal ultrasound. Cause for fetal hydrops is often ascertained during the same ultrasound exam.
   b. Postnatal: chest x-ray. Fluid analysis for lactate dehydrogenase (LDH), protein content, lipid level and profile, and cell count with differential.
   c. Fluid analysis leads to effusion classification as:
      1) Transudate: low in protein and cellular elements. Due to increased hydrostatic pressure.
      2) Exudate: higher concentrations of protein and lactate dehydrogenase. Due to infection, extravasation of parenteral fluids, lymphatic blockage.
      3) Chyle: high protein and lipid content especially after milk feed. Differential count reveals lymphocyte predominance.

4. Treatment
   a. Needle aspiration: reserved for in infants with respiratory failure. For persistent effusion, tube thoracostomy is done.
   b. Replacement of ongoing losses of fluid, albumin, immunoglobulin, and coagulation factors are necessary for prolonged chylous drainage.
   c. Chylous effusion: MCT oil, NPO, octreotide (adverse effects: PPHN, NEC).

Suggested Readings

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Questions

1. A term infant has inspiratory stridor noticed in the normal nursery a few hours after birth. The stridor was most noticeable when the infant cried. There were mild retractions but no oxygen desaturation. Mother had gestational diabetes during pregnancy. Infant was born by spontaneous vaginal delivery at 39 weeks after forceps-assisted delivery with a birth weight of 4.3 kg. What is the most likely diagnosis:
   a. unilateral vocal cord paralysis
   b. subglottic stenosis
   c. laryngomalacia
   d. hemangioma

2. A newborn was born at 36 weeks following spontaneous labor. Mother had late onset of prenatal care and the fetus was noted to have hydrops. At birth, the infant was noted to have poor respiratory effort and hydrops with skin edema and abdominal distention. Resuscitation included drainage of fluid from the chest and abdominal cavities and the infant was admitted to the NICU. Examination in the NICU reveals dysmorphic features, downsloping palpebral fissures, webbed neck, dysplastic pulmonary valve, and cryptorchidism. Analysis of pleural fluid revealed serosanguinous fluid with lymphocyte predominant cell count. What is the likely diagnosis?
   a. Congenital empyema
   b. Immune hydrops
   c. Cardiac failure
   d. Chylothorax

16 Apnea of Prematurity and Neonatal Respiratory Depression

NARAYAN PRABHU IYER and DEEPAK KUMAR

Basic Information

FETAL BREATHING

1. Fetus makes breathing movements in utero that are important for lung development and maturation of breathing control.
2. Fetal breathing is not a continuous process; instead it is characterized by periods of prolonged apnea lasting as long as two hours.
3. Apneas in fetus are more frequent and longer lasting at younger gestational ages.
4. Fetal breathing increases with maternal CO_2 inhalation suggesting intact central chemoreception.
5. Fetal response to hypoxia is also centrally mediated and results in diminished or absent breathing movements.
6. Diminished fetal breathing is associated with poor fetal health.
7. Fetal to neonatal transition: the discontinuous fetal breathing changes to a continuous neonatal breathing pattern. The sudden increase in arterial partial pressure of oxygen (Pao_2) at birth (compared to fetal Pao_2) silences the peripheral chemoreceptors. This silencing is not complete as evidenced by the fact that supplemental O_2 compared to room air at birth may delay the onset of the first cry.

NEONATAL BREATHING

1. Control of normal breathing resides within multiple centers in the bulbopontine region of the brainstem.
2. Afferent inputs into the respiratory control centers include signals from central and peripheral chemoreceptors, pulmonary stretch receptors, upper airway mechano-chemical receptors, reticular activating system neurons, and cortical inputs.
3. Central chemoreceptors:
   a. Located in the in the ventrolateral surface of the medulla.
   b. Respond to hypercarbia, H+ ion in Extracellular fluid (ECF).
   c. Activation results in increased respiratory rate and depth.
   d. Central chemosensitivity to hypercarbia is diminished in preterm infants, and this relative "insensitivity" is directly proportional to the level of prematurity.
   e. Among preterm infants, those with apnea of prematurity (AOP) have more insensitivity to hypercarbia than preterm infants of similar gestation but without AOP.
4. Peripheral chemoreceptors:
   a. Located near carotid artery bifurcation.
   b. Respond to changes in pH and Pao_2.
   c. Like central chemoreceptors, peripheral chemoreceptors also mature during the first few weeks of life in both term and preterm infants.
   d. Peripheral chemoreceptors cause ventilator depression during acute hyperoxia. This response is blunted in preterm infants.
   e. Peripheral chemoreceptors are activated during apnea and play a role in apnea termination.
5. Biphasic response to acute hypoxia:
   a. Adults show a sustained period of hyperventilation in response to acute hypoxia. In contrast, preterm infants and term infants up to 3 weeks' postnatal age show a biphasic response to acute hypoxia.
   b. In response to acute hypoxia, preterm infants have a transient increase in rate and depth of respiration and this is mediated through the peripheral chemoreceptors. This hyperventilatory response may be completely blunted in infants born extremely premature.
   c. After about 30 seconds of hyperventilation, there is progressive depression of ventilation and this response appears to be mediated by inhibitory signals from the bulbopontine region to peripheral chemoreceptors.
6. Upper airway reflexes and breathing pattern:
   a. Laryngeal mucosal receptors can elicit a strong protective airway reflex and can result in apnea, bradycardia, hypotension, and upper airway closure.
   b. Negative pressure in the upper airways can also lead to decreased ventilation. During upper airway obstruction (obstructive apnea), respiratory efforts result in the development of negative upper airway pressure, which in turn can lead to central apnea.
   c. Hypoxic ventilator depression and the blunted response to hypercarbia result in prolonged instability of respiratory pattern and apnea.
7. Other reflexes:
   a. Hering-Breuer (HB) inflation reflex: lung inflation stimulates stretch receptors, which send afferent impulses to the medulla. Efferent vagal nerve inhibition of further inspiration results in termination of inspiration.
   b. HB-reflex includes slowing of ventilatory frequency or apnea and bronchodilation.
   c. HB-reflex is strong in first few months of life; weak in adults.

d. The strength of the HB-reflex is greater at 36°C than at 24°C in newborn rats, suggesting newborns exposed to warm environment are more susceptible to inhibitory inputs.
e. Hyperthermia may predispose newborns to respiratory depression.

8. Manifestations of immature breathing pattern:
   a. Periodic breathing:
      1) It is a pattern of regular breathing alternating with pauses in respiration of at least 3 seconds, persisting through at least three cycles of breathing.
      2) Prevalence of periodic breathing is up to 80% in full-term infants and almost 100% in extremely-low-birth-weight infants.
      3) Prevalence reduces to reach a nadir by about 44 weeks of postmenstrual age (PMA).
      4) Low lung volumes, low pulmonary compliance, and low baseline oxygenation make preterm infants prone to having more severe and prolonged episodes of periodic breathing.
      5) Periodic breathing is associated with intermittent hypoxia and possibly bradycardia and may be associated with adverse neurodevelopmental outcomes.
      6) Pattern of periodic breathing changes with the phase of sleep. During REM sleep, periodic breathing is irregular with inconsistent cycle durations. During quiet sleep, periodic breathing is regular with consistent duration and intervals of breathing pauses.
   b. Apnea:
      1) Cessation of ventilation of longer than 15–20 seconds but can be shorter if associated with bradycardia and desaturation.
      2) Mechanism of bradycardia is unclear and usually follows apnea and oxygen desaturation but may be coincidental with apnea and may occur without oxygen desaturation.
      3) Apneic episodes are classified as:
         a) Central: lack of respiratory effort due to immaturity of the central nervous system and immature chemoreceptor functions/response causing absence of chest wall movement.
         b) Obstructive: obstructed breaths in the presence of respiratory efforts; airflow cessation due to absent coordination of respiratory musculature, pharyngeal instability, nasal obstruction, and neck flexion. Central regulation of the pharyngeal tone is important for airway patency maintenance.
         c) Mixed: there is initial loss of central respiratory drive along with delayed activation of upper airway muscles superimposed on a closed airway; these combinations of events result in prolonged mixed apnea.
      4) Causes of apnea:
         a) Preterm infants: idiopathic (apnea of prematurity), central nervous causes (seizures, intracranial hemorrhage, hypothermia, depressant drugs), pulmonary causes (pneumonia, especially due to RSV, laryngeal reflex, vocal cord paralysis, pneumothorax, tracheal occlusion caused by neck flexion), sepsis, metabolic causes (hypoglycemia, hypocalcemia, hyponatremia, and hypernatremia), and anemia.
         b) Term infants: intrapartum asphyxia, brainstem depression due to drugs (narcotics, magnesium sulfate, general anesthetics), airway obstruction (choanal atresia, mandibular hypoplasia), neuromuscular lesions (muscle weakness), trauma (phrenic nerve palsy, spinal cord transection), and central nervous conditions (seizures, Dandy-Walker malformation, central hypoventilation syndrome).

DISORDERS OF CONTROL OF BREATHING

Apnea of Prematurity (AOP)

1. Basic information:
   a. Pathophysiology: AOP is the consequence of immaturity of central respiratory control centers and the altered ventilator responses to hypercapnia and hypoxia. There is a genetic component to causation as there is greater concordance of AOP in monozygotic twins compared to same sex dizygotic twins.
   b. Incidence: varies from <10% for infants born >34 weeks' gestation; 60% in infants born with birth weight <1500 grams; and >85% in infants born with birth weight <1000 grams.
2. Clinical presentation: clinical symptoms may manifest during the first day of life, but usually appear later. Peak incidence of symptoms is between 4–6 week after birth, corresponding with increased sensitivity of peripheral chemoreceptors and, therefore, greater respiratory instability. Mixed apnea is the most common type of apnea during AOP.
3. Diagnosis: diagnosis is made clinically using bedside observation of prolonged apnea (>20 seconds) on standard impedance monitoring, especially when such apnea is associated with bradycardia and oxygen desaturation. Although there is no consensus, at least one visually confirmed apnea associated with bradycardia and desaturation is required to diagnose AOP. Impedance based monitors cannot be used to diagnose obstructive apnea and prolonged episodes of obstructive episodes are diagnosed when resultant central apnea or bradycardia and oxygen desaturation trigger an alarm.
4. Treatment: once other causes of apnea have been excluded (such as anemia), treatment for AOP is considered.
   a. Methylxanthines: caffeine, aminophylline, and theophylline.
      1) Methylxanthines act both peripherally and centrally.
      2) They activate central respiratory centers, increase sensitivity to hypercarbia, induce bronchodilation, and enhance diaphragm function.
      3) Beneficial effects include increased minute ventilation, more stable respiratory pattern, and reduced hypoxic respiratory depression.
      4) Side effects include increased metabolic rate, which may lead to transient slowing of physical growth, tachycardia, and irritability.

5) Although routine drug level monitoring is not recommended, if performed, the therapeutic level of caffeine is 5–25 μ/mL and toxicities are generally not seen until the levels exceed 40 μ/mL.
6) Other benefits of methylxanthines: in addition to improving AOP, methylxanthines also facilitate extubation, and caffeine treatment started within 3 days after birth is associated with reduced bronchopulmonary dysplasia (BPD), less need for patent ductus arteriosus (PDA) treatment, reduced severity of retinopathy of prematurity (ROP), and some long-term neurologic deficits.
7) Methylxanthines are usually stopped when AOP symptoms resolve, usually around 33–36 weeks of PMA. After treatment cessation, infants are monitored for a variable period of time (3–8 days) for reemergence of AOP symptoms.

b. Respiratory support: nasal continuous positive airway pressure (NCPAP), nasal intermittent positive pressure ventilation (NIPPV), high flow nasal cannula (HFNC), and invasive mechanical ventilation (IMV) have been used to treat the symptoms of AOP.
1) NCPAP helps improve functional residual capacity and prevents pharyngeal collapse, leading to significant reductions in AOP symptoms.
2) HFNC reduces the amount of dead space and can also provide continuous distending pressure like CPAP. Safety concerns have been raised as the pressure produced is unpredictable and can be very high.
3) If, despite methylxanthines and NCPAP, AOP symptoms persist, then NIPPV or IMV are required. When IMV is required, infants should be evaluated for infections, sepsis, and seizures.

c. Doxapram: doxapram is a nonspecific central nervous system stimulant sometimes used in the treatment of AOP. Doxapram requires continuous intravenous infusion, and side effects include hypertension, tachycardia, jitteriness, vomiting, and low seizure threshold.
d. Treatment of gastroesophageal reflux (GER): most evidence suggest that there is no causal link between GER and AOP. Physiologic observations have shown that apnea is more likely to lead to, rather than be caused by, GER. Antireflux medications have not been shown to reduce the number of AOP related episodes.
e. Other treatments include CO_2 inhalation, sensory stimulation, and low flow nasal cannula delivering room air.
f. Resolution with time:
1) AOP progressively improves over time and in most infants resolves by 34–36 weeks' PMA. In more immature infants, AOP symptoms may persist till 43–44 weeks' PMA.
2) Episodes of clinically intermittent hypoxia and bradycardia often continue beyond the resolution of clinically apparent apnea but are generally too brief to trigger an alarm or cause visible cyanosis.
3) Significant cardiovascular episodes (apnea >30 seconds or heart rate <50–60/minute for more than 5 seconds) can occur in healthy preterm infants after discharge.
4) Infants who had AOP-related symptoms within the last 5 days prior to NICU discharge have more likelihood to have a significant cardiovascular episode postdischarge. However, no consensus exists on the required number of AOP symptom-free days prior to discharging the infant.
5) Premature infants with history of AOP are at higher risk of RSV related apnea and apnea associated with exposure to general anesthesia (GA). The risk for apnea associated with GA does not reduce to <1% until after 54–56 weeks' PMA.

5. Neurodevelopmental outcome in infants with AOP:
a. Precisely defined predischarge apnea has been associated with lower developmental indices at 2 years of age.
b. Similarly, infants with greater cardiorespiratory events on home monitors after discharge are also associated with impaired neurodevelopmental outcome.
c. Impact of treatment of AOP in hospital or prevention of cardiovascular events postdischarge on neurodevelopmental outcomes is unknown.

Sudden Infant Death Syndrome (SIDS)

1. Basic information:
a. Sudden death of an infant that is unexplained by a thorough postmortem exam, which includes a complete autopsy, investigation of the scene of death, and review of the medical history.
b. SIDS is the third leading cause of infant mortality in the United States, representing 8% of all infant deaths.
c. Triple risk model has been proposed to explain causation: critical developmental period (first 6 months), vulnerable infant (preterm infant, growth restricted infant, exposure to smoking or drugs in utero), and extrinsic factors (prone/side sleep position, soft bedding, overbundling, overheating, bed sharing, and smoking or alcohol use).
d. The rate of SIDS peaks between 1–4 months of age, and 95% of cases happen by 6–8 months of age.
e. Back to Sleep campaign: The annual rate of SIDS dropped from 1.3–1.4/1000 (1992) live births before the Back to Sleep campaign to 0.55/1000 (2001) live births after the widespread use of supine sleep position.
f. Preterm infants have 2.5 to 2.7 times the risk of SIDS compared to term infants. Reasons for higher rates of SIDS in preterm infants include brainstem dysfunction and increased vulnerability to SIDS from prone positioning.
g. The current American Academy of Pediatrics policy statement on SIDS does not recommend the use of home monitors for the prevention of SIDS.

Apparent Life-Threatening Events (ALTE) or Brief Resolved Unexplained Events (BRUE)

1. Basic information:
a. An ALTE, or BRUE as it has been renamed, is defined as a sudden, unexpected change in an infant that is frightening to the caregiver and perceived as life-threatening.

b. Infants born preterm are at an increased risk for a BRUE. The incidence of BRUE varies from 0.5 to 10/1000 live births (high variability is due to different definitions), but incidence in preterm infants is reported to be 8%–10%.
c. About half of BRUE are idiopathic and are thought to be sleep related.
d. There is no evidence that BRUE are precursors of SIDS. Idiopathic BRUE and SIDS may share some common mechanisms. The risk of SIDS may be as much as 3 to 5 times greater in infants who have experienced BRUE compared with healthy controls.

Sleep Disordered Breathing (SDB)

1. Basic information:
   a. About 4% of children have SDB.
   b. Infants born preterm are at higher risk of SDB with some studies showing a two- to three-fold increased risk compared to infants born at term.
   c. SDB is associated with neurodevelopmental impairment in preterm infants and is likely mediated by intermittent hypoxia.
   d. Infants born preterm are also at higher risk for later obesity, which is an independent risk factor for SDB.

Suggested Readings

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Questions

1. A 32-year-old pregnant mother at 28 weeks' gestation is referred to you for a neonatology prenatal consult. According to the obstetrician, the fetus has reduced fetal movements, thin bones, and polyhydramnios. The ultrasound also notes the near total absence of fetal breathing. How will you explain the significance of the lack of fetal breathing to the mother?
   a. Fetal breathing is not significant indicator of fetal health
   b. Lack of fetal breathing implies severe periodic breathing in neonate after birth
   c. Regular fetal breathing at the rate of 30–40/minute is essential for establishment of neonatal breathing
   d. Fetal breathing is essential for lung development

2. You are doing teaching rounds with medical students and are demonstrating periodic breathing in a 28-week preterm infant who is 2 weeks old. How will you best describe the response of this infant to hypoxia?
   a. Immediate and persistent hyperventilation
   b. Biphasic response, early ventilatory depression and later hyperventilation
   c. Biphasic response, early hyperventilation and later ventilatory depression
   d. No predictable response

17 Assisted Ventilation, ECMO, and Pharmacologic Agents

PATRICIA R. CHESS

Assisted Ventilation

RESPIRATORY SUPPORT (TABLE 17.1)

- Utilized when oxygenation and/or ventilation are inadequate
- Attention taken to optimize positive end expiratory pressure (PEEP) to avoid atelectasis (suggests PEEP too low) and to avoid overdistention (suggests air trapping or PEEP too high), which can lead to impeded venous return to the thorax/heart and subsequent hypotension pneumothorax
- Regardless of method of respiratory support, in general target lungs 9–9 1/2 ribs expanded by chest xray (CXR) for most pathophysiologies, 8–8 1/2 ribs expanded if air leak (pneumothorax [PTX], pulmonary interstitial emphysema [PIE]), pulmonary hypoplasia, or congenital diaphragmatic hernia (CDH). PEEP has most impact on lung expansion
- Targeted tidal volume in preterm 4–6 cc/kg, term 5–8 cc/kg
- Any mode of ventilation that uses an endotracheal tube can lead to airway damage (acute or chronic) or subglottic stenosis (chronic), as well as present a risk of ventilator-associated pneumonia
- Positive pressure ventilation, including noninvasive ventilation, can lead to overdistention and increase the risk of a pneumothorax
- CO_2 mostly affected by tidal volume, rate, expiratory time
- Oxygenation mostly affected by mean airway pressure and fraction of inspired oxygen (Fio_2)

Types of Ventilation

- Continuous Positive Airway Pressure (CPAP) PEEP provides distending pressure to alveoli via continuous positive airway pressure (CPAP) prongs in nares to maintain alveolar distention and improve oxygenation in infants with adequate spontaneous respirations. Risk of pneumothorax and nasal septum breakdown.
- Synchronized intermittent mandatory ventilation (SIMV).
  - Volume targeted ventilation
    - Set rate, PEEP, inspiratory time (ITime), target volume, *delivers pressure needed to establish the set volume*, pressure limit set, risk of high pressure to maintain target volume, able to set pressure limit to minimize risk
    - Uses: BPD, homogeneous lung disease in full-term infant where compliance doesn't change significantly
  - Pressure targeted ventilation
    - Set rate, PEEP, ITime, peak pressure to be achieved, *does not guarantee a set volume*, risk of underventilation/atelectasis
    - Uses: rapidly changing compliance to minimize risk of pneumothorax such as RDS
- Control mode (e.g., assist control)
  - Each breath fully supported, risk of gas trapping
  - Use: fully support each breath in critically ill infant
- Pressure support mode
  - Delivers both mandatory and assisted (support) breaths; support breath peak inspiratory pressure slowly decreased to wean from mechanical ventilation
  - Use: facilitate gentle weaning
- High frequency oscillator ventilator (HFOV)
- Diaphragm in oscillator moves to and fro, providing active inspiration and expiration (only mode where expiration is active)
  - MAP: primarily affects oxygenation, to transition from CV to HFO typically set 1–2 cm H_2O above MAP on CV or consider = MAP on CV if air leak, adjust MAP based on saturations, CXR to targeted desired lung expansion
  - Frequency: Rate reflects number of to-fro movements of the diaphragm. In general,
    - Premature infants: 15 hertz
    - Term infants: 10 hertz
  - Power (amplitude, delta p): primarily affects CO_2 removal, reflects delta of diaphragm from midline, target shaking to groin
  - Risk of over/underdistention if PEEP not optimized, air leak if do not wean when compliance improves, impeded cardiac return if MAP too high
  - Use in air leak, homogeneous lung disease
- High frequency jet ventilator (HFJV)
  - Interrupted gas flow leads to "jet" spike of air down central air spaces for inspiration, swirling of air up periphery of air spaces of expired air
  - Active inspiration, passive expiration
  - Peak inspiratory pressure (PIP) and PEEP significantly attenuated on high frequency
  - Transitioning from CV to jet
    - Set PIP and PEEP similar to CV, adjust based on exam, CXR, blood gases
    - Jet rate based on GA and disease process, typically 240 (term) to 420 (premature) breaths per minute
  - Initially set CV (provides "background rate," PIP) in tandem with jet until PEEP optimized, wean rate on CV when possible with target CV rate zero
  - Uses: nonhomogeneous lung disease, air leak, pulmonary hypoplasia, cardiac compromise when high frequency ventilation is indicated, aspiration syndromes

Table 17.1 Modes of Respiratory Support

Name	Effects	Uses	Contraindication	Risks
Oxyhood	Provides supplemental O_2	Mild hypoxia without significant increased work of breathing or CO_2 retention	Inadequate ventilation	Hyperoxic end organ damage, primarily to lungs and in case of premature infants, ROP
Low Flow Nasal Cannula (LFNC <2 LPM); High flow nasal cannula (HFNC >2 LPM)	Dead space washout improves gas exchange	Weaning from mechanical ventilation	Apnea, NEC	Pneumothorax, gastric distension
Nasal Continuous Positive Airway Pressure (NCPAP)	Avoid atelectasis, stabilize FRC, improves apnea and intermittent hypoxia events	RDS, weaning from mechanical ventilation	Prolonged apnea, NEC	Pneumothorax, gastric distension, nasal bridge erosion
Noninvasive (asynchronous or synchronous) Positive Pressure Ventilation (NIPPV, sNIPPV)	Avoid atelectasis, stabilize FRC	Mild-moderate respiratory distress, weaning from mechanical ventilation	Early RDS, NEC	Pneumothorax, gastric distension, nasal bridge erosion
Synchronized Intermittent Mandatory Ventilation (SIMV)	Maintains lung expansion	Respiratory failure		Pneumothorax, volutrauma, atelectotrauma
Pressure Support Ventilation	Helps overcome elastic and resistive forces	Typically used in SIMV mode during weaning		Pneumothorax, volutrauma, atelectotrauma
Pressure/ Volume Control ventilation	Fully supports each breath	Severe respiratory failure		Pneumothorax, volutrauma, atelectotrauma, stacking breaths
High Frequency Jet Ventilation (HFJV)	Active inspiration, passive expiration	PIE, air leak, nonhomogeneous lung disease		Air trapping, hyperventilation
High Frequency Oscillatory Ventilation (HFOV)	Active inspiration and expiration	Homogeneous lung disease	Use with caution with cardiac dysfunction	Impeded blood return to heart

FRC, Function residual capacity; *NEC,* necrotizing enterocolitis; *RDS*, respiratory distress syndrome; *ROP,* retinopathy of prematurity.

Ventilation Strategies Based on Pathophysiology

- RDS: avoid atelectasis with optimal PEEP, adequate surfactant replacement, high rates, low tidal volume (lung has low compliance and short time constant so it empties quickly).
- BPD: provide low rates with higher tidal volumes to allow adequate time for expiration and minimize air trapping, overdistention (lung has high compliance and long time constant so it empties slowly).
- MAS: provide optimized PEEP and MAP, ensure adequate expiratory time: high risk of ball-valve air trapping/pneumothorax due to meconium plugs.
- Pneumonia: often homogeneous in neonates since hematogenous spread is common. Ensure adequate PEEP to achieve 9–9 1/2 rib expansion.
- Air leak (PIE, pneumothorax)/pulmonary hypoplasia/CDH: target 8–8 1/2 ribs, avoid overdistention, avoid PIP >25 in full-term infants.

Monitoring Babies on Mechanical Ventilation

- Standard ICU monitoring can help give clues to issues. Prolonged periods of no spontaneous respirations can suggest oversedation, significant neurologic compromise, or overventilation/hypocapnea with loss of respiratory drive. Tachycardia with hypotension can result if MAP is impeding venous return to the heart.
- Change in saturation can suggest need for suction, pneumothorax, change in compliance. Improved oxygenation suggests improved pulmonary function and weaning. MAP should be considered given risk of a pneumothorax if compliance improves and MAP is not weaned. Suggest using transcutaneous or frequent blood gas monitoring to monitor CO_2 in infants on high frequency ventilation since large swings can occur. End tidal CO_2 monitors can be used in term infants but will increase the dead space.
- Following pressure-flow and pressure-volume loops on CV can help guide management strategies, identifying changes in compliance, gas trapping, airway obstruction, etc. (Figs. 17.1–17.3).
- While there are limited data to support specific blood gas targets, Table 17.2 has been created based on relevant literature and expert opinion and can be used as a general guide to target blood gases. If one needs to utilize extreme settings on the ventilator to achieve these gases, consideration of modifying the target blood gas range should be discussed.

Respiratory Pharmacologic Agents

- Surfactant: given intratracheally to improve compliance in surfactant deficiency (RDS) or reverse surfactant inactivation (aspiration syndromes). Risks include transient hypoxia/bradycardia due to airway obstruction, nonhomogeneous distribution with subsequent unequal aeration and pneumothorax if compliance rapidly improves and ventilator pressures are not weaned.
- Aminophylline and caffeine have been shown to increase respiratory center activity and decrease severe apneas in preterm infants and can help facilitate extubation, decreases BPD rates.

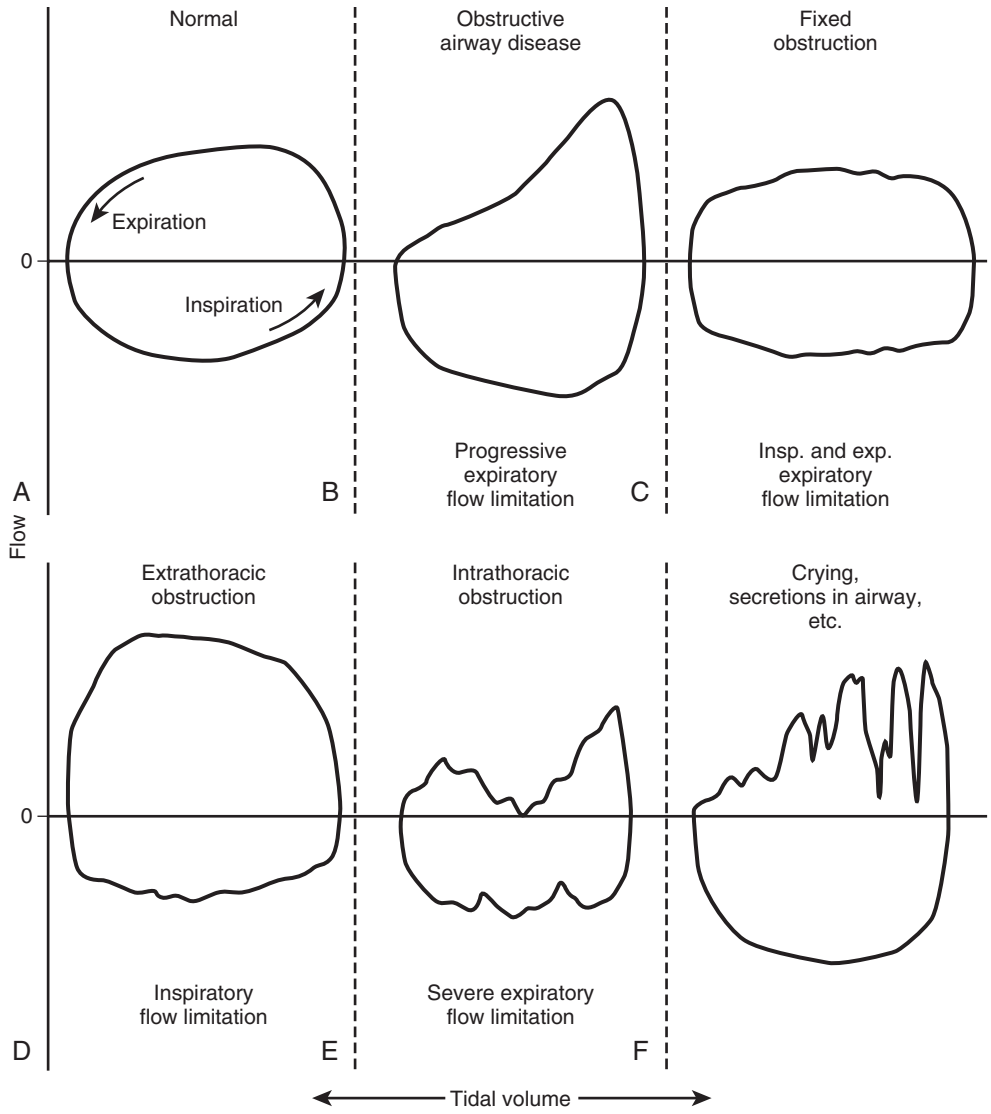

Fig. 17.1 Flow-volume loops in normal, abnormal conditions. Tidal flow–volume loops illustrating various manifestations of flow limitation that results from heterogeneity in airway resistance. (A) Normal loop. (B) "Ski-slope" loop observed with expiratory airflow limitation as seen in babies with bronchopulmonary dysplasia. (C) Extrathoracic airway obstruction with inspiratory and expiratory airflow limitation as seen in babies with subglottic stenosis or narrow ETT. (D) Intrathoracic inspiratory airflow limitation as seen in babies with intraluminal obstruction (close to the carina) or an aberrant vessel compressing the trachea. (E) Unstable airways or tracheomalacia. (F) This type of loop usually is suggestive of an erratic airflow limitation, as seen with airway secretions. (see Goldsmith et al. *Assisted ventilation of the Neonate.* 6th ed. Philadelphia: Elsevier; 2017 [Fig. 12.6, pg. 113].)

- Diuretics have been shown to facilitate extubation for premature infants but have not been demonstrated to have long term changes in outcome.
- Dexamethasone: synthetic glucocorticoid, improves compliance, decreases inflammation, has been shown to increase risk of CP, GI perforation when used early (<8 days), can affect growth, alveolarization, increase risk of infection, lead to hypertension and hyperglycemia. Late glucocorticoids (>8 days) have been associated with decreased mortality and risk of BPD. Use and timing of glucocorticoids need to take into consideration risk/benefit ratio and is still under investigation.
- Hydrocortisone: naturally occurring glucocorticoid, improves compliance, decreases inflammation, increases risk of infection, hyperglycemia, hypertension.
- Inhaled glucocorticoids: targeted delivery, decrease in pulmonary inflammation, limited studies on long-term benefits.
- Inhaled nitric oxide (iNO)
  - iNO is FDA approved to treat respiratory failure from pulmonary hypertension in infants >34 weeks' gestation.
  - NO is naturally occurring in vascular endothelial cells, formed from L-arginine by nitric oxide synthase which then diffuses into neighboring vascular smooth muscle cells activating guanylyl cyclase (GC). GC converts GTP to cyclic GMP leading to vascular relaxation via calcium efflux and decreased intracellular calcium.
  - (Fig. 17.4: Signaling pathway of NO)
  - NO is used as continuous inhaled gas (due to ½ life of 15–30 seconds) to promote relaxation of pulmonary vascular

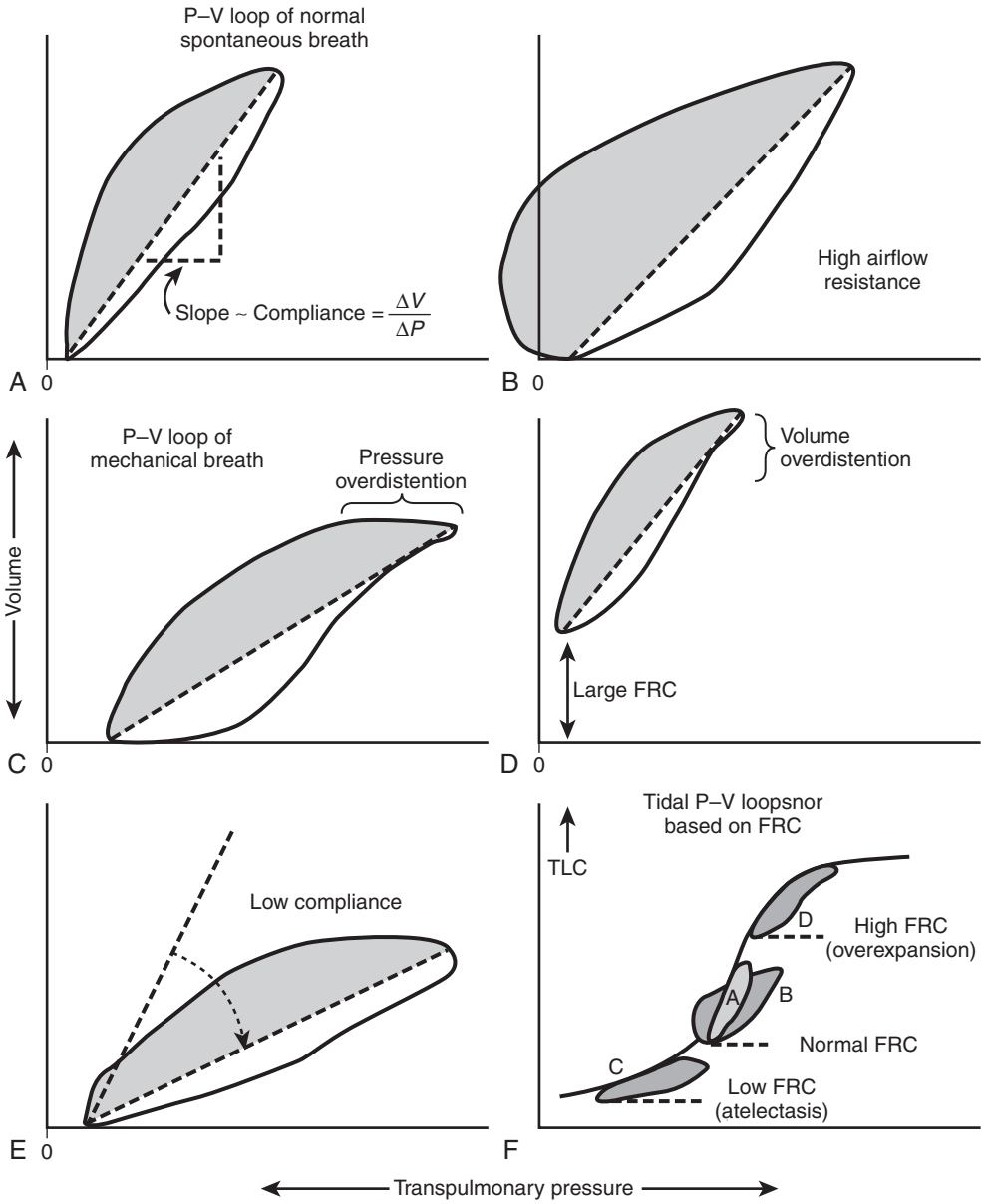

Fig. 17.2 Pressure-volume loops in normal, ventilated, and abnormal lungs. Pressure-volume (P–V) relationship illustrations show components of inspiratory elastic work and inspiratory elastic and resistive work. (A) A normal P–V relationship. (B) Increased expiratory resistive work (such as obstructive airway disease, meconium aspiration syndrome, or bronchopulmonary dysplasia). (C) Increased expiratory resistive work with excessive inspiratory pressure (such as overdistention due to high positive inspiratory pressure or high tidal volume). (D) Increased expiratory resistive work due to excessive functional residual capacity (such as overdistention due to air trapping, shortened expiratory time, etc.). (E) Decreased inspiratory elastic work (such as respiratory distress syndrome, pneumonia, atelectasis, etc.). (F) Comparison of P–V relationships affected by the functional residual capacity. *FRC,* Function residual capacity; *TLC,* total lung capacity. (From Goldsmith et al. *Assisted Ventilation of the Neonate.* 6th ed. Philadelphia: Elsevier; 2017 [Fig. 12.7, pg. 114].)

bed in infants with hypoxic respiratory failure. Center-specific protocols should be developed, but in general oxygenation index (OI) >15–25 is used as starting parameter for iNO initiation after other factors such as pulmonary expansion and cardiac function are optimized.

- iNO can lead to pulmonary edema if used in patients with left ventricular dysfunction or left-sided cardiac obstructive lesions, so important to obtain ECHO.
- Maximum dose typically used is 20 ppm, can wean quickly if no response and stop within 1 hour of starting, otherwise need to wean more slowly due to downregulation of endogenous iNO.
- Rebound pulmonary hypertension can occur with weaning due to downregulation of endogenous NO, especially at doses <5 ppm.
- High oxygen and iNO can lead to direct damage from toxic reactive oxidants (peroxynitrites and nitrogen dioxide).
- Risk of methemoglobinemia and elevated NO_2. Dose dependent: follow levels.
- Ensure ECMO availability, or at minimum if ECMO center not immediately available, ability to transfer to an ECMO center on iNO before initiating iNO in case escalation of care is needed.

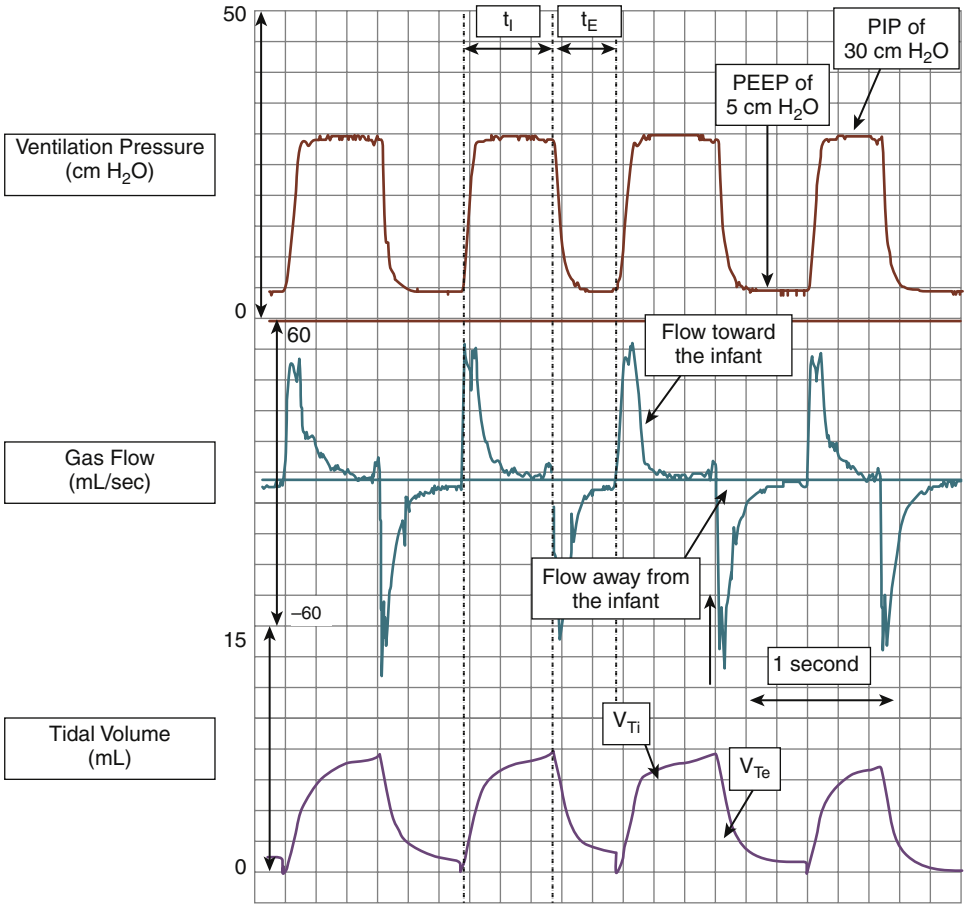

Fig. 17.3 Flow mechanics during positive pressure ventilation in neonate. Using this display on the conventional ventilator can give key information related to air leak, gas trapping, etc. *PEEP,* positive end expiratory pressure; *PIP,* peak inspiratory pressure. (From Goldsmith et al. *Assisted Ventilation of the Neonate.* 6th ed. Philadelphia: Elsevier; 2017 [Fig 26.7, pg. 284].)

Table 17.2 Target Arterial Blood Gases for Different Disease Processes

Diagnosis	RDS	PPHN/PNA (term)	PIE/PTX	CDH	BPD
pH	7.25–7.35	7.35–7.45	7.25–7.30	7.30–7.35	7.25–7.30
pCO_2	45–55	35–45	55–60	45–65	50–65
pO_2	50–70	60–100	50–60	60–80	50–60

BPD, Bronchopulmonary dysplasia; *CDH*, congenital diaphragmatic hernia; *PIE*, pulmonary interstitial emphysema; *PNA*, pneumonia; *PPHN*, persistent pulmonary hypertension of the newborn?; *PTX*, pneumothorax; *RDS*, respiratory distress syndrome.

Extracorporeal Membrane Oxygenation

- Used in cases of severe *reversible* cardiac or respiratory compromise not responsive to other therapies.
- Indication: original indications based on and Aa gradient that predicted an 80% mortality when ECMO first became available (OI >40, $AaDO_2$ 600–620). Subsequent medical advances (e.g., surfactant, iNO, high frequency ventilation) have improved survival in those situations, so additional indications such as ECHO assessment of cardiac dysfunction, refractory lactic acidosis, hypotension, or hypoxia are also considered before starting ECMO.
- Provides pulmonary (venovenous) or cardiopulmonary (venoarterial) support in infant with reversible cardiac and/or respiratory failure.
- Requires anticoagulation to avoid clotting circuit with subsequent risk of hemorrhage.
- If an infant with CDH needs a PIP >25 to maintain target blood gases (allowing permissive hypercapnia), ECMO should be strongly considered.
- When discussing ECMO as a treatment option, goals of care and expectations should be discussed with family, especially since infants sometimes unable to wean from circuit after extended period of time.
- Venous cannula in right atrium via internal jugular vein (IJV), arterial cannula in internal carotid artery terminates as it joins aorta.

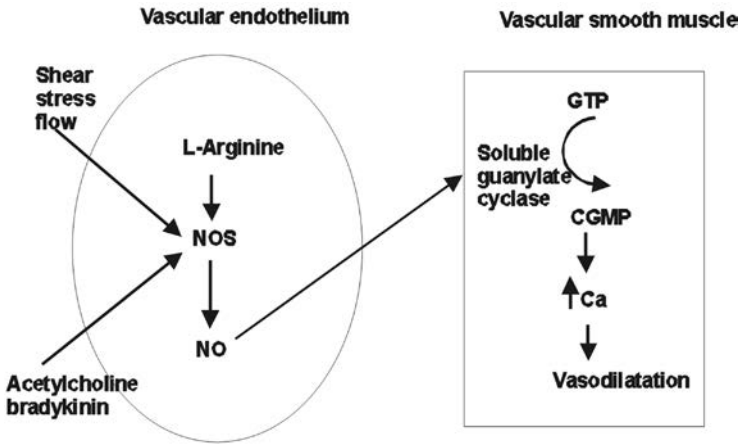

Fig. 17.4 Signaling pathway of NO.

- Risks: hemorrhage, infection, clots, long-term hearing loss, neurodevelopmental impairment.
- Contraindications
  - Irreversible fatal disease
  - Irreversible severe neurologic dysfunction
  - No uncontrolled bleeding
  - More than 7–10 days of injurious mechanical ventilation
  - Prematurity <34 weeks due to risk of IVH and technical limitation of placing adequate-sized cannula

Suggested Readings

Goldsmith, et al. *Assisted Ventilation of the Neonate*. 6th ed. Philadelphia: Elsevier; 2017.

Annich, et al. *ECMO: Extracorporeal Cardiopulmonary Support in Critical Care*. 4th ed. Ann Arbor: Extracorporeal Life Support Organization; 2012:11–30, 41–61.

West JB. *Respiratory Physiology: The Essentials*. 10th ed. Baltimore: Lippincott Williams & Wilkins; 2016.

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Questions

1. Which of the following are clinical situations for which ECMO is indicated?
   a. A neonate with transposition of the great arteries who has undergone a successful arterial switch palliation but is unable to maintain adequate blood pressure and oxygenation immediately postoperatively
   b. A 4-day-old with trisomy 21 and overwhelming sepsis and pneumonia on maximal ventilatory support, bilateral pneumothoraces, and an oxygenation index of 60 in spite of maximal medical therapy
   c. A 30-week-old, 1200-g infant with severe RDS unresponsive to multiple doses of surfactant on optimal ventilator support with an oxygenation index of 50
   d. A full-term infant with rupture of membranes at 18 weeks and persistent severe oligohydramnios whose parents chose to continue the pregnancy, who presents in the delivery room with severe increased work of breathing. The infant remains hypoxic with pO_2 20 mm Hg and pCO_2 110 mm Hg in spite of aggressive maximal cardiorespiratory support. A cardiac ECHO reveals normal anatomy, right ventricular dysfunction and significant right to left shunting at the ductal and atrial level. CXR suggests pulmonary hypoplasia

2. You are considering initiating iNO therapy for a 37-week-old infant of a diabetic mother with severe RDS. Which of the following is not indicated prior to initiation of iNO?
   a. Cardiac ECHO
   b. CXR
   c. Optimized lung expansion and ventilator support
   d. Surfactant replacement
   e. Steroid therapy

SECTION 5

Genetics and IEM

LAURIE STEINER, JOTISHNA SHARMA and GEORGIANNE LEE ARNOLD

18 Molecular Genetics

LAURIE STEINER

Basics of Human Genetics

- Most cells in the human body contain 46 chromosomes, 2 copies of each of the autosomes (1–22), and 2 sex chromosomes (XX or XY). Notable exceptions include red blood cells, which do not contain nuclei or DNA, and gametes (sperm or oocyte), which contain 23 chromosomes.
- Each chromosome contains hundreds to thousands of genes, which are regions of DNA that encode for protein. Humans have two copies of most genes: one paternally intertied copy and one maternally intertied copy.
- Humans have 20,000–25,000 genes. The total genetic information contained within a cell is referred to as the genome.

Decoding the DNA Blueprint

- DNA is composed of four bases: A (adenine), T (thymine), G (guanine), and C (cytosine). The genetic information encoded in DNA is first transcribed to RNA, which is then translated into protein.
- Protein coding genes are made up of exons and introns.
  - Regions of genes that code for protein are called exons.
  - The intervening sequences between exons are called introns.
  - Regions of the genome that are between protein coding genes are called intergenic.
  - Regions of DNA within intronic and intergenic regions often contain important regulatory sequences that determine how and when genes are expressed.

Three Different Types of RNA Participate in Protein Synthesis

- *Messenger RNA (mRNA).* DNA is transcribed into RNA by RNA polymerase to generate mRNA. Introns are removed from mRNA in a process called splicing. mRNA contains a series of three base pair sequences, called codons, that can code for a specific amino acid or code for termination of protein synthesis (stop codon). The genetic code is degenerate, because an amino acid can be encoded by more than one codon.
- *Transfer RNA (tRNA).* Each tRNA binds a specific amino acid and has a three base pair sequence that can pair with the complementary sequence in the mRNA. During the process of translating mRNA to protein, tRNA reads each codon and delivers the appropriate amino acid to the growing peptide.
- *Ribosomal RNA (rRNA).* Ribosomes translate mRNA into protein. Ribosomes are composed of proteins and rRNA.
- Some types of RNA, such as micro RNA and long noncoding RNA, are important regulators of gene expression and do not directly participate in protein synthesis.

Several Enzymes Play an Important Role in the Transmission of Genetic Information

- *DNA polymerase* is responsible for copying DNA during cellular replication.
- *RNA polymerase* transcribes DNA into RNA.
- *Reverse transcriptase* generates DNA from RNA. It is important for the function of retroviruses, such as HIV.

Epigenetic Gene Regulation

- Epigenetics refers to heritable modifications to DNA or DNA-binding proteins that change how genes are expressed without changing the underlying DNA sequence. Epigenetic modifications are critical determinants of developmental and cell type-specific gene expression. Disruption of normal patterns of epigenetic gene regulation is associated with both developmental disorders and cancer.
- DNA methylation is the process by which a methyl group is added to a cytosine and is a common form of epigenetic gene regulation.
  - Cytosine is more likely to be methylated when it is adjacent to a guanine (CpG). Areas of DNA rich in these regions are called CpG islands. Methylation of CpG islands is a common epigenetic mechanism of gene repression.
- Other common forms of epigenetic gene regulation include posttranslational modification of histone proteins and noncoding RNAs.

Uniparental Disomy and Disorders of Imprinting

- Uniparental disomy is the inheritance of two homologous chromosomes from one parent, instead of inheriting one copy from the mother and one copy from the father.
- Imprinting is the epigenetic silencing of a gene based on the parent of origin.
- Prader-Willi and Angelman syndromes, which are caused by deletion or uniparental disomy of 15q11-13, are classic disorders of imprinting.

- The genes on chromosome 15q11-13 are expressed based on parent of origin. Maternal uniparental disomy or deletion of the paternally inherited chromosome 15q11-13 results in Prader-Willi syndrome. Conversely, paternal uniparental disomy or deletion of the maternally inherited chromosome 15q11-13 results in Angelman syndrome.

Single Gene Disorders and Mode of Inheritance

- Genetic disorders caused by a single gene with predictable patterns of inheritance are called mendelian disorders.
  - Cystic fibrosis and sickle cell anemia are commonly encountered examples of mendelian disorders.
- Alleles are variants of genes. The most common allele is generally referred to as wild-type. Variants from the wild-type allele are referred to as mutant, although it is important to note that many variant (mutant) alleles do not cause disease.
- Single nucleotide polymorphisms (SNPs) are sequence variants that commonly occur in the population (generally with a frequency of >1%). A person's SNP profile generally varies based on his or her genetic/ethnic background. SNPs generally do not cause disease, but are used as markers in genome-wide association studies to identify allelic variants associated with complex genetic disease (conditions generally not attributable to a single gene disorder).
- Autosomal dominant disorders occur following the inheritance of a single copy of a mutated allele. Each generation of the family pedigree is affected, with each affected individual having an affected parent (Fig. 18.1A). An affected individual has a 50% chance of having an affected child. Huntington disease is a classic example of an autosomal dominant disorder.
- Autosomal recessive disorders occur following the inheritance of two mutated alleles. In autosomal recessive disorders, the parents are often carriers (heterozygous for the mutant allele) but are not affected because one wild-type allele is sufficient to prevent the disease phenotype (see Fig. 18.1B). If both parents are carriers, there is a 25% chance that their child will be affected. Cystic fibrosis is a classic example of an autosomal recessive disorder.
- Disorders with mitochondrial inheritance occur due to mutations in mitochondrial DNA. Mitochondria are organelles that generate energy for the cell by converting oxygen and nutrients into adenosine triphosphate (ATP). Mitochondria contain their own chromosome (mtDNA) that encodes for several genes essential for mitochondrial function. Disorders of mtDNA are inherited almost exclusively from the mother (see Fig. 18.1C).
- X-linked recessive disorders are caused by mutant alleles that reside on the X chromosome, and their inheritance pattern is affected by gender. Females are generally not affected. Males have a 50% chance of being affected if their mother is a carrier (see Fig. 18.1D). In females, each cell contains two copies of the X chromosome, however one copy is randomly silenced in a process called lyonization. In rare cases, females can be affected by an X-linked recessive disorder if the active X chromosome in the majority of their cells carries the mutant allele (i.e., they have silenced the majority of the X chromosomes that carry the wild-type allele). Hemophilia A is a classic example of an X-linked recessive disorder.
- X-linked dominant disorders are caused by mutant alleles that reside on the X chromosome with both genders affected. Males are more severely affected, with some X-linked disorders lethal in males. Each offspring of an affected female has a 50% chance of being affected, whereas among offspring of affected males, all daughters are affected but none of the sons (see Fig. 18.1E).

Structural Chromosomal Abnormalities That Contribute to Human Genetic Disease

- Mitosis is the process by which somatic cells divide to create two daughter cells that each contain 46 chromosomes.
- Meiosis is the process by which germ cells divide such that the daughter cells ultimately contain one copy of each autosomal chromosome and one copy of a sex chromosome (X or Y) for a total of 23 chromosomes.
- Aneuploidy refers to an abnormal number of chromosomes (i.e., more or less than the normal complement of 46 for somatic cells and 23 for germ cells). Aneuploidy occurs due to nondisjunction, which is the failure of chromosomes to appropriately segregate during cell division. Trisomy 21 is an example of a common aneuploidy.
- Incomplete failure of chromosomal segregation during cell division or inappropriate crossover of genetic information between chromosomes (called recombination) can result in abnormalities of chromosomal structure or copy number variations (too many or too few copies of a given gene). These include:
- Insertions and deletions, frequently called indels, are the addition or deletion of base pairs to the DNA sequence, respectively. Large indels (5–10 megabases) can be detected by G-banding on a karyotype. Smaller indels are detected by fluorescence in situ hybridization (FISH) or comparative genomic hybridization microarray. Many indels are incidental findings and have no known clinical significance. In contrast, other indels can have a profound clinical impact, because they change the copy number of a critical gene or set of genes. DiGeorge syndrome (22q11 deletion) is an example of a common deletion that results in human disease.
- Translocations are chromosomal rearrangements where genetic information is rearranged between two nonhomologous chromosomes. There are several types of translocation:
  - Balanced translocations result from an equal crossover of genetic information between nonhomologous chromosomes. In a balanced translocation, each daughter cell receives a complete complement of genetic information. Balanced translocations are often asymptomatic but can result in disease if:

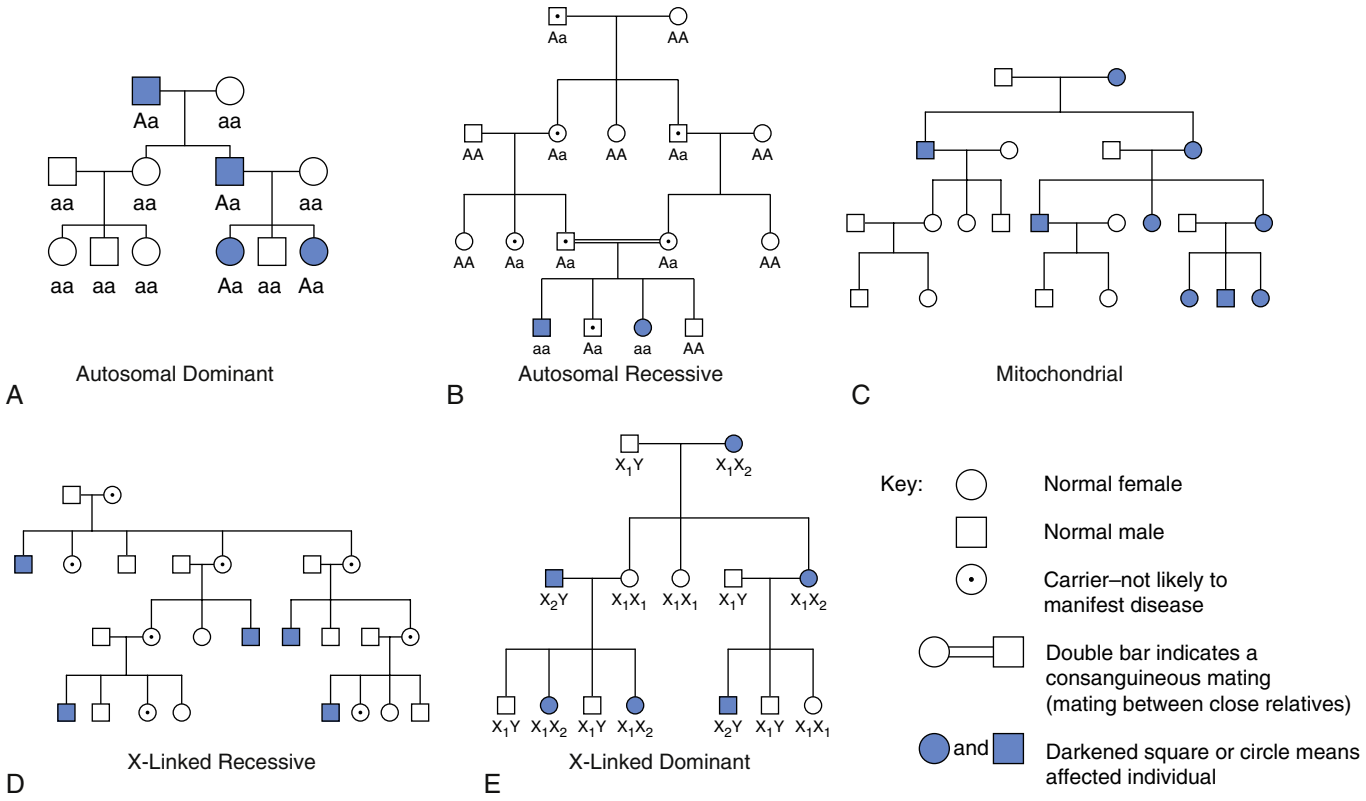

Fig. 18.1 (A–E) **Pedigrees demonstrating different modes of inheritance.** (Compiled from Figs. 4.3, 4.6, 4.8, 5.8, 5.12, and 5.15, in Jorde L, Carey J, Bamshad M. *Medical Genetics.* 5th ed. Philadelphia: Elsevier; 2016.)

- The translocation disrupts an important genetic regulatory element or gene.
- The translocation creates an abnormal fusion gene.
- The translocation results in an unbalanced amount of genetic material being passed on to offspring. For example, carriers of a robertsonian translocation of chromosome 21 are generally asymptomatic but have an increased risk of having a child with trisomy 21.

- Unbalanced translocations are the consequence of unequal crossover of genetic information between nonhomologous chromosomes and can result in gain or loss of genetic information.

- An inversion is a section of chromosome that is in the reverse orientation relative to the reference sequence. Inversions typically occur when there are two breaks in a chromosome and the intervening DNA sequence rotates 180 degrees before the breaks are repaired. As inversions are not associated with loss or gain of genetic information, they are often asymptomatic, but similar to translocations, inversions can be deleterious if they disrupt a critical gene or genetic regulatory element.

Diseases Caused by Trinucleotide Repeat Expansion

- Trinucleotide repeats are a series of three nucleotides, consecutively repeated, that occur within a region of DNA. During DNA replication, trinucleotide repeats are prone to "expansion mutation" where the number of triplet repeats in a given sequence increases. Beyond a certain threshold (which is different for each gene) the trinucleotide repeats interfere with the expression or function of their associated gene. Expansion of trinucleotide repeat sequences underlies >20 human genetic diseases, most notably fragile X syndrome, myotonic dystrophy, and Huntington disease.
- Trinucleotide repeats can occur in the region of the gene that codes for protein, resulting in a dysfunctional and sometimes toxic protein, as occurs in Huntington disease. Trinucleotide repeats can also occur in noncoding regions of the genome, and affect the expression of their associated gene, as occurs in fragile X syndrome.
- Anticipation is the process by which a disease has an earlier age of onset or increased severity with each successive generation of a family. Anticipation occurs in trinucleotide repeat diseases because expanded (but not normally sized) trinucleotide repeats tend to be unstable, with their size increasing with each subsequent generation.
- Expansion of trinucleotide repeats between generations can be impacted by the parent of origin. For example, in fragile X syndrome and myotonic dystrophy, anticipation occurs primarily when the expanded trinucleotide repeat sequence is transmitted from the mother.

Commonly Used Genetic Tests

- A karyotype assesses the number and appearance of the chromosomes. G-banding is a method of staining the

chromosomes to facilitate the detection of structural chromosome abnormalities, including translocations, inversions, and large insertions or deletions (indels). Karyotypes are readily available, and fairly low cost, but they can only be done on actively dividing cells and do not have sufficient resolution to detect abnormalities smaller than ~5 Mb.

- FISH uses fluorescent probes to detect specific genes or regions of the genome and is commonly used to detect insertions or deletions (Fig. 18.2). For example, FISH for 22q11 is frequently used to diagnose DiGeorge syndrome. FISH can also be used to diagnose aneuploidy. It often has a faster turnaround time than a karyotype because it does not require actively dividing cells.
- Array comparative genomic hybridization (aCGH; DNA microarray) is used to detect unbalanced copy number variations (indels) that are too small to be detected by karyotype. It is important to note that many indels detected by aCGH are not associated with any known disease phenotype. The resolution of aCGH varies based on the specific type of microarray used, but in general, aCGH can detect indels of ~200 kb or larger.
- Targeted mutation screening determines the sequence of a single gene or small group of genes. Targeted mutation screening is used when clinical findings suggest a specific mendelian disorder with a known disease-causing allele. For example, if an infant has an elevated immunoreactive trypsinogen (IRT) on newborn screening, then targeted mutation screening can be done on the CFTR gene to evaluate for cystic fibrosis.
- Whole exome sequencing (WES) uses next generation sequencing technologies to determine the sequence of all of the protein-coding regions (exons) in the genome and can also detect variants as small as 1 bp. The goal of WES is to find variants in protein coding genes that may be responsible for a disease phenotype. In neonates, WES is most commonly used in critically ill infants suspected to have an underlying genetic disorder but that do not have an obvious unifying diagnosis.
- Whole genome sequencing uses next generation sequencing technologies to determine the sequence of the entire genome. Due to high cost and the extremely complex bioinformatic analyses required, whole genome sequencing is not commonly used for clinical evaluations at this time.

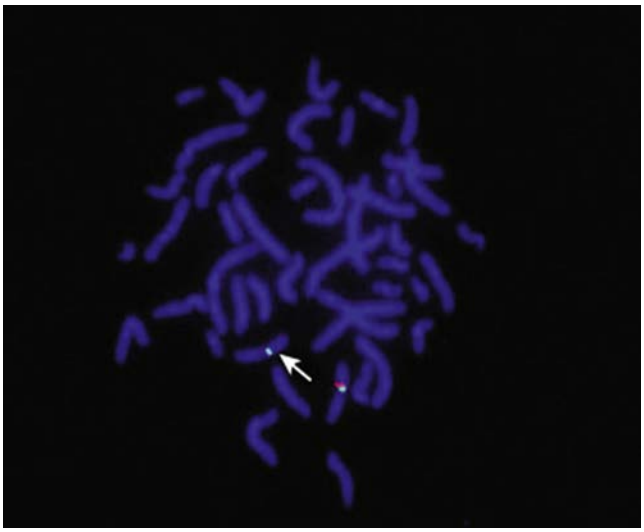

Fig. 18.2 Fluorescence in situ hybridization (FISH) assay demonstrating a microdeletion. Two fluorescent spots are visualized for the control probe *(green)*, indicating that it is annealing to the control region on homologous chromosomes. The single fluorescent spot visualized with the experimental probe *(red)* indicates deletion of the test region on one chromosome *(arrow)*. (From Gilner J, Kuller J, Valea F. *Reproductive Genetics in Comprehensive Gynecology.* 7th ed. Philadelphia: Elsevier; 2017:22–47.)

Diagnostic Approach to the Infant With Suspected Genetic Disease

- A genetic work-up should be considered in any infant that has more than one major and one minor abnormality that are not clearly attributable to environmental exposures such as fetal alcohol syndrome or diabetic embryopathy.
  - Major anomalies have a significant medical impact and are never part of normal variation (e.g., congenital heart disease).
  - Minor anomalies do not have a medical impact but are uncommon in the general population (e.g., single palmar crease).
- The first step in the genetic evaluation/consultation should be a detailed prenatal and birth history, family history, and physical examination. The initial diagnostic approach will be determined by the results of this evaluation.
  - If a specific genetic disorder is suspected, targeted genetic evaluation is indicated. For example, if an infant has clinical features consistent with trisomy 21, a karyotype or FISH for chromosome 21 would be the appropriate evaluation.
  - If the initial evaluation does not reveal a causative exposure or strongly implicate a specific genetic diagnosis, a karyotype and aCGH are generally the first-line studies and provide a diagnosis in ~20% of patients.
    - If karyotype and aCGH microarray do not provide a diagnosis, the choice of further studies, such as targeted mutation screening and/or WES, depends on clinical findings and should be done in consultation with a clinical geneticist.

Newborn Screening for Genetic Disorders

- All 50 states and the District of Columbia offer newborn screening. The goal of newborn screening is early identification of treatable genetic conditions.
- The majority of states use tandem mass spectrometry (MS/MS) on dried blood spots, often referred to as Guthrie cards, to screen for inborn errors of metabolism. MS/MS permits analysis of many different metabolites from a single sample. Newborn screening panels vary by state, but most include disorders of amino acid metabolism, organic acid metabolism, and fatty acid oxidation. Screening for endocrine disorders, including congenital hypothyroidism

and congenital adrenal hypoplasia, is also included in most newborn screening panels.
  - A positive newborn screen in a well, term neonate requires referral to a clinical geneticist (if positive for inborn error of metabolism) or endocrinologist (if positive for endocrine disorder) for confirmatory testing and management.
  - Of note, samples from premature or critically ill neonates may be difficult to interpret and are more likely to generate false-positive and false-negative results.
- Newborn screening for cystic fibrosis is done in all 50 states and the District of Columbia, and is done by measuring immunoreactive trypsinogen (IRT) on dried blood spots. Infants with an elevated IRT are referred for confirmatory testing via sweat testing and/or mutation analyses of the CFTR gene.
- Newborn screening for sickle cell disease and other hemoglobinopathies is also performed in all 50 states and the District of Columbia. Screening is done on dried blood spots using a combination of isoelectric focusing (IEF) and high-performance liquid chromatography (HPLC). Infants with a positive newborn screening result should be referred to a pediatric hematologist for confirmatory testing with hemoglobin electrophoresis.
- The majority of infants are also screened for hearing loss after birth. Hearing loss can be due to genetic or environmental factors.

Suggested Readings

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Wagner T, Bhoj E. Contemporary evaluation of the neonate with congenital anomalies. *NeoReviews*. 2017;18(9):522–531.

Zin A. Inborn errors of metabolism. In: Martin R, Fanaroff A, Walsh M, eds. *Fanaroff and Martin's Neonatal-Perinatal Medicine – Diseases of the Fetus and Infant*. Philadelphia: Elsevier Saunders; 2015; Chapter 99, 1553–1615.

Questions

1. A male infant has hypotonia, poor feeding, and cryptorchidism. You suspect Prader-Willi syndrome (PWS). Evaluation of the 15q11-13 region does not reveal any deletions. You should next evaluate for:
   a. point mutations in the PWS critical region
   b. duplication of the 15q11-13 region
   c. uniparental disomy of the 15q11-13 region
   d. other causes of neonatal hypotonia

2. Diseases with this mode of inheritance are almost exclusively transmitted from the mother:
   a. imprinted
   b. autosomal recessive
   c. trinucleotide repeats
   d. mitochondrial

3. You are asked to evaluate an infant for hypotonia. You note that the infant has significant hypotonia and feeding difficulties. The mother is well-appearing, but has difficulty releasing your handshake. Both the mother and infant are subsequently diagnosed with myotonic dystrophy. The phenomenon described here, where the infant is more severely affected than the mother, is known as:
   a. anticipation
   b. imprinting
   c. mitochondrial inheritance
   d. uniparental disomy

4. You are called to evaluate an infant with tetralogy of Fallot, cleft palate, and hypocalcemia. After your initial evaluation, you suspect the child may have DiGeorge syndrome. What is the most appropriate initial test to order?
   a. Karyotype
   b. Fluorescence in situ hybridization (FISH)
   c. Whole exome sequencing (WES)
   d. Sequencing of the TBX1 gene

5. Which of the following is a limitation of newborn screening?
   a. Preterm or critically ill neonates often have false-positive results.
   b. Current screening techniques can only evaluate for a few metabolites on each sample.
   c. Cystic fibrosis is not reliably detected by most newborn screening programs.
   d. Many states do not screen for sickle cell disease.

19 Patterns of Congenital Disorders

JOTISHNA SHARMA

Chromosomal Disorders

- Incidence: 1%–2% of live births
- 2% of pregnancies in women >35 years
- 50% of all spontaneous first trimester abortions
- 5% of couples with two or more miscarriages

Types of Chromosomal Abnormalities

- Numerical: alteration in the normal chromosomal number (46)
  - Aneuploidy
    - Loss (i.e., monosomy) or gain (i.e., trisomy) of individual chromosome from the diploid set
    - Monosomy
      - Autosomal monosomies are typically lethal early in pregnancy
      - Survival possible in mosaic forms
    - Trisomy: presence of three chromosomes
      - Most common type of aneuploidy
      - May be mosaic
  - Polyploidy
    - Euploid cells with more than the normal diploid number of 46 (2n), that is, 3n, 4n
    - Common abnormality in losses during first trimester of pregnancy losses
    - Triploidy: three haploid sets of chromosomes (3n)
  - Mosaicism: two or more cell lines in a single individual
- Structural: alteration in the structure of the chromosomes
  - Deletion: portion of chromosome missing or deleted
  - Inversion: portion of chromosome broken off, turned upside down, and reattached; results in genetic material inversion
  - Duplication: portion of genetic material is duplicated, resulting in extra genetic material
  - Translocation: two types
    - Balanced translocation
      - Equal exchange to chromosome segments between two chromosomes
    - Robertsonian translocation
      - One chromosome joins the end of another at the centromere
      - Involving chromosomes 1, 14, 15, 21, and 22
      - Relatively common: 1:1000
      - Phenotypically normal
      - Increased risk for offspring of carriers
  - Rings: portion of chromosome broken off and reattached in form of a ring/circle
  - Isochromosomes: one arm of chromosome is missing (monosomy) and the other duplicated in a mirror image fashion (trisomy)

Trisomy 21 (T21) "Down Syndrome"

BASIC INFORMATION

- Most common chromosomal abnormality with incidence of one per 700 live births

Etiology

- Meiotic nondisjunction (>90%): associated with advanced maternal age (>35 years)
- Translocation (3%–5%): two types
  - De novo: arises from balanced translocation carrier parent and results in unbalanced trisomy offspring
  - Translocated chromosome 21 rearranges with another acrocentric chromosome (usually chromosome 14), leading to robertsonian translocation
- Mitotic nondisjunction or mosaic (3%): phenotype varies from normal to a typical T21

CLINICAL PRESENTATION

Prenatal

- Karyotyping: amniocentesis and chorionic villus sampling (CVS) in first trimester
- Maternal serum quad screen test: decreased α-fetoprotein, decreased unconjugated estriol, increased total human chorionic gonadotropin (HCG), increased inhibin A
- Ultrasound (US) findings include: nuchal translucency/thickening, shortened long bones, underdeveloped/absent fetal nasal bone (70%), echogenic small bowel, "double-bubble" sign (duodenal atresia)

Physical Examination and Associated Abnormalities

- *General*: hypotonia[a] (80%), joint hyperflexibility[a] (80%), poor Moro reflex[a] (85%)
- *Craniofacial and neurologic*: flat facial profile[a] (90%), brachycephaly, upslanting palpebral fissures[a] (80%), late closure of fontanelles, inner epicanthal folds, open mouth with protruding tongue, atlantoaxial instability (1%–2%), seizures (5%–10%; often manifest during infancy), incomplete fusion of vertebral arches of lower spine (37%)

[a] Principal features in the neonate.

- *Developmental delay*: motor (worse in first 3 years of life), language delay
- *Cognitive impairment*: affected by genetic and environmental factors, autism (1%)
- *Dentition*: hypodontia and delayed dental eruption
- *Eyes*: Brushfield spots with peripheral hypoplasia of iris, fine lens opacities (59%) on slit lamp examination, nystagmus (35%), strabismus (45%), cataract (15%), myopia (70%)
- *Ears*: hearing loss (75%), middle ear effusions (60%–80%)
- *Neck*: excess skin on back of neck[a] (80%)
- *Hands and feet*: hypoplasia of midphalanx of fifth finger[a] (60%) with clinodactyly (50%), single palmer crease[a] (45%), palmar axial triradius (84%), wide gap with deep plantar groove between first and second toes
- *Cardiac (40%)*: atrioventricular canal (AV canal) defects, ventricular septal defect (VSD), atrial septal defect (ASD), patent ductus arteriosus (PDA), tetralogy of Fallot (TOF)
- *Gastrointestinal anomalies (12%)*: duodenal atresia (2%–5%), diastasis recti, tracheoesophageal fistula (TEF), Hirschsprung disease, imperforate anus
- *Skin and hair*: cutis marmorata (43%), dry hyperkeratotic skin with time (75%)
- *Genitalia*: male (micropenis, decreased testicular volume)
- *Endocrine*: hypothyroidism (5%; association with thyroid autoantibodies or thyroid agenesis), short stature, fertility (primary gonadal failure results in infertility, rare cases of female fertility)
- *Hip and pelvis*: hip dysplasia/dislocation (6%), avascular necrosis, slipped capital femoral epiphyses
- *Hematologic*
  - Transient myeloproliferative disorder (TMD) (10%): regresses by 3 months of age
    - Risk of later onset of leukemia (10%–30%): *GATA1* gene mutation
  - Leukemia (1%)
    - Megakaryoblastic leukemia (AMKL)
    - Acute lymphoblastic leukemia (DS-ALL): mutations in the JAK-STAT pathway
  - Polycythemia (18%–64%), neonatal thrombocytopenia, defects in T cell maturation and function with increased infection risk
- *Others*: eleven ribs, tracheal stenosis, obstructive sleep apnea (50%–75%)

DIAGNOSIS AND EVALUATION

- Genetic test
  - Fluorescent in situ hybridization (FISH): identifies extra chromosome 21, but doesn't detect translocation
  - Karyotype: high resolution chromosomal analysis to confirm translocation
- Echocardiogram (Echo)
- Gastrointestinal radiography and contrast studies: based on clinical concerns
- Hematologic: Complete blood count (CBC) at birth and as needed
- Ophthalmologic exam: first month of life, then annually
- Hearing screen
  - At birth with follow-up assessment by 3 months of life
  - Age appropriate testing at 6 months, then annually
- Screen for hypothyroidism
  - Within first 2 weeks of life (usually newborn screen)
  - Thyroid-stimulating hormone (TSH) and free thyroxine (fT4) level
  - Follow-up screening at 6, 12 months of life, then annually
- Growth
  - Parameters at birth 10%–25% percentile range
  - Postnatal growth restriction not uncommon

TREATMENT

- Genetic: confirm diagnosis and provide genetic counseling
  - One child with T21: maternal recurrence risk of another affected child 1% higher than her age-specific risk (more significant in younger mothers)
  - De novo translocation: recurrent risk is less than 1%
  - Mother with robertsonian translocation
    - Risk for another translocation T21 fetus is 15% at amniocentesis and 10% at birth
  - Father is translocation carrier: recurrence risk lower (1%–2%)
- Surgical intervention (as needed)
- Treatment for hypothyroidism
- Early intervention and developmental therapy

PROGNOSIS

- Causes of mortality: congenital heart disease, infection (pneumonia)
- 50% survive to 60 years
- When older than 40 years of age: neurodegenerative disease with features of Alzheimer disease

Trisomy 18 (T18) "Edward Syndrome"

BASIC INFORMATION

- Second most common multiple malformation syndrome with incidence of one per 6000 live births
- Associated with a high rate of in utero demise: 5% of conceptuses survive to birth
- 3:1 female preponderance

Etiology

- Presence of extra chromosome 18 (complete, mosaic, or partial trisomy 18q)
- Most commonly nondisjunction: complete trisomy (94%)
- Associated with advanced maternal age (>35 years)

CLINICAL PRESENTATION

Prenatal

- Karyotyping: amniocentesis and CVS
- Maternal serum triple screen test: decreased α-fetoprotein, decreased unconjugated estriol, decreased total human chorionic gonadotropin (HCG)
- US findings include: growth restriction, oligohydramnios or polyhydramnios, limb anomalies, absence of nasal bone (55%), heart defects, choroid plexus cyst

Physical Examination and Associated Abnormalities

- *General*: small for gestation age (SGA)[b], single umbilical artery[b], weak cry, one-third preterm and one-third post-term[b], small placenta[b]
- *Craniofacial and neurologic*: microcephaly, prominent occiput[b], wide fontanelles, cleft palate/lip, small mouth[b], micrognathia[b], hypotonia in newborn period, hypertonia beyond neonatal period[b], seizures (25%–50%), marked to profound psychomotor and intellectual disability[b], Dandy-Walker malformation, agenesis of corpus callosum
- *Eyes*: short palpebral fissures[b], inner epicanthal folds, colobomas of iris, cataract
- *Ears*: low-set malformed auricles[b]
- *Hands and feet*: clenched hands[b], overlapping digits[b], absence of distal crease on fifth finger[b], hypoplastic nails[b], hypoplastic/absent thumb[b], "Rocker bottom" feet, short hallux, syndactyly of second and third toes[b]
- *Hip and pelvis*: limited hip abduction[b], small pelvis, dislocated hip[b]
- *Thorax and pulmonary*: short sternum (decreased number of ossification centers)[b], small nipples[b], eventration of diaphragm
- *Cardiac (80%–100%)*: VSD[b], ASD[b], PDA[b], bicuspid aortic valve (AV), pulmonic stenosis (PS), coarctation of aorta (CoA), TOF
- *Gastrointestinal*: hernia (inguinal, umbilical)[b], diastasis recti[b], Meckel diverticulum, omphalocele, tracheoesophageal fistula, extrahepatic biliary atresia
- *Skin and hair*: redundancy[b], cutis marmorata[b], hirsutism of forehead and back[b]
- *Genitourinary*: horseshoe kidney (66%), ectopic kidney, cryptorchidism and hypospadias (male) [b], hypoplasia of labia majora with prominent clitoris (female)

DIAGNOSIS AND EVALUATION

- Genetic test
  - FISH: quicker time to diagnosis, may assist in plan of care
  - Karyotype: high resolution chromosomal analysis to confirm translocation
- Other investigations: Echo, brain MRI, ophthalmologic exam

TREATMENT

- Genetic: confirm diagnosis and provide genetic counseling
  - Maternal recurrence risk of T18 in future pregnancy is 1% > her age-specific risk
- Infant care options: medical and surgical interventions or palliative care attained after discussion amongst medical providers and parents

PROGNOSIS

- Very poor: 50% mortality in first week of life
- >90% infants die in first 6 months of life
- Only 5% alive at 1 year of life; few have survived to childhood
- Increased risk of kidney and liver cancer in survivors
- Causes of mortality: central apnea (early deaths), infection, congestive heart failure

Trisomy 13 (T13) "Patau Syndrome"

BASIC INFORMATION

- Incidence: one per 5,000–10,000 live births
- High rate of in utero demise: only 2%–3% of fetuses survive to birth

Etiology

- Due to presence of extra chromosome 13 (complete, mosaic, or partial trisomy 13q)
- Most commonly nondisjunction: complete trisomy
- Associated with advanced maternal age (>35 years)

CLINICAL PRESENTATION

Prenatal

- Karyotyping: amniocentesis and CVS
- US findings include: increased nuchal translucency (21%), growth restriction, central nervous system and facial anomalies (64%), absence of nasal bone (35%), heart defects (54%)

Physical Examination and Associated Abnormalities

- *General*: SGA[c], microcephaly[c], single umbilical artery[c]
- *Craniofacial and neurologic*: holoprosencephaly[c] (50%), cutis aplasia[c] (50%), sloping forehead[c], wide fontanelles[c], cleft lip[c] (60%–80%) ± cleft palate, micrognathia, apnea, hypertonia/hypotonia, seizures (EEG with hypsarrhythmia), agenesis of corpus callosum, cerebellar hypoplasia, myelomeningocele
- *Eyes*: colobomas of iris[c], microphthalmos[c], retinal dysplasia[c], shallow orbital ridges, upslanting palpebral fissures, absent eyebrows, anophthalmos, cyclopia
- *Ears*: abnormal helices[c], low-set ears[c], hearing loss
- *Neck*: excess skin on back of neck
- *Hands and feet*: distal palmar axial triradii[c], single palmer crease[c], hyperconvex narrow fingernails[c], flexion of fingers with/without overlapping[c], camptodactyly[c], postaxial polydactyly[c], cleft between first and second toes, hypoplastic toenails, equinovarus
- *Hips and pelvis*: hypoplasia of pelvis with shallow acetabular angle[c]
- *Thorax and pulmonary*: thin posterior ribs with or without missing rib[c], situs inversus of lungs. diaphragmatic defect
- *Cardiac (80%)*: VSD[c], PDA[c], ASD[c], dextrocardia[c], PS, hypoplastic aorta, bicuspid AV
- *Gastrointestinal*: hernia (inguinal and umbilical)[c], omphalocele, Meckel diverticulum
- *Skin*: capillary hemangiomata (forehead)[c]

[b] Abnormalities occur in ≥50% of patients.

[c] Abnormalities occur in ≥50% of patients.

- *Genitourinary*: polycystic kidney (30%), hydronephrosis, horseshoe kidney, male (cryptorchidism[c], abnormal scrotum[c]), female (bicornuate uterus[c], hypoplastic ovaries)
- *Hematologic*: increased frequency of nuclear projections in neutrophils ("drumstick" appearance)[c], persistence of embryonic and/or fetal hemoglobin[c]
- *Others*: flexion deformity of large joints, *S*-shaped fibula

DIAGNOSIS AND EVALUATION

- Genetic test
  - FISH: quicker time to diagnosis, may assist in plan of care
  - Karyotype: high resolution chromosomal analysis to confirm translocation
- Other investigations: Echo, brain MRI, ophthalmologic exam

TREATMENT

- Genetic: confirm diagnosis and provide genetic counseling
  - Maternal recurrence risk of T13 in future pregnancy is 1% greater than her age-specific risk
- Options of care of infant, which includes medical and surgical interventions or palliative care, attained after discussion amongst medical providers and parents

PROGNOSIS

- Overall prognosis extremely poor with 80% mortality during neonatal period
- Median survival is 7 days of life
- Rare childhood survivors with profound cognitive impairment, feeding difficulties

Turner Syndrome (45,X)

BASIC INFORMATION

- Phenotype associated with loss of all or part of one copy of the X chromosome in a female conceptus
- Incidence: one per 2500 female newborns
- 0.1% of fetuses with a 45,X complement survive to term: more than 99% spontaneously aborted

Etiology

- Faulty chromosomal distribution leading to 45,X individual
- In 80% of cases, paternally derived X chromosome that is lost
- 50% due to the 45,X karyotype or loss of one entire X chromosome cases (monosomy)
- 50% due to variety of X chromosome anomalies including: deletions, isochromosomes, translocations, mosaicism
- SHOX gene: important for bone development and growth
  - Loss of one copy of this gene responsible for short stature and skeletal abnormalities in Turner syndrome
- Advanced maternal age NOT a risk factor

CLINICAL PRESENTATION

Prenatal

- Karyotyping: amniocentesis and CVS
- US findings include: cystic hygroma (26%), fetal hydrops (11%), increased nuchal translucency (13%), and heart defects (13%)

Physical Examination and Associated Abnormalities

- *General*: wide phenotype variability, short stature, webbed neck (50%)
- *Craniofacial and neurologic*: high arched palate (>80%), epicanthal folds (40%), hearing loss, anomalous auricles (>80%)
- *Neck*: low posterior hairline
- *Hands and feet*: lymphedema (>80%), nail hypoplasia, cubitus valgus (>70%), distal palmar axial triradii (40%), medial tibial exostosis (60%)
- *Hips and pelvis*: hip dislocation
- *Thorax and pulmonary*: shield chest, widely spaced nipples (>80%), pectus excavatum
- *Cardiac (30%–50%)*: bicuspid AV (30%), CoA (10%), aortic stenosis, mitral valve prolapse
- *Skin*: excessive pigmented nevi (>50%), loose skin
- *Genitourinary*: horseshoe kidney, double/cleft renal pelvis, gonadal dysgenesis

DIAGNOSIS AND EVALUATION

- Karyotype: chromosomal analysis
- Other investigations: Echo

TREATMENT

- Genetic: confirm diagnosis and provide genetic counseling
  - Majority are due to sporadic event: monosomy (nondisjunction) or mosaic
  - No adequate data on recurrence risk
  - Partial deletion of X chromosome: rare and can be inherited
- Growth issues (short stature) concern: growth hormone therapy offered at 4–5 years of age
- Primary ovarian failure
  - Due to gonadal dysplasia (streak gonads) greater than 90%
  - Delay of secondary sexual characteristics and primary amenorrhea
  - Cyclic hormonal therapy is initiated at the age of puberty
  - Infertility is common, but may be treated with assisted reproductive therapy
- Exploratory laparotomy
  - 6% of females with Turner syndrome have 45X/46XY mosaicism
  - To remove any residual gonadal tissue (eliminate risk of gonadoblastoma)

PROGNOSIS

- Intellectual development: most normal intelligence, difficulties with spatial and perceptual reasoning

- Increased risk for dissection of the aorta: aortic root dilation (8%–42% prevalence)
- Morbidity: related to diabetes mellitus, hypertension, and ischemic heart disease

Triploidy (69, XXX or 69, XXY)

BASIC INFORMATION

- Karyotype containing three copies of each chromosome
- Occurs in 2% of conceptuses
- Majority of triploid fetuses spontaneously abort: live births are rare
- 15% of chromosomally abnormal pregnancies

Etiology

- Extra set of chromosomes is paternally derived in 69% of cases
- 60% of cases have been XXY
- Mosaicism (combinations of diploid and triploid, mixoploid) has been documented
- Advanced maternal age is not a risk factor

CLINICAL PRESENTATION

Malformations of the fetus (newborn)

- Disproportionate prenatal growth deficiency
- Neural tube defects, hydrocephalus
- Holoprosencephaly, ocular and auricular malformations
- Cardiac defects
- Third and fourth syndactyly of fingers
- Abnormal placenta (large and cystic)
- Partial hydatidiform moles

PROGNOSIS

- No data to indicate increased risk of recurrence
- A triploid pregnancy sometimes is preceded or succeeded by a molar pregnancy

Deletion Syndromes

- Partial monosomy of a chromosome can lead to a recognizable pattern of malformations
- Deletion or loss of genetic material from the short *(p)* arm of chromosome

Chromosome 1p36 Deletion Syndrome (1p36)

BASIC INFORMATION

- Incidence: one per 10,000 live births
- Monosomy for the distal short arm of chromosome 1, or deletion of 1p36
- Most frequently occurring subtelomeric deletion

Etiology

- Majority of deletions arise de novo

CLINICAL PRESENTATION

Physical Examination and Associated Abnormalities

- Microcephaly, frontal bossing, midface hypoplasia, orofacial cleft
- Hypotonia, seizures, infantile spasm, diffuse brain atrophy, hearing loss
- Cardiac: PDA, VSD, ASD, Ebstein anomaly, cardiomyopathy
- Brachydactyly, camptodactyly, scoliosis, delayed bone age
- Renal anomalies, cryptorchidism, micropenis, hypoplastic labia minora

DIAGNOSIS AND EVALUATION

- Genetic test
  - High-resolution karyotype: may not detect all deletions
  - Confirmatory test: FISH and array comparative genomic hybridization (CGH)
- Other investigations: Echo, brain MRI, EEG, audiology and ophthalmologic exam

PROGNOSIS

- Feeding issues: poor suck and swallowing, auditory and visual impairment
- Intelligence quotient (IQ) generally less than 60, survive to adulthood

Wolf-Hirschhorn Syndrome (4p-)

BASIC INFORMATION

- Incidence: one per 50,000 live births
- Distal deletions of the short arm of chromosome 4

Etiology

- De novo mutation: >80% of 4p deletions
  - Deleted chromosome is paternally derived (80%), recurrence risk very low
- Translocation: 10%–15%
  - 2:1 excess of maternally derived 4p deletions
  - Parental chromosomal analysis indicated for recurrence risk counseling

CLINICAL PRESENTATION

Physical Examination and Associated Abnormalities

- Intra-uterine growth restriction (IUGR), microcephaly, cleft lip/palate, cutis marmorata, scoliosis
- "Greek warrior helmet" facies: hypertelorism, epicanthal folds, beaked nose, high forehead with prominent glabella
- Optic nerve defects, coloboma, hypotonia, seizures
- Cardiac: ASD, PS
- Cryptorchidism, hypospadias, clitoral hypoplasia

DIAGNOSIS AND EVALUATION

- Genetic test:
  - High-resolution karyotype: may not detect small submicroscopic deletions
  - Confirmatory test: microarray, cytogenetic analysis using 4p telomere probes
- Other investigations: Echo, ophthalmologic exam

PROGNOSIS

- Feeding issues, failure to thrive, developmental delay is common
- One-third of infants die in first year of life

Cri du chat Syndrome (5p-)

BASIC INFORMATION

- Incidence: one per 50,000 live births
- Partial monosomy of chromosome 5p

Etiology

- De novo mutation (>90% of 5p deletions)
  - Deleted chromosome is paternally derived (80%)
  - Recurrence risk very low (<1%)
- Translocation: 10%
  - Malsegregation of balanced translocation in carrier parent
  - Recurrence risk 10%–15% of unbalanced translocation
  - Parental chromosomal analysis indicated for recurrence risk counseling

CLINICAL PRESENTATION

Physical Examination and Associated Abnormalities

- Low birth weight, microcephaly, round face, hypertelorism, downward-slanting palpebral fissures, broad nasal bridge, short philtrum
- Hypotonia, agenesis of corpus callosum, cerebral atrophy, cerebellar hypoplasia
- Cardiac: ASD, VSD, TOF
- Unusual cry (cat-like cry): ascribed to abnormal laryngeal development
- Renal anomalies: renal agenesis, horseshoe kidney

DIAGNOSIS AND EVALUATION

- Genetic test: high-resolution karyotype
- Other investigations: Echo, renal ultrasound (US), brain MRI

PROGNOSIS

- Feeding issues during infancy, intellectual disability and developmental delay
- Most individuals have normal life expectancy

Microdeletion Syndromes

- Disorders result from inappropriate dosage of crucial genes in a given genomic segment via structural mechanisms (deletion)
- In many of the microdeletion syndromes, possibility that a reciprocal duplication of the exact same region may also occur

22q.11.2 Deletion Syndrome (DiGeorge Syndrome)

BASIC INFORMATION

- Incidence: one per 3000 live births
- Most common microdeletion syndrome in humans

Etiology

- 90% of deletions occur de novo
- Less than 10% inherited from an affected parent (considered autosomal dominant)
- Interstitial deletion of chromosome 22q11.2
- Clinical phenotype related to haploinsufficiency of one of these genes (*TBX1)*
  - *TBX1* encodes a T-box transcription factor
- Reciprocal duplications of the 22q11.2 common deletions reported
  - 70% inherited the duplication (usually from a normal parent)

CLINICAL PRESENTATION

Physical Examination and Associated Abnormalities

- Microcephaly (40%–50%), hypertelorism, hooded eyelids, bulbous nasal tip
- Cleft lip/palate, conductive hearing loss, small mouth, micrognathia
- Hypotonia (70%–80%), hyperextensible fingers/toes (63%)
- Cardiac (85%): interrupted aortic arch type B, truncus arteriosus, TOF
- Thymus and parathyroid: aplasia/hypoplasia, hypocalcemia
- Renal agenesis, hypospadias, abnormal T cell function

DIAGNOSIS AND EVALUATION

- Genetic test: FISH or DNA microarray (80%–90% detected)
  - Both parents of affected child tested to determine if they carry the deletion
- Other investigations: Echo, renal US, brain MRI

PROGNOSIS

- Developmental and learning disabilities: speech and language delay
- Death, usually due to cardiac defects

Single Gene (Mendelian) Disorders (see Chapter 18)

- Familial: dominant, recessive, autosomal, or sex-linked
  - Autosomal dominant (AD) disorders
    - When affected individual has normal parents, may be due to:

- New mutation
  - Skipped generation (nonpenetrance of the genes)
- Gonadal mosaicism (gene present in cells of gonad of one parent)
- Autosomal recessive (AR) disorders
  - Risk increased with consanguinity
  - Each sibling of an affected individual carries a one-quarter risk of being affected and a two-thirds risk of being a carrier
- X-linked recessive and X-linked dominant disorders (see Chapter 18)
- Pedigree analyses of families useful to determine the inheritance pattern
- Genetic heterogeneity: two different genes cause the same phenotype
  - Can be caused by more than one genetic mechanism
  - Molecular diagnosis assists in defining mode of inheritance

Fragile X Syndrome

BASIC INFORMATION

- Incidence: one in 4000 males, one in 8000 females
- Individuals with developmental delay, intellectual disability, and/or autism
  - 1%–3% have a full mutation
- Most common inherited cause of intellectual disabilities
- Most common known cause of autism
- The phenotype is identified most readily in males
- Carrier mother has 50% chance of passing mutated gene to each of her children
- Carrier father will pass permutation gene to all his daughters (become carriers), but not to his sons
- Fragile X permutation can be passed silently through generations

Etiology

- X-linked dominant inheritance
- Due to expansions of a trinucleotide repeat (CGG) in the 5' untranslated region of the *FMR1* gene located at the Xq27.3
  - Normal individuals have from 6–54 repeats
  - Male and female permutation carriers have 54–200 repeats
  - Affected individuals (full mutation) have >200 repeats

CLINICAL PRESENTATION

Physical Examination and Associated Abnormalities

- Macrocephaly, prominent forehead, elongated face, prognathism (puberty)
- Large ears, pale blue irides, epicanthal folds, high arched palate, cleft palate
- Hypotonia, pectus excavatum, mitral valve prolapse, aortic dilation
- Hand flapping or biting (60%), poor eye contact (90%), anxiety
- Hyperactivity/hyperarousal, aggression outburst, autism spectrum disorder (60%)
- Males: mild to profound intellectual disability (IQ 30–55)
- Females with full mutation: IQ less than 70 (30%–50%)
- Female permutation carriers: 20% risk for premature ovarian failure
- Fragile X–associated tremor/ataxia syndrome (FXTAS)
  - Deficits in executive function, atypical parkinsonism, cerebellar tremor, dementia
  - 46% of male and 17% of female permutation carriers develop symptoms after age 50

DIAGNOSIS

- DNA analysis of the FMR1 gene

PROGNOSIS

- Normal life span, sensory processing disorders are common
- Infancy: feeding problems (GER) and otitis media
- Growth rate increased in the early years, delayed motor milestones

Mitochondrial Disorders

- Maternally inherited
- Results in dysfunction of the mitochondria with inadequate production of energy in critical tissue
- Clinically multisystem involvement:
  - Visual loss, progressive myopathy, seizures, encephalopathy, diabetes
- High spontaneous mutations
- Wide spectrum of severity (due to heteroplasmy)
- Affected females transmit disease to their offspring (male and female)
  - Risk approaches 100% (human egg source of all the mitochondria of the offspring)
  - Clinical phenotype occurs when a threshold of abnormal to normal mitochondria exceed in the critical tissue
  - Phenotypically unaffected daughters of affected women also have risk of vertical transmission
  - Lack of clinical disease does not preclude that some of the daughter's mitochondria may harbor the mutation
- Affected males have normal offspring

Non-Mendelian Inheritance

PARENT OF ORIGIN EFFECTS

- Genomic imprinting
  - Only one copy of the normal two copies of genes (one each inherited from mother and father) either is active or "turned on"
  - The active copy depends on the parent of origin
- Uniparental disomy (UPD)
  - The two copies of a chromosome pair or part of a chromosome come from the same parent
  - Associated with advanced maternal age

ANGELMAN SYNDROME

- Maternally derived deletion chromosome 15q11-13 (60%)
- Paternal UPD (40%) chromosome 15

BECKWITH WIEDEMANN SYNDROME

- 85% sporadic
- Less than 5% genetic including paternal UPD—two copies of paternally derived chromosome 11p15.5

PRADER-WILLI SYNDROME

Introduction

- Prevalence: one in 15,000

Etiology

- Loss of activity on the long arm of chromosome 15 (15q11-13) due to
  - Imprinting (70%): paternally derived deletion of 15q11-13
  - Maternal UPD (25%–30%): possess two normal maternally derived chromosome 15
  - Mutation of the imprinting center or translocation (1%–3%)

Clinical Presentation

- Central hypotonia, almond-shaped eyes, small down-turned mouth
- Small hands and feet, micropenis, hypoplastic scrotum, cryptorchidism

Diagnosis

- Methylation analysis detects all three molecular defects (deletion, UPD, mutation); abnormal in 99% affected
  - If methylation pattern is abnormal, then perform:
    - FISH for detection of a deletion
    - Molecular assay to confirm maternal UPD
- An abnormal methylation analysis and normal FISH and UPD studies indicate an imprinting defect
- Counseling
  - Recurrence risk negligible for de novo deletions
  - Recurrence risk without deletions is one in 1000

PROGNOSIS

- Hypotonia improves in first year of life
- Hypothalamic and primary gonadal dysfunction
- Developmental delay: speech and gross motor
- Intellectual disability is mild to moderate
- Feeding
  - Infancy: poor feeding and failure to thrive
  - Childhood: hyperphagia and obesity with subsequent diabetes risk
- Behavioral issues: temper tantrums, obsessive compulsive disorder

Multifactorial Disorders

- Familial clustering is observed
- Many common malformations have different birth frequencies in different populations

Table 19.1 Recurrence Risk for Some Multifactorial Defects

Defect	RECURRENCE RISK (FOR) Normal Parents of One Affected Child	Future Males	Future Females
Cleft lip with or without cleft palate	4%–5%		
Cleft palate alone	2%–6%		
Cardiac defect (common type)	3%–4%		
Pyloric stenosis	3%	4%	2.4%
Hirschsprung disease	3%–5%		
Clubfoot	2%–8%		
Dislocation of hip	3%–4%	0.5%	6.3%
Neural tube defects (anencephaly, myelomeningocele)	3%–5%		
Scoliosis	10%–15%		

Adapted from Smith's Recognizable Patterns of Human Malformation, Jones KL, Jones MC and Del Camp M. 7th Edition, 2013

- Majority of defects' risk in offspring of normal parents with an affected child is 2%–5% (Table 19.1): 20–40 times the frequency in the general population
- Second-degree relatives (uncles, aunts) marked decrease risk compared to first-degree relatives
- As the number of affected family members increases, so does the risk for recurrence
- Consanguinity: inbreeding increases the number of "susceptibility genes" and risk
- The more severe the malformation, the greater the risk for recurrence
- Recurrence risk increased for relatives of the least affected gender (if gender differences noted)

Suggested Readings

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Questions

1. A 38-weeks-gestation newborn infant at birth is noted to be small for gestational age, have microcephaly, cleft lip and palate, narrow hyperconvex fingernails, developed central apnea shortly after birth, and an echocardiogram showed ventricular septal defect (VSD). This infant most likely has:
   a. Trisomy 21
   b. Fetal alcohol syndrome
   c. Trisomy 13
   d. Trisomy 18
   e. Prader-Willi syndrome

2. A full-term, appropriate for gestational age (AGA) male infant has persistent hypoglycemia despite adequate calorie feeds, orally. He is also noted on physical examination to have a large tongue and exophthalmos. What is the mode of inheritance of this infant's condition?
   a. Autosomal dominant
   b. Uniparental disomy
   c. Autosomal recessive
   d. X-linked recessive
   e. X-linked dominant

20 Nongenetic Etiologies for Congenital Defects

GEORGIANNE LEE ARNOLD

- Basic information
  - Not all birth defects are genetic in origin
  - Nongenetic factors can cause malformations, deformations, and disruptions
  - Malformations
    - Permanent, abnormal development of a structure
    - The defect occurs during early embryonic development
    - Examples of malformations:
      - congenital heart defects
      - neuronal migration defects
      - unilateral or bilateral clefts
      - limb agenesis
  - Deformations
    - Abnormalities in a structure caused by an extrinsic force
    - Timing is typically during later fetal development
    - Fairly common
    - Often responsive to physical therapy
    - Often the result of abnormal uterine shape, unusual fetal positioning, or secondary to a malformation in a sequence—renal malformations resulting in oligohydramnios, leading to fetal compression with deformation of feet (club feet) and face (facial flattening)—i.e. Potter Syndrome
      - Examples of deformations
        - Fetal akinesia sequence
        - Torticollis-plagiocephaly deformation sequence
        - Positional congenital hip subluxation
        - Positional scoliosis
  - Disruptions
    - Abnormalities in a structure caused by interference with or breakdown of a normal developmental process
    - Examples of disruptions:
      - Amniotic band sequence
        - Basic information
          - Caused by amnion rupture
        - Clinical presentation
          - Amnion strings wrap around limbs, causing constriction rings/amputations
          - Can cause facial clefts
          - Clubfoot is common
        - Diagnosis and evaluation
          - Clinical examination
        - Treatment
          - Supportive
      - Porencephaly secondary to cerebrovascular accident
      - Basal ganglia cysts from energy deficiency disorders
      - Teratogens

Teratogens

- Basic information
  - Cause nongenetic birth defects through maternal exposure
  - Vulnerable periods
    - Embryogenesis (through 8 weeks): period of organogenesis when exposure is most likely to result in structural birth defects
    - Fetal period—(9–40 weeks): fetal and brain growth most likely to be affected
    - Examples of windows of greatest vulnerability
      - Heart: first 8 weeks
      - Limbs: first 12 weeks
      - Palate: first 12 weeks
  - Genetic effects may affect susceptibility to teratogens
- Environmental Factors: Includes Drugs of Abuse, Medications, and Environmental Exposures (Table 20.1)
  - Fetal alcohol spectrum disorders
    - Basic information
      - Disrupts fetal development at all stages of pregnancy
      - Leading preventable cause of birth defects and neurodevelopmental abnormalities
    - Clinical presentation
      - Variable spectrum of structural and developmental anomalies
    - Diagnosis and evaluation
      - Institute of Medicine diagnostic categories
        - Fetal alcohol syndrome (FAS)
          - Evidence of prenatal alcohol exposure
          - Evidence of central nervous system (CNS) abnormalities
          - Facial abnormalities: short palpebral fissures, smooth philtrum, thin upper lip narrow
          - Growth deficits
        - Partial FAS (pFAS)
          - Some features of FAS
        - Alcohol-related neurodevelopmental disorder (ARND)
          - Prenatal alcohol exposure and some CNS structural or functional abnormalities
        - Alcohol-related birth defects (ARBD)
          - One or more: heart, kidney, skeletal, immune
          - Seen in conjunction with FAS or pFAS
    - Treatment
      - Symptomatic only
  - Antiepileptic medications
    - Basic information

Table 20.1 Partial List of Common Teratogens

Category	Teratogen	Time of Susceptibility	Fetal Effects
Drugs of abuse	Alcohol	Any	Fetal alcohol spectrum disorders (structural, CNS, growth, neurodevelopmental)
	Cocaine	Any	Low birth weight, microcephaly
	Nicotine	Any	Cleft lip/palate. low birth weight, microcephaly
Antiepileptic	(Categorical)		Heart, hypospadias, and facial clefts
	Valproate	Any	Neural tube defects, anatomic, and neurodevelopmental defects
	Phenytoin	Any	Fetal hydantoin syndrome (facial, skeletal [digital], neurodevelopmental)
ACE inhibitors	Various	First trimester	Cardiac, neural tube defects
		Trimesters 2–3	Renal dysplasia and failure, oligohydramnios
Cancer/Immune	Methotrexate	Any (highest 6–8 weeks)	Limb defects, CNS, GI, heart, neurodevelopmental
	Thalidomide	20–36 days	Limb defect, CNS, eye, ear, heart, GI, others
	Aminopterin	First trimester	Neural tube defects, facial clefts
	Retinoic acid	First trimester	CNS, neural tube defects, microcephaly, facial clefts, limb defects, others
Psychiatric	Lithium	First trimester	Cardiac, particularly Ebstein anomaly
Anticoagulant	Warfarin	Any	Facial (nasal hypoplasia), CNS, cardiac defects, fetal hemorrhage
Environmental	Mercury	Any	CNS defects, neurocognitive defects
	Radiation	2–18 weeks	Microcephaly, neurocognitive defects
	Temperature	Any	Neural tube defects, cardiac, facial defects
Maternal metabolic disorders	Diabetes	Preexisting	Caudal regression, renal, cardiac defects
		Gestational	Macrosomia
	PKU	Any	Cardiac, GI defects, microcephaly, neurocognitive defects
Infection	Toxoplasmosis	First trimester	Fetal death
		Second trimester	Hydrocephalus, intracranial calcifications, chorioretinitis
	Rubella	Trimesters 1–2	Hearing loss, cataract, retinopathy, cardiac defect

- Two to three times increased risk of birth defects in various studies
- Risk depends on specific drug and dose
- In general, risks increased for heart, hypospadias, and oral clefts
- Polytherapy significantly increases risks
- Valproate
  - Significant risks of various anatomic and neurodevelopmental defects
  - 1%–2% risk for neural tube defects
- Phenytoin: fetal hydantoin syndrome
  - Distal digital hypoplasia, intrauterine growth retardation, facial dysmorphism, intellectual disability
- ACE inhibitors
  - First trimester: increased risk for cardiac, neural tube and other defects
  - Second and third trimesters: risk for renal dysplasia and failure, oligohydramnios
- Cancer/immune drugs
  - Methotrexate
    - Most severe effects at 6–8 weeks postconception
    - Limb defects, CNS anomalies, GI/cardiac defects, intellectual disability
  - Thalidomide
    - Limb defects prominent
    - All organs and neurodevelopment can be affected
    - Most severe risks days 20–36
  - Aminopterin
    - Neural tube defects, facial clefts
    - Interferes with folic acid
  - Retinoic acid
    - CNS, neural tube defects, microcephaly, facial clefts, limb defects, others
  - Lithium
    - Ebstein anomaly and other cardiac defects
    - Dose dependent
  - Warfarin
    - Characteristic facial defects (nasal hypoplasia)
    - Cardiac, CNS defects, stippled epiphyses
    - Fetal hemorrhage
  - Environment
    - Mercury
      - Neural tube defects, neurocognitive defects
    - Radiation
      - Microcephaly, neurocognitive defects
      - Peak vulnerability 8–18 weeks
      - High doses required (equivalent 500 chest x-rays)
    - Temperature (maternal fever >38.9 °C)
      - Neural tube defects, cardiac defects, clefts
- Maternal metabolic disorders
  - Diabetes
    - Prepregnancy diabetes
      - Up to nearly four times higher risk of birth defect
      - Related to prepregnancy glucose control and BMI
      - Highest risk caudal regression, renal, cardiac
    - Gestational diabetes
      - Occurs later in pregnancy
      - Structural birth defect risk not significantly elevated
      - Macrosomia, delivery issues, neonatal hypoglycemia
  - Phenylketonuria
    - Cardiac, GI defects, microcephaly, neurocognitive defects

- Outcome related to maternal phenylalanine level
- Infections
  - Toxoplasmosis
    - First trimester: fetal death
    - Second trimester: hydrocephalus, intracranial calcifications, chorioretinitis
  - Rubella
    - Risk in trimesters one and two
    - Triad of deafness, eye abnormalities (cataract, retinopathy, microphthalmia), cardiac (pulmonary artery stenosis, patent ductus arteriosus
- Assisted reproductive technology (ART)
  - 30%–40% increase in nongenetic birth defects in some studies
  - GI, lower limb reduction defects higher in ART
  - Intracytoplasmic sperm injection potentially associated with imprinting defects (specifically Prader-Willi and Beckwith-Wiedemann syndromes)

Suggested Readings

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Questions

1. The diagnosis of partial fetal alcohol syndrome requires:
   a. short palpebral fissures
   b. smooth philtrum
   c. thin upper lip
   d. central nervous system abnormalities
   e. evidence of prenatal alcohol exposure

21 Evaluation of Infants With Congenital Anomalies

JOTISHNA SHARMA

Basic Information

- 3% of newborns in the United States affected by a major congenital anomaly
- 1% of newborns have multiple congenital anomalies
- Congenital anomalies present in 10% of neonatal intensive care admissions
- Major congenital anomaly: five times increased risk of morbidity
- Major congenital anomaly identified prenatally: three times increased risk of death in utero

CONGENITAL ANOMALY

- Structural defect identified at birth
  - Internal or external

MAJOR ANOMALY

- Defect with significant impact on individual function
- Requires medical, surgical, or cosmetic intervention

MINOR ANOMALY

- Defect without significant impact on person's overall function
- Usually does not need surgical, medical, cosmetic intervention
- Incidence varies (14%–41%)
- Pattern of minor anomalies, may represent a genetic syndrome

RELATIONSHIP BETWEEN MAJOR AND MINOR ANOMALIES

- 20% of patients with major anomalies have three or more minor anomalies
- If patient has one minor anomaly only 4% have major anomaly

DYSMORPHISM

- Abnormal external physical features
- Clues to underlying developmental defect or normal variant

BASIS FOR CONGENITAL ANOMALY

- Malformation (see also Chapter 20)
  - Structural defect in tissue formation or abnormal morphogenesis
  - Examples: neural tube defect, congenital heart defects, cleft palate
  - Cause
    - Genetic
    - Teratogenic
  - Recurrence risk dependent on cause
- Deformation (see also Chapter 20)
  - Defects due to abnormal mechanical forces on morphologically normal tissue in utero
  - Associated with
    - Multiple gestations
    - Uterine malformations
    - Oligohydramnios
  - Example: club feet, hip dislocation
  - Occur in 2% of births
  - Rarely genetic cause
  - 90% undergo spontaneous resolution
  - Recurrence risk low
- Disruption
  - Defects due to destruction or interruption of normal developmental process
  - Usually affecting a body part, rather than a specific organ
  - Example: vascular interruption
    - Monozygotic twinning
    - Prenatal exposure to cocaine
  - Example: limb reduction defects from amniotic bands
  - Rarely genetic cause
  - Recurrence risk low
- Dysplasia
  - Defective morphology due to abnormal organization of cells within a specific tissue
  - Tissue specific, for example, skeletal dysplasia
  - Localized or generalized

MULTIPLE CONGENITAL ANOMALIES

- Definition
  - Two or more major malformations (example cardiac defect, tracheoesophageal fistula, imperforate anus) *OR*

- Three or more minor malformations (example club foot, hypertelorism, low-set ears)
- Patterns
  - Sequence
    - Pattern of multiple anomalies
    - Due to a single cause
    - Example: Potter sequence or the oligohydramnios sequence, Pierre-Robin sequence
  - Association
    - Nonrandom occurrence of multiple malformations
    - No known cause
    - Example: VACTERL (vertebral defects, anal atresia, cardiac defects, tracheoesophageal fistula, renal anomalies, and limb abnormalities)
  - Syndrome
    - Recognized pattern of anomalies
    - Due to a specific cause (inherited)

Etiology of Congenital Anomalies

EVALUATION

- History
  - Prenatal history
    - Maternal health
      - Age
        - Risk of nondisjunction chromosomal anomalies rises with maternal age
    - Maternal immunization: rubella, varicella
    - Maternal disease
      - Diabetes: three-fold increase in congenital anomalies
      - Obesity
      - Seizure disorder
    - Pregnancy and fetal health
      - Amniotic fluid volume
        - Polyhydramnios
        - Oligohydramnios
        - Anhydramnios
      - Premature labor
      - Premature rupture of membrane
      - Fetal movement
    - Type of conception
      - Natural
      - Assisted reproductive technologies (ART) (see chapter 20)
        - Risk of major malformations approximately 1.3 times greater in ART-conceived children, including:
          - congenital heart defects
          - neural tube defects
          - facial cleft
          - gastrointestinal malformations
          - genitourinary malformations
          - imprinting disorders
        - Overall malformation rates similar for intracytoplasmic sperm injection (ICSI) and in vitro fertilization (IVF)
        - Increased urogenital defects (hypospadias) with ICSI
    - Exposures
      - In utero infections
      - Medications
      - Smoking
      - Substance abuse
      - Environmental agents (teratogens)
        - Alcohol
        - Thalidomide
        - Warfarin
        - Trimethadione
        - Valproate
        - Hydantoin
    - Prenatal testing
      - Maternal quad screen
      - Chorionic villus sampling (CVS)
      - Ultrasonography
      - Amniocentesis
  - Birth history
    - Gestational age at delivery
    - Fetal position at delivery (breech)
    - Length of labor
    - Type of delivery
    - Evidence of fetal distress such as meconium-stained amniotic fluid
    - Apgar scores
    - Need for delivery room resuscitation
    - Birth parameters
      - Weight
      - Length
      - Head circumference
    - Physical examination at birth: noting any malformations
  - Neonatal medical history
    - Medical status
      - Need for cardiorespiratory support
      - Growth pattern
      - Development
      - Review of systems (ROS)
- Family history
  - Critical to genetic evaluation
  - Pedigree analysis
    - Three generation pedigree schematic diagram
  - Ethnicity: both sides of family
  - Consanguinity
  - First-degree relatives with similar anomalies
  - Extended family history
    - Identify relatives with congenital anomalies, developmental abnormalities
    - Photographs helpful
  - Reproductive histories
    - Infertility
    - Miscarriages (more than two first-trimester miscarriages increases the risk of a balanced translocation in one parent)
    - Stillbirths (~25% of stillbirths have malformations, and ~50% have a genetic cause)
    - Couples with more than two pregnancy losses: recommend chromosomal analysis or karyotyping
- Physical examination (Tables 21.1 and 21.2)
  - Measurements
    - Growth parameters
      - Weight
      - Length

Table 21.1 Physical Findings With Differential Diagnoses

Organ	Manifestation	Differential Diagnoses
Growth parameter	Small for gestational age (SGA)	Chromosomal abnormalities, genetic syndromes, congenital infections, Multiple gestation
	Large for gestational age (LGA)	Infant of diabetic mother (IDM), Beckwith-Wiedemann syndrome, Sotos syndrome (cerebral gigantism)
Head	Macrocephaly	Familial (autosomal dominant), Hydrocephalus, Achondroplasia, Neurocutaneous syndrome
	Microcephaly	Familial (autosomal dominant, autosomal recessive), Chromosomal abnormalities, Genetic syndrome, Congenital infections
	Large fontanelle	Hypothyroidism, Trisomies 21, 18, 13 Zellweger syndrome, Hypophosphatasia Cleidocranial dysostosis
	Small fontanelle	Craniosynostosis, Hyperthyroidism, Hyperparathyroidism, Abnormal brain growth
	Dolichocephaly (increase AP skull diameter)	Premature infants, Trisomy 18
	Brachycephaly (decrease AP skull diameter)	Trisomy 21, Microdeletion syndromes, Crouzon syndrome
	Craniosynostosis	Apert syndrome, Pfeiffer syndrome, Carpenter syndrome, Crouzon syndrome
	Frontal bossing	Achondroplasia, Rickets, Hydrocephalus
Hair	Sparse	Ectodermal dysplasia, Cartilage-hair hypoplasia Oculodentodigital syndrome
	Hirsutism	Cornelia de Lange syndrome, Fetal hydantoin syndrome Fetal alcohol syndrome, Trisomy 18, Familial ethnic variation
	Abnormal scalp hair pattern	Microcephaly: lack of normal parietal whorl Turner and Noonan syndromes: low posterior hairline Trisomy 13: cutis aplasia (punched-out scalp lesions)
Eyes	Hypotelorism	Holoprosencephaly, Trisomy 13, Parry-Romberg disease
	Hypertelorism	Cri du chat syndrome, Wolf-Hirschhorn syndrome, DiGeorge syndrome, Achondroplasia, Midline facial anomalies
	Epicanthal folds	Trisomy 21, Fetal alcohol syndrome, Turner syndrome
	Upward slant of palpebral fissure	Trisomy 21
	Downward slant of palpebral fissure	Treacher Collins syndrome, Apert syndrome, Mandibular dysostosis, Noonan syndrome
	Short palpebral fissure	Microphthalmia, Fetal alcohol syndrome, Trisomy 21, DiGeorge syndrome
	Coloboma	Treacher Collins syndrome, CHARGE syndrome, renal hypodysplasia
	Synophrys (fusion of eyebrows in midline)	Cornelia de Lange syndrome, Microdeletion syndromes, Familial
Ears	External anomalies	CHARGE syndrome, DiGeorge syndrome
	Low-set ears	Trisomy 21, Trisomy 18, Trisomy 13, Turner syndrome, Noonan syndrome, DiGeorge syndrome, Cri du chat syndrome
	Preauricular pits/tags	Familial Branchiootorenal (BOR) syndrome
	Microtia	IDM, Prenatal exposure to isotretinoin, thalidomide, alcohol, Treacher Collins syndrome, Goldenhar syndrome
Nose	Hypoplastic alae nasi	Hallermann-Streiff, Microdeletion syndromes
	Broad nose	Frontonasal dysplasia, Microdeletion syndromes
	Depressed nasal bridge	Achondroplasia, Trisomy 21
	Single nostril	Holoprosencephaly
Mouth	Microstomia	Trisomy 18, Fetal valproate syndrome, Hallermann-Streiff, Holoprosencephaly
	Macrostomia	Mandibular dysostosis, Lateral facial cleft, Angelman syndrome, Noonan syndrome, Beckwith-Wiedemann syndrome, Treacher Collins syndrome
	Prominent full lip	Williams syndrome
	Thin upper lip	Fetal alcohol syndrome, Cornelia de Lange syndrome
	Median cleft lip	Holoprosencephaly
	Cleft lip and palate	Pierre-Robin sequence, Stickler syndrome, DiGeorge syndrome
	Hypertrophied alveolar ridges	Smith-Lemli-Opitz syndrome
	Macroglossia	Beckwith-Wiedemann syndrome, Trisomy 21, Hypothyroidism
	Micrognathia	Pierre Robin sequence, Stickler syndrome
Neck	Excessive skin folds	Turner syndrome, Noonan syndrome, Trisomy 21
Chest	Small thoracic cavity	Skeletal dysplasia: thanatophoric dysplasia, Jeune asphyxiating thoracic dystrophy
	Short sternum	Trisomy 18
	Pectus excavatum and carinatum	Skeletal dysplasia, Connective tissue disorders

Continued

Table 21.1 Physical Findings With Differential Diagnoses—cont'd

Organ	Manifestation	Differential Diagnoses
Abdomen	Hypoplasia of abdominal musculature (prune belly)	Eagle-Barrett syndrome (intrauterine bladder outlet obstruction)
	Omphalocele	Beckwith-Wiedemann syndrome, Trisomy 13
Anus	Imperforate	Caudal regression sequence, VACTERL
Genitalia	Hypogenitalism	Prader-Willi syndrome, Smith- Lemli-Opitz syndrome
	Ambiguous genitalia	Denys-Drash syndrome
	Virilization	21-hydroxylase deficiency
Spine	Tufts of hair, sinuses	Spinal cord anomalies
Skin	Thick, coarse	Costello syndrome
	Cutis marmorata/livedo reticularis	Trisomy 21, hypothyroidism, Cornelia de Lange Familial: autosomal dominant
	Café au lait spots	NF1
	Hypopigmented macules	Tuberous sclerosis
	Irregular pigmented lesions in whorls	Incontinentia pigmenti
	>1 hemangioma	Possible internal hemangioma
	Edema, generalized	Trisomy 21, Turner syndrome, Noonan syndrome (RASopathies)

- Head circumference
- Head and neck
  - Shape and size of head
  - Shape and size of fontanelles: anterior and posterior
  - Scalp defects
- Eyes
  - Canthal measurements
  - Inner and outer canthal distances
  - Interpupillary distances
  - Palpebral fissure
  - Lengths
  - Upward or downward slanting
  - Epicanthal folds
- Nares
  - Shape of nasal tip and ala nasi
  - Columella length
  - Choanal patency
- Mouth and throat
  - Shape of palate and uvula
  - Cleft lip or palate
  - Tongue deformities
  - Lip pits
  - Frenula
  - Natal teeth
- Chin
  - Retrognathic
- Ears
  - Lengths
  - Placement
  - Folding
  - Preauricular and postauricular pits, tags
- Neck
  - Webbing or excess nuchal folds
- Thorax and chest
  - Inter-nipple distance
  - Chest circumference
  - Auscultation of lungs and heart
- Abdomen
  - Organomegaly
  - Ascites
  - Cord vessels (number)
  - Umbilical hernia
- Genitourinary
  - Hypospadias
  - Chordee
  - Cryptorchidism
  - Microphallus
  - Ambiguous genitalia
- Anus
  - Patent
  - Tags
  - Placement
- Back
  - Spine shape
  - Spine defects—meningomyelocele
  - Sacral dimple, tag, tuft of hair
- Extremities
  - Polydactyly (>five digits)
    - Preaxial
    - Postaxial
  - Syndactyly (fusion of digits)
  - Clinodactyly (incurving of the digits)
  - Extremity length
  - Hand and foot length
- Dermatoglyphics
  - Single transverse palmar crease—85% of patients with trisomy 21
  - Wide space between the great and second toes—50% of patients with trisomy 21
- Skin
  - Phakomatoses
    - Café au lait spots—associated with neurofibromatosis type 1
    - Ash leaf spots (detected with use of Wood lamp)—associated with tuberous sclerosis
  - Irregular pigmentation
    - Hypomelanosis of Ito: suggests chromosomal mosaicism
  - Hemangiomas
- Neurologic examination

Table 21.2 Minor Anomalies of Extremities-Associated Syndromes

Manifestation	Differential Diagnoses
Hypertrophy of limbs	Beckwith-Wiedemann syndrome, Klippel-Trenaunay-Weber syndrome
Hemiatrophy	Russell-Silver syndrome
Rhizomelia (proximal shortening of the limbs)	Achondroplasia
Mesomelia (shortening of the middle segment)	Thanatophoric dysplasia
Single palmar crease	Trisomy 21
Clinodactyly (incurving of the fifth digit)	Trisomy 21
Clinodactyly of fourth and fifth fingers radially and second finger in an ulnar direction	Trisomy 18 Trisomy 13
Lymphedema of hands and feet	Turner syndrome, Noonan syndrome
Rocker-bottom feet	Trisomy 18
Acheiria (congenital absence of entire hand)	Amniotic band syndrome, Cornelia de Lange syndrome, Fetal hydantoin syndrome, incontinentia pigmenti
Acheiropodia (absence of both hands and feet)	Horn-Kolb syndrome
Radial (preaxial side of limb) deficiency	Fanconi anemia, thrombocytopenia (absent radius syndrome)
Polydactyly (partial or complete supernumerary digits)	Most common limb malformation Postaxial >preaxial in African Americans Isolated is Autosomal Dominant (AD) Postaxial: Trisomy 13, Chondroectodermal dysplasia, Meckel-Gruber syndrome, Bardet-Biedl syndrome Preaxial: Carpenter syndrome, Majewski short rib-polydactyly syndrome
Syndactyly (fusion of digits)	Minimal fusion of second and third toes common, benign Extensive syndactyly: Trisomy 21, Smith-Lemli-Opitz syndrome, Pfeiffer syndrome, Apert syndrome
Brachydactyly (shortening of ≥1 digit due to anomalous development)	Skeletal dysplasia, Albright hereditary osteodystrophy, Trisomy 21
Arachnodactyly (unusually long, spider-like digits)	Marfan syndrome, Homocystinuria
Arthrogryposis (multiple congenital contractures)	Spinal muscular atrophy Sporadic Associated with oligohydramnios
Joint hypermobility	Marfan syndrome, Ehlers-Danlos syndrome, Kabuki syndrome
Camptodactyly (irreducible flexion of the digits)	Isolated AD Trisomy 8 Trisomy 10q Freeman-Sheldon syndrome

  - Neurologic status usually most reliable prognostic predicator
  - Tone
  - Reflexes
  - Unusual movements
  - Feeding ability
  - Seizure activity
- Adjunct studies
  - Evaluation of internal organ malformation
    - Echocardiogram
    - Abdominal ultrasound (US)
  - Identification of organ system involvement
    - Ophthalmology examination
    - Skeletal survey
    - Electromyography (EMG)
  - Assessment of neurologic function
    - Magnetic resonance imaging (MRI) of brain
    - Electroencephalogram (EEG)
    - Nerve conduction studies
- Specialized laboratory tests (see also Chapter 18)
  - Karyotype
    - Analysis of stretched and stained chromosome preparation
    - Confirm clinical diagnosis
    - May explain a set of major malformations not classically encountered together
  - Fluorescence in situ hybridization
    - Small deletions detected
  - DNA microarray
    - Detecting copy number changes (smaller deletions or duplications not detectable by karyotype)
    - Performed in targeted or genome-wide fashion
    - Comparative genomic hybridization
    - Single nucleotide polymorphism or oligonucleotide arrays
  - Molecular analysis
- Diagnosis
  - May be no unifying diagnosis
  - Treatment and prognosis based on organ involvement and degree of impairment

Suggested Readings

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Questions

1. Several studies have shown that there is a small but definite increase in congenital malformations in neonates following artificial reproductive technology (ART) conception. In which type of ART is an increased incidence of urogenital abnormalities, specifically hypospadias, likely to occur?
   a. In vitro fertilization (IVF)
   b. Gamete intrafallopian tube transfer (GIFT)
   c. Intracytoplasmic sperm injection (ICSI)
   d. Embryo cryopreservation
   e. Blastocyst culture

2. Amniotic band sequence is caused by:
   a. deformation
   b. disruption
   c. malformation
   d. syndrome
   e. association

3. Deformations most commonly occur during:
   a. the zygote period
   b. the blastula period
   c. the embryo period
   d. the fetal period
   e. the birth process

4. Arthrogryposis (congenital joint contractures) can be described as a:
   a. dysplasia
   b. syndrome
   c. disruption
   d. deformation
   e. none of the above

22 Inborn Errors of Metabolism

GEORGIANNE LEE ARNOLD

Basic Information

Considerably more common than previously recognized (as many as 1:2000 births).

Metabolic Tests

- Three most commonly used basic metabolic tests: plasma amino acids, urine organic acids, plasma acylcarnitine analysis (Table 22.1).
- It is critical to prioritize collecting samples in the acute setting when testing is most sensitive.
- Other suspicion-directed specific tests might be indicated as well.
  - Plasma amino acid analysis:
    - Typically identifies protein metabolic disorders.
    - Urine or CSF amino acid analysis may be required for some disorders.
  - Urine organic acid analysis:
    - Typically identifies organic acidemias and fatty acid oxidation disorders.
  - Plasma acylcarnitine profile analysis (by tandem mass spectrometry):
    - Particularly sensitive for protein and fatty acid oxidation disorders.
    - In some cases, can be done on dried blood spots (e.g., newborn screening).

Table 22.1 Common Metabolic Tests for Inborn Errors of Metabolism[a]

Test	Usual Sample	Secondary Samples[b]	Indication
Amino acid analysis	Plasma	Urine CSF	Suspected protein metabolism disorder (also to measure alanine in energy deficiency disorders)
Organic acid analysis	Urine	Vitreous humor (postmortem)	Suspected protein metabolism disorder, suspected energy deficiency disorder
Acylcarnitine analysis	Plasma	Blood spot card Urine	Suspected protein metabolism disorder or fatty acid oxidation disorder

[a]These should be performed in the acute state if possible.
[b]In specific cases

Metabolic Disorder Classification

- Metabolic disorders can be classified in three categories (Box 22.1): disorders of intoxication, energy deficiency, or complex molecules.
- All categories can present at any age, from prenatal onset to adulthood (Table 22.2).

DISORDERS OF INTOXICATION

Basic Information

- "Intoxication" with abnormally accumulating metabolite.
- Most commonly from defect in amino acid (protein) metabolism (Fig. 22.1), occasionally other substrates (e.g., galactose, fructose; Fig. 22.2).
- Infant usually well at birth (maternal-placental unit clears most metabolites), but becomes ill in days to years.
  - Often presents with "newborn crash"
    - Well appearing newborn develops poor feeding/vomiting, abnormal tone, altered mental status.
  - Other times for initial presentation include changing from breast to formula feedings, or during an intercurrent illness (with catabolism)
- Made worse by ingestion of offending metabolite or fasting (when body increases metabolism of endogenous stores for energy).
- Prevention of catabolism and dietary restriction of the offending metabolite are the mainstays of treatment.

Specific Disorders of Intoxication

- Phenylketonuria (PKU)
  - Basic information
    - Relatively common (1:15,000 births)
    - Due to defect in changing the amino acid phenylalanine into tyrosine
    - Phenylalanine accumulates and intoxicates the brain
  - Clinical presentation
    - If untreated: intellectual disability, fair complexion, eczema, and neurologic abnormalities
    - If treated early: relatively normal cognitive outcome
  - Diagnosis and evaluation
    - Detectable on newborn screening but requires at least 24 hours for phenylalanine accumulation to become significant
    - Diagnosis by plasma amino acid analysis, with significant elevation of phenylalanine and elevated ratio of phenylalanine to tyrosine
  - Treatment
    - Restrict dietary phenylalanine (protein)
    - Replete tyrosine and other essential amino acids

- Affected women must be under excellent control during pregnancy to avoid teratogenic effects on the fetus, including fetal microcephaly, congenital heart and other structural defects, and intellectual disability
- Maple syrup urine disease (MSUD)
- Basic information
  - Results from impaired metabolism of the branch chain amino acids valine, leucine, and isoleucine.

Box 22.1 Common Inborn Errors of Metabolism Detected on Newborn Screening or Having Neonatal Presentation

Disorders of Intoxication

- Protein
  - Amino acidopathies
    - Phenylketonuria
    - Maple syrup urine disease
  - Urea cycle defects
  - Organic acidemias
- Carbohydrate
  - Galactosemia
  - Hereditary fructose intolerance

Disorders of Energy Deficiency

- Glucose metabolism disorders
  - Glycogen storage disorders
  - Disorders of gluconeogenesis
  - Pyruvate carboxylase deficiency
  - Fructose-1,6-bisphosphatase deficiency
  - Pyruvate dehydrogenase deficiency
- Mitochondrial disorders
- Fatty acid oxidation defects

Disorders of Complex Molecules

- Peroxisomal disorders
  - Peroxisome assembly disorders
    - Zellweger syndrome
  - Single enzyme disorders
    - X-linked adrenoleukodystrophy
    - Others
- Lysosomal disorders
  - Lysosomal storage disorders
  - Lysosomal targeting disorder
    - I-cell disease
- Cholesterol synthesis disorders
  - Smith-Lemli-Opitz syndrome

- Pan-ethnic, but more common in the Mennonite population.
- Name refers to the odor detectable in concentrated urine (also noted in earwax), but this odor is not often clinically prominent.
- Clinical presentation
  - Acute intoxication with leucine leads to mental status changes, neurologic irritability, cerebral edema, and coma. Chronic intoxication results in intellectual disability.
- Diagnosis and evaluation
  - Laboratory findings include ketosis, and plasma amino acid analysis reveals significant elevations of valine, leucine, isoleucine, and the pathognomonic metabolite alloisoleucine.
  - Significant ketosis is always abnormal in the newborn and should raise concern for a metabolic defect.
  - The disorder is detectable on newborn screening. The infant might be ill before the screening results are available.
- Treatment
  - Acute treatment of the MSUD crisis follows basic principles of protein metabolic crisis management (Box 22.2).
    - *Restrict* (the offending metabolite, leucine).
    - *Reduce* abnormal metabolite production from metabolism of amino acids for energy (by forcing anabolism with high caloric supplementation).
    - *Remove* the abnormal metabolite, leucine (by dialysis if needed).
    - *Restore* enzyme function (some patients respond to thiamine).
    - *Replete* deficient products when indicated (valine and isoleucine supplementation are usually needed).
  - Chronic management requires dietary leucine restriction and supplementation of other essential amino acids.
  - Prevention of catabolism is a mainstay of chronic treatment.
  - Liver transplantation can correct the hepatic genetic defect.

Urea Cycle Defects

- Basic information
  - Nitrogen is removed from amino acid (as ammonia) and detoxified in the urea cycle (see Fig. 22.1).
  - Enzymatic defects can occur in any of the steps of the urea cycle and can appear at any age.

Table 22.2 Classification of Inborn Errors of Metabolism

Disorder Class	Presentation	Treatable	Treatment Options
Intoxication	Prenatal: rare Postnatal: days to years	Commonly	Restrict offending substrate Reduce metabolite formation (prevent fasting/promote anabolism) Restore enzyme (vitamin cofactor, transplantation, etc.) Replete deficient products
Energy metabolism	Prenatal: occasional (when severe) Postnatal: birth to years	Sometimes	Restrict offending substrate Reduce metabolite formation and prevent energy deficiency Restore enzyme (vitamin cofactor, etc.) Replete deficient products
Complex molecules	Prenatal: common Postnatal: birth to years	Rarely (but improving)	Enzyme replacement (some disorders) Bone marrow transplant (some disorders) Supplement deficient products (some disorders)

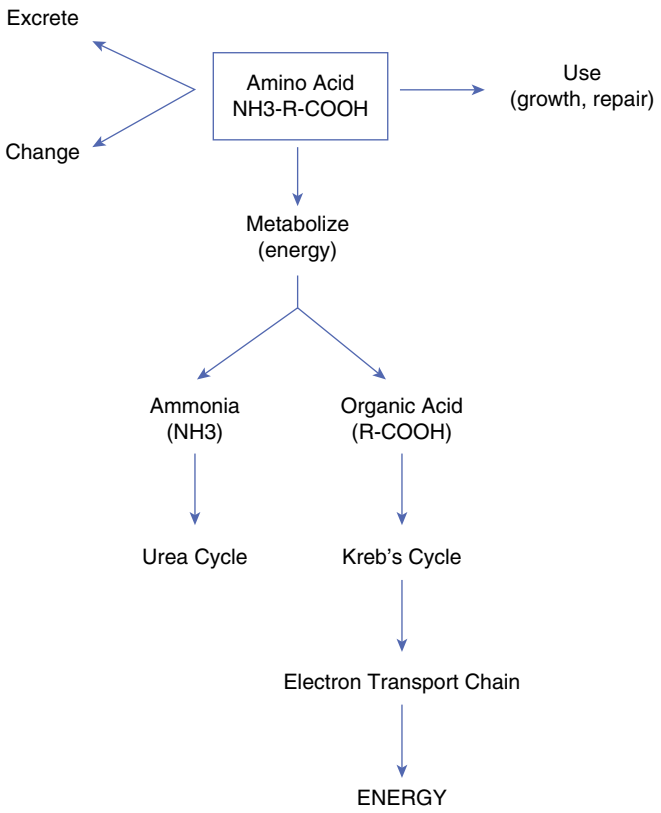

Fig. 22.1 Metabolism of protein.

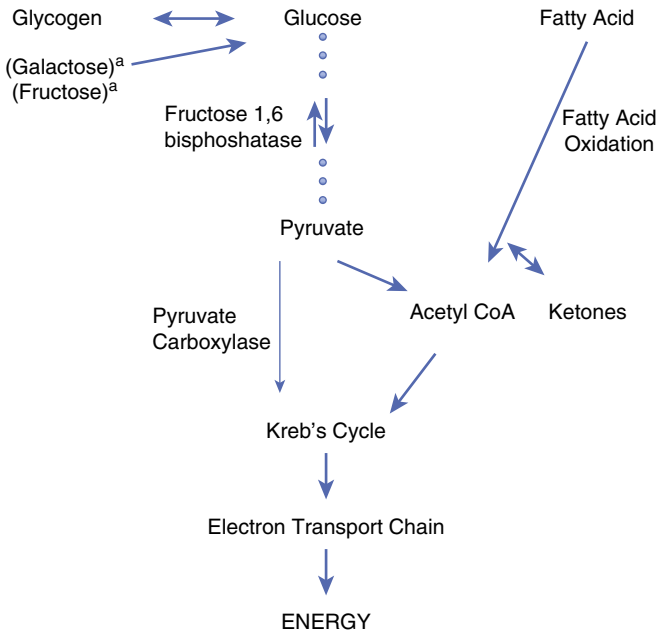

Fig. 22.2 Energy metabolism from glucose and fatty acid oxidation. [a]Galactosemia and hereditary fructose intolerance are considered disorders of intoxication.

- Clinical presentation
  - Commonly presents with "newborn crash" (but can present at any age, even adulthood).
  - Presentation includes altered mental status, respiratory alkalosis/tachypnea, vomiting/poor feeding, neurologic irritability (initially clonus/hyperreflexia, later flaccidity/coma), and cerebral edema.
  - Ketoacidosis is uncommon in urea cycle defects (but can occur).
  - Ornithine transcarbamylase (OTC) deficiency is carried on the X chromosome. Carrier females are at risk for hyperammonemia during stress (including newborn stress, and particularly postpartum during uterine involution).
  - Duration of hyperammonemia predicts outcome better than ammonia level.
- Diagnosis and evaluation
  - Measure ammonia, plasma amino acids (particularly citrulline and arginine), and orotic acid (preferably in the acute state).
  - The specific enzymatic defect can be confirmed by DNA or enzyme analysis.
  - Newborn screening can identify some urea cycle defects, but is not sensitive for the detection of OTC deficiency or other proximal defects. The infant might be ill before the screening results are available.
- Treatment
  - Pillars of management of protein management disorders (see Box 22.2).

Box 22.2 Principles of Acute Management of Metabolic Crisis in Intoxicating Protein Metabolism Disorders

1. Restrict offending substrate
2. Reduce endogenous production of the abnormal metabolite by restoring anabolism
   a. Intravenous glucose at 8–10 mg/kg/min in infants and children
   b. Intralipid if appropriate (except in fatty acid oxidation disorders)
   c. Nonoffending amino acids (with metabolic nutritionist assistance)
   d. Enteral feeding when tolerated (with metabolic nutritionist assistance)
   e. Restore carefully calculated intake of protein after 24 hours (even if ammonia is still high)
3. Remove the abnormal metabolite
   a. Ammonia scavenging medications, when indicated
   b. Dialysis if indicated
   c. Increase urinary excretion (carnitine, conjugation, etc. as indicated)
4. Restore enzyme function
   a. Enzyme cofactors, if applicable
   b. Enzyme replacement, if applicable
5. Replete deficient products, if applicable

- *Restrict* protein intake.
- *Reduce* ammonia production by reversing catabolism with high calorie intake.
- *Remove* ammonia by ammonia scavenging drugs (sodium phenylacetate, sodium benzoate, and dialysis, if necessary).

- *Restore* enzyme activity (provide carglumic acid if *N*-acetylglutamate synthase (NAG-S) deficiency is suspected).
- *Replete* deficient products (citrulline or arginine).
- It is important to reinstitute carefully measured protein intake within 24 hours, or negative nitrogen balance will worsen the crisis.
- Chronic management includes careful regulation of protein intake, ammonia scavenging drugs, and prevention of catabolism.
- Liver transplantation can correct the metabolic defect.
- After initial presentation, most crises are associated with conditions leading to catabolism, such as intercurrent infections and fasting.

Organic Acidemias

- Basic information
  - After the ammonia is removed from the amino acid, the remaining carbon skeleton is now an organic acid, and is metabolized to produce energy, typically through the Krebs cycle (see Fig. 22.1).
  - Common disorders of organic acid metabolism (organic acidemias) include propionic acidemia, methylmalonic acidemia, or isovaleric acidemia.
- Clinical presentation
  - The "newborn crash" is a common presentation, but can present at any age.
  - Systemic effects include ketoacidosis, bone marrow suppression, and secondary biochemical impairment of the urea cycle with hyperammonemia.
    - Hyperammonemia can be profound, and in some cases difficult to distinguish from urea cycle defects.
    - Bone marrow suppression leads to varying degrees of neutropenia, anemia, and thrombocytopenia (which can resemble neonatal sepsis).
  - Acidosis with elevated anion gap.
- Diagnosis and evaluation
  - Ketoacidosis in the neonate is always abnormal, and an organic acidemia should always be suspected in the differential diagnosis.
  - Plasma amino acid analysis typically notes elevated glycine. Urine organic acid analysis and plasma acylcarnitine analysis usually identify the specific disorder, and DNA or enzyme analysis can confirm.
  - The organic acidemias are generally detectable on newborn screening. The infant might be ill before the screen result is available.
- Treatment
  - Treatment of acute organic acidemias resembles acute urea cycle defects (see Box 22.2).
    - Restrict protein.
    - Reduce abnormal metabolite production with high calorie intake.
    - Remove abnormal metabolites; ammonia scavenging agents can be controversial, but can be instituted while waiting for studies that will differentiate urea cycle from organic acid disorders, and dialysis may be necessary.
    - Restore enzyme activity (vitamin B_{12}, the cofactor for methylmalonyl CoA mutase, should be supplemented acutely until a cobalamin responsive form of methylmalonic acidemia is ruled out).
    - Replete carnitine deficiency.
  - Chronic management includes careful regulation of protein intake and prevention of catabolism, along with carnitine and other supplements.
  - Liver transplant is partially corrective, but metabolic stroke risk remains.
  - Like other protein intoxication disorders, crises are often associated with poor oral intake and catabolism.
- Nonprotein intoxication disorders (see Fig. 22.2)
  - Galactosemia
    - Basic information
      - A defect in galactose metabolism (a sugar found in milk).
    - Clinical presentation
      - Findings in untreated patients include cataracts, liver disease, failure to thrive, *Escherichia coli*, sepsis.
    - Diagnosis and evaluation
      - Detectable on newborn screening.
        - Enzyme is assayed in red cells, so transfusion can reduce screening sensitivity.
        - Infant may already be ill by the time the screen is returned.
    - Treatment
      - Urgent medical evaluation of screen-positive infants.
      - Galactose-free diet.
      - Mild to moderate intellectual disability is common even with dietary treatment.
  - Hereditary fructose intolerance
    - Basic information
      - A defect in fructose metabolism.
      - Fructose is found predominantly in table sugar (sucrose) and fruit.
      - Some infant formulas (even elemental) and pacifier-dipping solutions contain sucrose/fructose.
    - Clinical presentation
      - Acute symptoms include hypoglycemia, hypophosphatemia, shock, and liver dysfunction.
      - Chronic symptoms include failure to thrive and liver dysfunction.
    - Diagnosis and evaluation
      - Diet history is critical, as problems generally begin after the introduction of fructose/sucrose in the diet.
      - Diagnosis can be confirmed by DNA analysis.
      - Newborn screening is not available for this disorder.
    - Treatment
      - Dietary restriction of sucrose and fructose.

DISORDERS OF ENERGY DEFICIENCY

- Basic information
  - Result primarily from a direct block in energy production, usually in carbohydrate or fatty acid metabolism (see Fig. 22.2).
  - Glucose, the basic carbohydrate, is metabolized for energy via glycolysis, then the Krebs cycle, and ultimately the respiratory chain.
  - Fat oxidation also supplies its end products to the Krebs cycle and respiratory chain, as well as producing ketone bodies which can be exported to distant tissues for metabolism.

- The maternal-placental unit cannot compensate for intracellular energy deficiency. Thus, prenatal onset can occur, particularly in some of the most severe pyruvate metabolism disorders (see Table 22.2).
- The most metabolically active regions of the brain (basal ganglia) are most vulnerable to cell death from acute energy deficiency, leading to cystic degeneration.
- Newborn screening does not generally detect these disorders (except fatty acid oxidation disorders).

- Pyruvate dehydrogenase (PDH) deficiency
  - Basic information
    - Rate-limiting step between glycolysis and the Krebs cycle (see Fig. 22.2).
    - Results in impaired ability to create energy from carbohydrates.
    - Severity can vary widely, from mild to neonatal lethal.
    - The most common neonatal severe presenting genetic defect is X-linked dominant; females can be as severely affected as males.
  - Clinical presentation
    - Neurologic abnormalities including hypotonia, intellectual disability, seizures, ataxia, and other symptoms.
    - Basal ganglia damage and/or metabolic strokes are seen, or develop and progress over time, and neonatal lactic acidosis can be profound.
  - Diagnosis and evaluation
    - Metabolic findings include lactic acidosis, as well high alanine on plasma amino acids.
    - MRI findings can be helpful in raising clinical suspicion.
    - Diagnosis is by DNA or enzyme analysis.
    - The disorder is not diagnosed on newborn screening.
  - Treatment
    - This disorder is the exception to the general rule that metabolic crises should be treated with high dose glucose. High dose glucose should NOT be given in PDH deficiency.
    - Some cases respond to a ketogenic diet.
    - Some might respond to thiamine or lipoic acid cofactors.
- Pyruvate carboxylase deficiency
  - Basic information
    - First step in gluconeogenesis (the creation of glucose).
    - Wide variation in severity, from neonatal lethal to milder forms.
  - Clinical presentation
    - Findings include ketosis and lactic acidosis (significant ketosis is always abnormal in the neonate).
    - Hypoglycemia is not a particularly common finding.
    - The infant can have profoundly altered mental status and abnormal tone.
  - Diagnosis and evaluation
    - In the most severe cases, there is secondary biochemical impairment of the urea cycle and hyperammonemia.
    - Plasma amino acids may reveal high plasma citrulline and alanine levels.
    - Diagnosis is by DNA or enzyme analysis.
    - The disorder is not diagnosed by newborn screening.
  - Treatment
    - Provide glucose (8–10 mg/kg/min) and protein calories to prevent activation of gluconeogenesis.
    - Chronic management includes a high carbohydrate and protein diet, and prevention of fasting.
- Fructose-1,6-bisphosphatase deficiency
  - Basic information
    - A defect in gluconeogenesis (see Fig. 22.2).
    - Most infants do not become ill until liver glycogen stores are exhausted (thus might not present when on frequent feedings).
  - Clinical presentation
    - Fasting or poor feeding can precipitate hypoglycemia and ketoacidosis with lactic acidosis.
  - Diagnosis and evaluation
    - Urine organic acids may reveal glycerol (it is important to be certain the glycerol did not originate from skin care products).
    - Diagnosis is primarily by DNA analysis.
    - The disorder is not detected by newborn screening.
  - Treatment
    - Avoidance of fasting and fructose.
    - During acute episodes or when fasting, give high dose glucose and intralipid similar to protein metabolic disorders (see Box 22.2).
- "Mitochondrial disease" (defects in oxidative phosphorylation)
  - Basic information
    - Genes regulating mitochondrial function are encoded in both nuclear and mitochondrial DNA.
    - Neonatal onset disease is more commonly associated with genetic defects in nuclear genes.
    - 13 enzymes involved in oxidative phosphorylation (and their transfer RNA) are encoded within the mitochondrial DNA and show maternal inheritance.
    - Consider mitochondrial disease when two or more nonembryologically related organ systems are affected.
  - Clinical presentation
    - Can present at any age, with some of the most severe disorders presenting in the neonatal period.
    - Acute neonatal presentation typically includes lactic acidosis but can also include dysfunction in one or more high energy-requiring organs such as brain, liver, or heart.
    - Later presentations include intellectual disability, hypotonia, seizures and other neurologic dysfunction, endocrine disorders, and others.
  - Diagnosis and evaluation
    - Elevated alanine is common in plasma amino acid analysis.
    - DNA analysis may be helpful in reaching a diagnosis.
    - Not diagnosed by newborn screening.
  - Treatment
    - Varies based on the specific defect.
    - Avoid catabolism.
    - Diet should be tailored to the individual defect.
    - Some patients are treated with "mitochondrial cocktails" including coenzyme Q10, carnitine, and various enzyme cofactors including thiamine, biotin, and others.
- Fatty acid oxidation defects
  - Basic information
    - Fat oxidation provides 9 kcal/g (compared to ≈4 kcal from protein or carbohydrates).
    - Fats are chains of carbons and hydrogens.

- One (four-step) cycle of fatty acid oxidation removes two carbons that are metabolized to energy through the Krebs cycle, or can be converted to a ketone that can be exported to other tissues (see Fig. 22.2).
- Fatty acid oxidation enzymes have chain length specificity.
  - Long-chain (12–18 carbons)
  - Medium-chain (6–10 carbons)
  - Short-chain (<6 carbons)
- There can be secondary effects from intoxication with accumulation of fatty acid oxidation intermediates.
- After the neonatal period, absence of ketosis during hypoglycemia is an important diagnostic clue.

- Medium-chain acyl-CoA dehydrogenase (MCAD) deficiency
  - Basic information
    - The most common fatty acid oxidation disorder (approximately 1:15,000 births).
    - Neonatal presentation can be seen in the most severely affected infants or in those with inadequate calorie intake.
    - Infants become symptomatic when liver glycogen is exhausted, most commonly during fasting and intercurrent illnesses when oral intake is depressed.
  - Clinical presentation
    - Hypoglycemia, altered mental status or tone.
    - Transient hepatomegaly.
  - Diagnosis and evaluation
    - Diagnosis is confirmed by plasma acylcarnitine analysis and urine organic acid analysis.
    - This disorder is detectable by newborn screening. A screen positive infant is a medical emergency until it can be determined that infant feeding is adequate.
  - Treatment
    - Treatment is avoidance of fasting.
    - Administer glucose at 8–10 mg/kg/min during fasting or intercurrent illness.
- Disorders of long-chain fatty acid oxidation (very long-chain acyl-CoA dehydrogenase [VLCAD] deficiency and long-chain hydroxyl acyl-CoA deficiency [LCHAD]/trifunctional protein [TFP] deficiency)
  - Basic information
    - Variable severity, can present from neonatal to adulthood.
    - Long-chain fatty acids require esterification to carnitine to pass into the mitochondria for oxidation.
    - Several additional defects occur in the process of carnitine esterification or passage through the mitochondrial membrane (not reviewed here).
  - Clinical presentation
    - Severe presentations include hypoglycemia, hypotonia, altered mental status, and hepatomegaly and can be fatal.
    - Later presentations can include myopathy and recurrent rhabdomyolysis.
  - Diagnosis and evaluation
    - Diagnostic metabolites identified on urine organic acid analysis and plasma acylcarnitine analysis.
    - These disorders are diagnosable on newborn screen; a screen positive child is a medical emergency until severe disease is ruled out.
    - Diagnosis can be confirmed with DNA, enzyme, or other metabolic testing.
  - Treatment
    - Restriction of dietary long-chain fat and supplementation with medium-chain fat.
    - Prevention of catabolism, IV glucose during fasting (8–10 mg/kg/min).

DISORDERS OF COMPLEX MOLECULES

- Basic information
  - Metabolic processes occurring in organelles.
  - Disorders of the peroxisome and the lysosome, as well as cholesterol metabolism, can have a neonatal phenotype and are reviewed here.
- Peroxisomal defects
  - Basic information
    - Peroxisomes responsible for cellular detoxification, oxidation of the longest chain fats (>20 carbons), synthesis of plasmalogens (phospholipids involved in myelin/nerve cell integrity), production of bile acids, and other functions.
  - Peroxisomal assembly defects
    - Basic information
      - Absent (or "ghost") peroxisomes.
      - Most severe is Zellweger (cerebrohepatorenal) syndrome.
      - Milder presentations/later onset (neonatal adrenoleukodystrophy or infantile Refsum disease).
    - Clinical presentation
      - Dysmorphic features (resembling trisomy 21, hepatomegaly with liver dysfunction, bile acid deficiency, leukodystrophy, profound hypotonia, chondrodysplasia punctata, and other abnormalities.
    - Diagnosis and evaluation
      - Peroxisomal function testing (very long-chain fatty acids, plasmalogens, other peroxisomal testing).
      - Note: phytanic acid elevations are not seen until the child has ingested significant amounts of phytanic acid in dairy/food.
      - Diagnosis confirmed by DNA testing.
      - Not directly diagnosed by newborn screen, but might be identified secondarily on screening for X-linked adrenoleukodystrophy.
    - Treatment
      - Supportive/palliative only.
      - Cholic acid, adrenal hormone replacement, gastrostomy feedings, and others.
  - Single-gene peroxisomal disorders
    - Basic information
      - Peroxisomes intact except lacking a single enzyme.
      - Disorders include X-linked adrenoleukodystrophy, rhizomelic chondrodysplasia punctate, bile acid deficiencies, etc.
      - Presentation and testing specific to the individual disorder.
- Lysosomal storage disorders (LSD)
  - Basic information
    - Site of cellular debris degradation.
    - Numerous LSD can present with prenatal/neonatal hydrops.
    - Diagnosis is by enzyme assay or DNA analysis.

- Some are treatable by enzyme replacement, substrate reduction therapies, or bone marrow transplant, but not curable.
- Newborn screening is expanding for a number of LSD.
- Mucolipidosis type II (I-cell disease)
  - Basic information
    - Defect in targeting all enzymes for entry into the lysosome.
  - Clinical presentation
    - Coarse features, hepatomegaly, dysostosis multiplex (resembles severe Hurler syndrome).
  - Diagnosis and evaluation
    - All lysosomal enzymes elevated in blood (due to failure to enter the lysosome).
    - Diagnosis confirmed by biopsy or DNA analysis.
    - Not detectable by newborn screening.
  - Treatment
    - Supportive/palliative only.
- Disorders of cholesterol synthesis
  - Basic information
    - Cholesterol is a precursor for steroid hormones, bile acids, myelin, cell membranes, and embryogenesis.
    - A defect is identified in nearly every step of cholesterol synthesis.
    - Common manifestations include multiple congenital and developmental anomalies, and skeletal and skin abnormalities.
    - Includes disorders with chondrodysplasia punctata (e.g., Conradi-Hünermann syndrome, CHILD syndrome), skin abnormalities (CHILD syndrome), and others.
  - Smith-Lemli-Opitz syndrome
    - Basic information
      - Defect in the last step of cholesterol synthesis.
    - Clinical presentation
      - Neuronal migration abnormalities, skeletal anomalies (including characteristic two to three toe syndactyly, genital undervirilization (in males).
      - Milder cases with more subtle features.
    - Diagnosis and evaluation
      - Elevated 7-dehydrocholesterol (precursor to cholesterol).
      - Disorder not detected by newborn screening.

METABOLIC ENCEPHALOPATHY

- Basic information
  - Associated with all three categories of metabolic defects.
    - Acute encephalopathy more likely to be associated with intoxication or energy deficiency disorders.
    - Intoxicating metabolites include ammonia, amino acids, organic acids, lactate, and other accumulated substances.
  - Ammonia should always be measured early in the investigation of unexplained mental status changes, particularly in the presence of neurologic irritability/clonus/hyperreflexia/coma, or unexplained tachypnea/respiratory alkalosis.
    - Any patient undergoing lumbar puncture or toxicology analysis to look for occult causes of unexplained mental status changes should also have basic metabolic testing, including blood ammonia.
    - Urine ketones should be assessed in presence of concern for a metabolic disorder.
- **Metabolic Causes of Acidosis**. The anion gap reflects the presence of unmeasured anions. Bicarbonate loss in urine or stool is typically accompanied by hyperchloremia, which maintains a normal anion gap. Elevated anion gap can be due to excess presence of an anion (e.g. lactate, ketones, organic acid).
  - Normal anion gap acidosis
    - Bicarbonate loss (renal or stool) - Rarely metabolic except in the case of Fanconi-type renal tubular acidosis
  - Elevated anion gap acidosis - Frequently metabolic in the neonate (Profound ketoacidosis is ALWAYS abnormal in a neonate)
    - Organic acidemia
    - Energy deficiency or gluconeogenic disorders
    - Occasionally seen in severe urea cycle defect.
- **"Remember to think of" Metabolic Causes of Neonatal Seizures**. Although these disorders are rare, they not routinely detected on "regular" metabolic testing (such as amino or or organic acid analysis or newborn screening) and so must be specifically considered in the differential diagnosis:
  - Glycine encephalopathy
    - Commonly burst-suppression, intractable
    - Check ratio of CSF to plasma glycine
  - Sulfite oxidase or molybdenum cofactor deficiency
    - Commonly burst-suppression, intractable
    - Look for low uric acid (low in molybdenum cofactor deficiency)
    - Dipstick fresh urine for sulfite
    - Notify laboratory of suspected diagnosis when sending amino acid analysis
    - Consider checking for s-sulfocysteine
  - Pyridoxine, Folinic Acid or Pyridoxal-5'Phsophate Dependent Epilepsies
    - Typically respond to B6
    - Response is NOT always "instant"
    - Some require Pyridoxal-5'phosphate or folinic acid, or both
  - Glut-1 Deficiency
    - Abnormal glucose transport into the brain
    - Low ratio of CSF to plasma glucose
    - May respond to ketogenic diet

Suggested Readings

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Valle D, Beaudet AL, Vogelstein B, Kinzler, KW, Antonarakis, SE, Ballabio, A, Gibson KM, Mitchell G, eds. *The Online Metabolic and Molecular Bases of Inherited Disease*. New York, NY: McGraw-Hill; 2014.

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Questions

1. A 3-day-old girl began feeding poorly on day two of life. She now has depressed mental status, clonus, and respiratory alkalosis. Which test should be sent for emergently?
   a. Very long-chain fatty acids
   b. 7-dehydrocholesterol
   c. Ammonia
   d. Lysosomal enzymes
   e. Cholesterol

2. A newborn male has profound hypotonia and features suggestive of trisomy 21. He is found to have hepatomegaly, hyperbilirubinemia, and synthetic liver dysfunction. Which diagnosis should be considered?
   a. Zellweger syndrome
   b. Mucopolysaccharidosis
   c. Smith-Lemli-Opitz syndrome
   d. Pyruvate carboxylase deficiency
   e. Krabbe disease

3. A breast-fed newborn girl has high anion-gap acidosis, hypoglycemia and altered mental status. Urinalysis reveals 4+ ketones. The ketosis is suggestive of:
   a. Normal response to hypoglycemia
   b. Fatty acid oxidation defect
   c. Peroxisomal defect
   d. Organic acidemia
   e. Lysosomal storage disease

4. Poorly treated maternal phenylketonuria puts a fetus at risk for:
   a. having PKU
   b. cataracts
   c. intracranial calcifications
   d. limb defects
   e. microcephaly

SECTION 6

Nutrition

WILLIAM W. HAY JR and KENDRA HENDRICKSON

23 Nutrition and Growth: The Fetus

WILLIAM W. HAY JR and KENDRA HENDRICKSON

CHANGES IN BODY COMPOSITION

Growth of Fetal Size

- Fetal weight increases exponentially in the middle of gestation, then slows during the latter third of gestation
- Normal human fetuses grow: average rate of ~17 g/kg/day from 28–40 weeks, with symmetrical growth of head and length

Developmental Change of Fetal Body Composition

- Nonfat dry weight and nitrogen content (predictors of protein content and lean body mass) show a linear relationship with fetal weight and an exponential relationship with gestational age (GA)
- 80% of the nitrogen content of the fetus is in protein
- With advancing gestation, fetal protein synthesis rate declines
  - Skeletal muscle has lower protein synthetic rate in late gestation than in earlier gestation
- Fat production in the fetus begins at start of the third trimester
  - Rate of fetal fat accretion is linear between 36–40 weeks' gestation
  - By end of gestation: fat accretion ranges from 1.6–3.4 grams/kg/day
  - By term: fat content of the human fetus is 12%–18% of body weight
    - <10% in severely intrauterine growth restriction (IUGR) fetuses
    - >20% in macrosomic infants of diabetic mothers
- Rate of fetal fatty acid oxidation is low due to:
  - Low plasma fatty acids concentration
  - The carnitine palmitoyl transferase enzyme system is not sufficiently developed to deliver long-chain fatty acids to the respiration pathway inside the mitochondria
- Fetal water content increases directly with body weight (as fraction of body weight, decreases with advancing gestation)
- Extracellular water decreases are greater than intracellular water as gestation advances due to:
  - Increased cell number and increase cell size
- Many tissues in the fetus (brain, liver, lung, heart, and skeletal muscle) produce glycogen over the second half of gestation
  - Liver glycogen content: most important store of carbohydrate (CHO) for systemic glucose needs immediately after birth
  - Skeletal muscle glycogen content increases during late gestation (source of glucose for glycolysis within the myocytes)
  - Lung glycogen content decreases in late gestation with
    - Loss of glycogen-containing alveolar epithelial cells
    - Development of type II pneumocytes
    - Onset of surfactant production
  - Cardiac glycogen essential for postnatal cardiac energy metabolism and function
- Fetal liver glycogen concentration is ~80–120 mg/gm at term, twice adult concentration
- Macrosomic fetuses of diabetic mothers: high body and organ contents of glycogen
- IUGR fetuses have normal to increased hepatic glycogen content

NUTRIENT REQUIREMENTS

Glucose

- Principal substrate in the fetus for: maintenance of energy production and expenditure, energy storage in, energy requirements of protein synthesis and growth
- Glucose utilization rates (GUR) in the human fetus
  - Higher at mid-gestation: 7–9 mg/kg/min at 24–28 weeks' gestation when fetal brain size, fetal growth, and protein synthetic rates are twice than at term
  - GUR declines to 3–5 mg/kg/min at term (as bone, fat, and muscle increase as fractions of body weight)

Amino Acids (AAs)

- Supplied to the fetus at 3.5–4 g/kg/day at 24–28 weeks' gestation (decreases to 2.5g/kg/day at term)

Fatty Acids (FAs)

- FA uptake rates by the fetus have not been measured
  - FAs are used for structural components of membranes and for growth of adipose tissue in later gestation
  - Fatty acid oxidation rates are low in the fetus (due to limited supply and lack of enzymes necessary for mitochondrial fatty acid uptake)

FACTORS THAT INFLUENCE INTRAUTERINE GROWTH

Hormonal Factors

- Fetal insulin production begins at the start of the second trimester and increases in response to glucose and AAs as gestation progresses.
- Insulin and AAs promote the production of IGF-1 (insulin growth factor) (enhances growth).
- The predominant growth-regulating effect of insulin in the fetus is its capacity to enhance glucose utilization.

Maternal, Placental, and Fetal Factors

- Fetal weight in late gestation correlates positively with placental weight.
- Oxygen transport to the fetus by the placenta: facilitated by increases in uteroplacental blood flow.
- Transport of glucose and AAs determined by trophoblast membrane exchange area, transporter concentrations, and activity in the trophoblast membranes.
- AAs are actively concentrated in the trophoblast intracellular matrix by Na+/K+-adenosine triphosphate-(ATP) ase-F and H+-dependent transporter proteins at the maternal-facing microvillus membrane of the trophoblast and then transported into the fetal plasma to concentrations higher than maternal levels.
- Net total fetal AAs uptake is 30%–40% of the combined carbon requirements for oxidative metabolism and provides 100% of the fetal nitrogen requirements.
- AAs are directly transported from maternal to fetal plasma by the placenta or may be metabolized into other AAs, then interact with metabolic pathways in the fetus that
  - Recycle certain AAs to the placenta
  - Promote vascular development (arginine producing nitric oxide)
  - Promote oxidation (ketoisocaproic acid from leucine)
  - Promote protein synthesis (including synthesis of nonessential AAs)
- Skeletal muscle in later gestation is a major consumer of both essential and nonessential AAs from the circulation.
- Rate of glucose transfer from maternal to fetal plasma directly related to the maternal glucose concentration.
- Placental glucose transport increases progressively over gestation.
  - Reflecting growth of the surface area of the trophoblast
  - Reflecting increased numbers of glucose transporters
- The concentration of glucose in the fetal plasma declines relative to maternal plasma glucose in the second half of gestation.
- Three principal mechanisms responsible for the increase in glucose clearance:
  - The size, cellularity, and glucose metabolic rate of the brain increase relative to other fetal tissues and organs.
  - Progressive development of fetal insulin secretion by the expanding mass of pancreatic islets and beta cells.
  - Increased growth of insulin-sensitive tissues (skeletal muscle, heart, adipose tissue).
- Evidence for a relatively high rate of fetal oxidation of AAs comes from three observations:
  - AAs are taken up by the fetus in excess of their rate of deposition in fetal protein.
  - Fetal urea production rates are high.
  - Fetal infusions of carbon-labeled AAs in animal models demonstrate fetal production and excretion of labeled carbon dioxide.
- Free FAs are transported by concentration dependent transporters.
  - Transport is increased when maternal concentrations are high.

Newborn Infants

CHANGES IN BODY COMPOSITION

- Significant portion of preterm infants have IUGR, tend to be SGA
- First few postnatal days: all newborn infants lose extracellular fluid and thus body weight
- The more preterm the infant, the slower the growth of the body in all compartments
- Majority of very preterm infants remain relatively growth restricted by term gestation
  - The main cause is insufficient nutrition (primarily of protein).
  - Other causes include: intermittent hypoxia, stress with increased catabolic hormone secretion, and sepsis.
- By term: preterm infants are shorter and lighter than term infants (with relatively more fat than lean mass)

ENERGY REQUIREMENTS

- Energy needs for preterm infants to achieve normal growth rates (Table 23.1).
  - Total energy intake must be sufficient to support basal metabolism (~50 kcal/kg/day)
  - Growth requires additional energy (25–35 kcal/kg/day)
  - Energy lost in stools increases with enteral feeding (5–10 kcal/kg/day)
  - Physical activity accounts for 1%–2% of total energy expenditure in preterm infants
  - Total energy needs are reduced by 5–10 kcal/kg/day for infants in incubators/radiant warmers
- There is no evidence that energy intake above normal levels enhances neurologic development or achieves appropriate growth and body composition.
- Higher energy intakes in preterm infants result in greater fat accumulation compared to normally growing fetuses of the same GA.

PROTEIN INTAKE IN NEWBORNS

Essential and Nonessential Amino Acids

- *Essential AAs*: cannot be synthesized in body cells, must be provided from exogenous sources for normal maintenance and growth, indispensable for growth

Table 23.1 Energy Requirements for Preterm Infants to Achieve Normal Growth Rates (kcal/kg/day)

Enterally Fed Infants		Intravenously Fed Infants	
Resting energy expenditure (REE)	50	Resting energy expenditure	50
Activity (0%–30% above REE)	0–15	Activity	0–5
Thermoregulation	5–10	Thermoregulation	0–5
Thermic effect of feeding (synthesis)	10	Thermic effect of feeding (synthesis)	10
Fecal loss of energy	10	Fecal loss of energy	0
Energy storage (growth)	25–35	Energy storage (growth)	25
TOTAL	100–130	TOTAL	85–95

- Essential AAs include leucine, isoleucine, valine, lysine, threonine, tryptophan, methionine, phenylalanine, and histidine
- *Nonessential AAs* can be synthesized in body cells
  - At critical stages of development (in the fetus or preterm infant of similar GA) some may not be synthesized sufficiently (conditionally essential AAs)

Protein Requirements of Newborns

- Protein requirement of the healthy term infant in the first month of life is 2.0 g/kg/day
- Protein requirement of preterm infants is higher (2.5–4.5 g/kg/day) depending on GA
- Protein accretion is linearly related to protein intake at any energy intake:
  - ~2.0 g/kg/day at term
  - 2.5–3.0 g/kg/day at ~30–36 weeks
  - 3.5–4.0 g/kg/day at ~24–30 weeks
- Rates of protein synthesis and the requirements for amino acid and protein supply are the same in preterm infants as in normally growing fetuses of the same GA
- Critical amount of amino acid for preventing growth faltering in very preterm infants (<30–32 weeks) is ~1.5 g/kg/day
- Protein accretion increases directly with protein intake and sufficient energy for protein synthesis to maximal rates for GA
- AAs >3.5–4.0 g/kg/day parenterally or 4.0–4.5 g/kg/day enterally in very preterm infants offer no advantage
- Excess protein intake can produce higher blood urea and ammonia concentrations (seldom toxic levels)
  - Increased ammonia and urea are appropriate as protein intake is increased (suggests normally functioning amino acid oxidation and urea synthesis)
  - Venous plasma concentrations of urea (>60 mg/dL) and ammonia (>100 μmol/L) are usually confounded by renal and liver failure
  - Protein intake > carbohydrate (CHO) diets in preterm infants produces leaner infants by term
  - Higher protein intake with adequate CHO intake results in lower weight gain, but higher percentage of lean body mass

Protein Metabolism in Newborn Infants

- Protein digestion begins in the stomach and duodenum with acid hydrolysis
- Basal and pentagastrin-stimulated acid secretion doubles from the first to fourth week after birth in preterm infants
- Proteases (enterokinase) produced in the upper small intestine in response to food
- Activation of trypsinogen is essential
  - Key enzyme in initiating the cascade of protein digestion by proteases
- Trypsinogen levels: 6% (25–30 weeks' gestation) and 29% at term of older children
- Despite low GI proteases in preterm infants: no evidence of insufficient protein digestion
- Hydrolyzed protein formulas: increase amino acid absorption
  - Reduce time to full enteral feeds
  - Do not promote greater protein balance for the same protein intake
  - Have lower total amino acid contents than nonhydrolyzed protein formulas

FAT INTAKE IN NEWBORNS

Features of Essential Fatty Acid Deficiency

- Clinical cases of essential fatty acid (EFA) deficiency are relatively rare
- EFA deficiency (severe and prolonged) can lead to a clinical syndrome consisting of:
  - Dermatitis (perianal region)
  - Thrombocytopenia
  - Infection
  - Failure to thrive
  - An increased triene/tetraene ratio
- Prevention of EFA deficiency: enteral feeding of milk as soon as possible after birth
- Term and preterm formulas have added DHA and ARA
- The requirement for EFA met by 0.5–1.0 g/kg/day intake in the form of IV lipid, or as 2g/kg/d for Smof lipid emulsions (from soybean oil) as 20% (0.2 g/mL) solution
- Preterm infants may benefit from PUFAs supplementation (important for growth and brain and visual development)

Essential and Nonessential Fatty Acids

- Preterm infants have insufficient capacity for de novo synthesis of LC-PUFAs (need from diet)
- Linoleic acid (18:2, ω-6) and α-linolenic acid (18:3, ω-3) are the only fatty acids known to be essential for complete nutrition

Fat Requirements of Preterm and Full-Term Infants

- Human neonates have relatively high white fat content: 12%–18% of body weight at term
- The term infant also has stores of brown fat (necessary for neonatal thermogenesis)
- In utero fat deposition occurs predominantly during the last 12 to 14 weeks of gestation
- Dietary fats important to sustain growth, provide EFA, and promote the absorption of fat-soluble vitamins
- Fat intakes of 2–3 g/kg/day IV in the first few days of life provide sufficient LC-PUFAs and calories for basal metabolism and prevention of EFA deficiency
- Recommended dietary fat intakes in infants consist of 40%–55% of total calories (4.4–6.0 g/100 kcal) as provided by normal breast feeding

Fat Metabolism in Newborn Infants

- Newborn infants absorb fat less efficiently than older children
- Preterm infants demonstrate even greater deficiencies in fat digestion and metabolism
- Preterm infants malabsorb 10%–30% of dietary fat due to a small bile acid pool and relative lack of pancreatic lipase
- Bile acids are lower in preterm infants
- Bile stimulated lipase activity is higher in milk of mothers delivering preterm than in those delivering at term
- Bile acids are essential to emulsify large fat globules of long-chain fatty acids and to facilitate lipid hydrolysis
- Additional fat digestion: by lingual and gastric lipases (lipase in human milk)

- Pancreatic lipases are less available for fat digestion and absorption
- Preterm formulas and human milk fortifiers have high percentages of fat from medium-chain triglycerides (do not need bile acid emulsification)

CARBOHYDRATE INTAKE IN NEWBORNS

Carbohydrate Metabolism in Newborn Infants

- Newborns exhaust the supply of stored glucose from the liver within 12 hours of birth if milk/formula or IV glucose is not provided
- The normal glucose utilization rate in the term newborn is 4–6 mg/kg/min
- 50% of an infant's energy needs are normally provided by CHO metabolism
- Glucose is the primary energy source for brain metabolism
- Preterm infant: glucose is largely derived from exogenous CHO sources once glycogenolysis has exhausted stored hepatic glucose
- Gluconeogenesis develops soon after birth and is not easily suppressed by increases in plasma glucose or insulin concentrations
- Maintenance of normal plasma glucose concentrations is fundamental
  - Vital organs (brain and heart) take up glucose according to plasma glucose concentrations and not IV infusion rates or rates of hepatic glucose production
- When plasma glucose concentrations decline: newborn brain may use ketone bodies as additional energy sources
  - Limited in very preterm and SGA infants with IUGR
- Mechanisms for enteral CHO digestion and absorption mature in a defined sequence in the human fetus
  - Sucrase, maltase, and isomaltase are fully active by 24–28 weeks' gestation
  - Lactase is not fully active at birth until term
  - Pancreatic amylase activity remains low until after term birth
  - Salivary amylase activity is present even in very preterm infants
- Other CHO (mannose, inositol), oligosaccharides (prebiotics) have important roles in nutrition and organ development for the preterm infant
  - Mannose is an essential CHO for protein glycosylation and normal neural development
  - Inositol is present in high concentrations in human milk and can be synthesized by newborn infants of ≥33 weeks' gestation
- Predominant CHO in human milk is lactose (glucose + galactose)
  - Galactose provides 50% of the calories derived from lactose
    - Major metabolic role in energy storage
      - Newborn liver readily incorporates galactose from the portal circulation into hepatic glycogen
- Provision of 40%–50% of total caloric intake as CHO (10–12 g/kg/day) prevents accumulation of ketone bodies and hypoglycemia in the newborn
  - This amount of CHO is supplied as lactose in human milk or formulas
- Digestion of complex CHO occurs in the lumen of the intestine, and nutrient absorption occurs at the enterocyte interface (microvillus membrane)
- CHO absorption limited initially in neonates by a relative deficiency of lactase (splits lactose into glucose and galactose)
  - Lactase activity in infant <34 weeks' gestation is 30% of normal term infant
  - Lactase functional activity increases with feeding in preterm infants and approaches term levels by 10 days after birth
  - 20% of dietary lactose reach the colon in neonates where it lowers pH
    - Promotes colonic growth of *Bifidobacterium* and *Lactobacillus*
- Preterm formulas have reduced lactose content (40%–50% of the total CHO)
  - Milk fortifiers provide little to no lactose
- If signs of lactose intolerance (frequent loose stools, abdominal distention, or positive stool reducing substances), a lactose-free infant formula may be considered
  - Helpful for calculations: energy from fat: 9 kcal/g; protein: 4 kcal/g; carbohydrate: 4 kcal/g

Large and Small for Gestational Age Infants

POSTNATAL GROWTH PATTERNS OF SGA INFANTS

- Small for gestational age (SGA) infants; not growth restricted in utero and with small mothers and fathers tend to grow along the lower growth percentiles at which they were born
  - Tend to be shorter later in life
  - Head circumference growth increases in proportion to length and weight
- SGA infants with recent IUGR
  - Due to nutritional deficiency from placental insufficiency
  - Tend to catch up in growth
- Chronically IUGR fetuses develop decreased capacity for amino acid synthesis into protein and for cell growth
  - Leads to decreased muscle mass and glucose intolerance (reduced glucose uptake and utilization capacity)
- Chronically SGA/IUGR infants have downregulated capacity for protein synthesis and net protein accretion and often have evidence of increased protein breakdown
  - Persistent slower growth is common
    - Later life shorter stature, smaller brains, and reduced neurocognitive development
- No consensus about the optimal amount of protein to feed SGA/IUGR infants
  - Provide weight-appropriate amounts of milk and limiting amino acid in TPN to 3.0–3.5 g/kg/day
  - Evidence for benefit or risk from such restricted nutrition for these IUGR infants is lacking

FETAL ORIGINS OF ADULT ONSET DISORDERS

- Fetal nutrition deprivation produces adaptive mechanisms to help ensure survival to birth
- Programming: these adaptive mechanisms that may persist after birth into adulthood include:

- Upregulation of glucose and insulin sensitivity from increased glucose transporters and insulin receptors
- Diminished insulin secretion
- Reduced muscle mass and lean body growth (includes bone and brain)

- Such programming allows later life insults ("second hits") of excess energy and leads to obesity, type 2 diabetes, and cardiovascular disorders
- Both IUGR and macrosomic infants tend to develop this common later life phenotype
- The more preterm the infant at birth, the higher the prevalence of hypertension, obesity, metabolic syndrome, and fatty liver index in an adult who was born preterm vs. an adult born at term
- Rapid postnatal growth rate: weight gain > growth rates of length and head circumference, sign of excess energy intake and production of fat (risk of later obesity)

IUGR and SGA Infants

- IUGR refers to a slower than normal rate of fetal growth
  - Undernutrition from placental insufficiency is the leading cause of IUGR in developed countries
  - Maternal undernutrition the leading cause in less developed countries

Classification of Fetal Growth

- SGA infants have a birth weight <10th percentile for gestational age
- Appropriate for gestational age (AGA) infants have a birth weight between the 10th and 90th percentiles for gestational age
- Large for gestational age (LGA) infants have a birth weight >90th percentile for gestational age
- IUGR infants have a slower than normal rate of fetal growth at any gestational age
- Macrosomic infants weigh >4500 g at term birth
- Normal birth weight infants weigh >2500 g at term birth
- Low birth weight (LBW) infants weigh <2500 g at any gestational age
- Very low birth weight (VLBW) infants weigh <1500 g at any gestational age
- Extremely-low-birth-weight (ELBW) infants weigh <1000 g at any gestational age
- IUGR infants characteristically develop both hyper- (usually early after birth) and hypoglycemia (usually later)
- Initial hyperglycemia in IUGR neonates due to: decreased pancreatic insulin secretion reduced fetal pancreatic beta cell proliferation (response to reduced glucose, amino acid, growth factor stimulation, and hypoxia)
  - IUGR fetuses tend to produce glucose from their livers (which normal fetuses do not) by uniquely developed hepatic insulin resistance in response to glucocorticoids and hypoxia
  - After birth (24–72 hours) hyperglycemia: due to continued stress and hypoxia with high rates of IV glucose infusion
- Once stabilized, IUGR newborn infants often develop hypoglycemia, can continue for days to weeks
- Causes of hypoglycemia in IUGR infant
  - IUGR fetuses respond to chronically reduced glucose supply and concentrations by upregulating glucose transporters and the maintenance of glucose utilization by all organs (sustaining normal cellular metabolism)
  - As oxygenation improves, catecholamines diminish, reducing their suppression of insulin secretion
  - Frequent feedings day and night are the best approach to treating mild to moderate hypoglycemia
  - Rarely, diazoxide can be used to suppress insulin secretion; this agent has serious side effects, including pulmonary edema and pulmonary hypertension

Large for Gestational Age (LGA) Infants

- LGA infants can be normal (e.g., from large mothers and fathers), or from excess energy intake and fat production (macrosomia), the latter due to infants of gestational diabetics and infants whose mothers were obese or with metabolic syndrome
- Exposure to high glucose concentrations produces a common fetal and neonatal phenotype of excess adiposity and high insulin secretion rates, especially in response to sudden hyperglycemia, leading to rebound hypoglycemia (asymptomatic and symptomatic)
- Optimal management expectant: enteral feeding started as soon as possible after birth to diminish IV glucose stimulation of insulin secretion
- Smaller and more frequent feedings, and often continuous enteral feeding via OG/NG tubes, can prevent hyperinsulinism
- Term IDMs: not acutely hypoglycemic have total GUR of only 3–4 mg/kg/min, considerably below the infusion rates many of these infants receive
  - Contributing to this lower body weight specific utilization rate is the larger fat mass in these infants
  - Adjusting IV glucose infusion rates to a body weight more consistent with the head circumference often helps avoid advancing to higher glucose infusion rates with risk of stimulating excess insulin secretion (the brain is where most of the glucose is used in the body)

Suggested Readings

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Questions

1. During the third trimester of fetal growth, the largest fractional increase in body composition is the result of:
   a. water
   b. fat
   c. brain
   d. lean body mass

2. Essential amino acids are:
   a. used for oxidation
   b. used for protein synthesis
   c. used for growth of the brain
   d. required as part of nutrient supplies
   e. all of the above

3. Which of the following regarding neonatal nutrition is false?
   a. Rates of protein synthesis and the requirements for amino acid and protein supply to meet them are the same in preterm infants as in normally growing fetuses of the same gestational age.
   b. The critical amount of amino acid or protein nitrogen for preventing growth faltering in very preterm infants <30–32 weeks is less than 1.5 g/kg/day.
   c. There is no advantage to protein metabolism or growth (body weight or composition) with more than 3.5–4.0 g/kg/day parenterally or 4.0–4.5 g/kg/day enterally in very preterm infants.
   d. Excess amino acid or protein intake always produces higher blood urea and ammonia concentrations but these seldom are in toxic ranges.

24 Minerals, Vitamins, and Trace Minerals

WILLIAM W. HAY JR and KENDRA HENDRICKSON

Minerals (Table 24.1)

NEONATAL MINERAL REQUIREMENTS AT VARIOUS GESTATIONAL AGES

- Sodium (Na), chloride (Cl), and potassium (K) intakes restricted right after birth due to:
  - Delayed urinary flow rates: exacerbated by RDS
  - Avoid volume overload
- Once urinary flow rates established: requirements of Na, K, and Cl are between 2 and 4 mmol/kg/day (higher for preterm infants)
- After this period: urinary excretion of electrolytes depends on intake
- Cl intake restricted when dilutional acidosis occurs
- Cl added: when respiratory failure leads to CO_2 retention, with bicarbonate retention and metabolic alkalosis
- Typical urinary concentrations for Na are 20–40 mmol/L and K 10–30 mmol/L
- In infants receiving diuretic therapy: urinary Na concentrations can reach up to 70 mmol/L
- Insufficient Na intake impairs longitudinal growth and lean mass gain

REQUIREMENTS OF CALCIUM AND PHOSPHORUS AT VARIOUS GESTATIONAL AGES

- Enteral absorption rates for both calcium (Ca) and phosphorus (P) are limited in preterm infants
  - Enhanced with calcium and phosphorus enriched preterm formulas
- Adequate enteral intake for term infants in the first 6 months of life:
  - Calcium: 70 mg/kg/day
  - Phosphorus: ~100 mg/day
- Requirements for preterm infants are much higher due to more active bone formation and remodeling:
  - Calcium: 150–220 mg/kg/day
  - Phosphorus: 60–140 mg/kg/day
  - Ideal Ca:P ratio 1.8:1 to 2:1 mg, weight basis
- Fortification of human milk: ensure adequate intakes of calcium and phosphorus to preterm infants fed human milk (natural mother's milk and donor milk)
- Recommended IV intakes of calcium and phosphorus lower than enteral requirements:
  - Calcium: 65–100 mg/kg/day
  - Phosphorus: 50–80 mg/kg/day
  - Ideal Ca:P ratio of 1.3:1 to 1.7:1 mg, weight basis
- Risk factors in preterm infants for calcium and phosphorus deficiency (subsequent rickets) are:
  - Gestational age <27 weeks or birth weight <1000 grams
  - Long-term parenteral nutrition (>4–5 weeks)
  - Severe BPD requiring diuretics
  - Fluid restriction
  - Long-term steroid treatment
  - History of necrotizing enterocolitis (NEC)
  - Intolerance to enteral formula or human milk

Vitamins (Table 24.1)

REQUIREMENTS FOR VITAMINS IN NEWBORN INFANTS

- Vitamins: organic substances, present in trace amounts in natural food and essential to normal metabolism
- Biologic roles of many vitamins are not completely understood in preterm infants
- Vitamins generally are given on a weight specific basis (not gestational age (GA))
- Because vitamins have a central role in many metabolic processes, signs of vitamin deficiency are nonspecific: lethargy, irritability, and poor growth
- Routine supplementation of vitamins above the recommended doses not advised
- Table 24.1 shows recommended vitamin intake for enterally fed preterm infants

MANIFESTATIONS OF WATER-SOLUBLE VITAMIN DEFICIENCIES

- Water-soluble vitamin deficiencies are uncommon in preterm and term infants
- Vitamin B_1 (thiamine): important in the pentose phosphate pathway and oxidative decarboxylation of α-keto acids
  - Thiamine deficiency (Beriberi)
    - Clinical syndrome with neurologic and cardiac symptoms
    - Not seen in newborn infants (adequate B_1 in breast milk/formula)
- Vitamin B_2 (riboflavin): catalyzes oxidation-reduction reactions
  - Riboflavin deficiency: dermatitis, cheilosis, and glossitis
- Vitamin B_3 (niacin): mediates oxidation-reduction reactions

Table 24.1 Recommended Vitamin and Trace Mineral Intakes for Enterally Fed Preterm and Term Infants

	Term (per 100 kcal)	Preterm (per 100 kcal)
Vitamin A (μg RE)[a]	60–150	365–1000
Vitamin D (IU)	40–100	400–1000
Vitamin E (mg α-TE/100 kcal)[b]	0.5–5	2–10
Vitamin K (μg RE)	1–25	4–25
Vitamin C (mg)	6–15	18–55
Pantothenic acid (mg)	0.3–1.2	0.5–1.9
Biotin (μg/kg)	1–15	1.5–15
Thiamine-B_1 (μg)	30–200	140–300
Riboflavin-B_2 (μg)	80–300	200–400
Niacin-B_3 (μg)	550–2000	900–5000
Pyridoxine-B_6 (μg)	30–130	50–300
Cobalamin-B_{12} (μg)	0.08–0.7	0.1–0.8
Folic acid (μg)	11–40	35–100
Zinc (mg)	1.5–2	1.3–2.3
Manganese (μg)	1–100	6.3–25
Copper (μg)	60–160	100–250
Iodine (μg)	8–35	6–35
Selenium (μg)	1.5–5	1.8–5

[a]RE: retinol equivalents
[b]TE: tocopherol equivalents

- Niacin deficiency (pellagra):
  - Classical "four D" conditions of dermatitis, diarrhea, dementia, and death
- Vitamin B_4 (biotin) deficiency symptoms include:
  - Glossitis, dermatitis, loss of appetite, nausea
- Vitamin B_5 (pantothenic acid): is a component of coenzyme A (CoA)
  - Transferring acyl groups (succinyl CoA, fatty acyl CoA, and acetyl CoA)
  - A component of fatty acid synthase
  - Deficiency not seen in preterm infants
- Vitamin B_6 (pyridoxine): precursor to pyridoxal phosphate that functions as a coenzyme for enzymes that catalyze reactions involving amino acid metabolism
  - Deficiency conditions are not seen in preterm infants
- Vitamin C (ascorbic acid): deficiency classically causes scurvy
  - Characterized by sore, spongy gums, loose teeth, fragile blood vessels, swollen joints, and anemia (not seen in preterm infants)
  - Vitamin C promotes GI iron absorption and serves as an antioxidant
- Vitamin B_{12} (cyanocobalamin) is important for hematopoiesis
  - Vitamin B_{12} deficiency causes megaloblastic anemia and associated neurologic dysfunction
  - Deficiency states, although rare, can be seen in
    - Breastfed infants whose mothers follow a strict vegan or vegetarian diet that is deficient in vitamin B_{12}
    - Infants with short bowel syndrome (SBS) where the terminal ileum is removed
- Folate (vitamin B_9): functions to receive one-carbon fragments from donors (serine, glycine, histidine) and transfer them to intermediates in the synthesis of amino acids (AAs)
  - Most common vitamin deficiency in the United States (particularly in pregnant women)

MANIFESTATION OF FAT-SOLUBLE VITAMIN DEFICIENCIES

- Infants with fat malabsorption due to cholestatic liver disease or SBS are at risk for developing fat-soluble vitamin deficiency
  - Fat-soluble vitamin supplementation may be necessary in these patients
- Vitamin A is essential for growth and differentiation of epithelial tissues (includes the lung)
  - Preterm infants have low stores of vitamin A at birth
  - Preterm infants with lung disease have lower plasma vitamin A levels than those without lung disease
  - Vitamin A deficiency may contribute to the development of BPD
    - Vitamin A supplementation has not become standard practice (due to need for repeated IM injections)
- Vitamin D is essential for bone health
  - Infants who require assisted ventilation, have no exposure to UV light in the hospital, and limited exposure after discharge have minimal cutaneous synthesis of vitamin D
  - Recommended enteral intake of vitamin D is 200–400 IU per day
    - This dose maintains adequate (>50 nmol/L) serum concentrations of vitamin D and helps to prevent vitamin D-deficiency associated rickets
    - Higher doses (800–1000 IU per day) have been recommended for infants with extreme prematurity, SBS, cholestasis, long-term exposure to diuretics and/or steroids
- Vitamin E: major natural antioxidant, protecting lipid-containing RBC cell membranes against oxidative injury, reducing hemolysis, and may prevent neonatal oxygen toxicity (retinopathy of prematurity (ROP) and intraventricular hemorrhage (IVH))
  - Recommended enteral vitamin E intake is 3.3–16.4 IU/kg/day
  - The dietary ratio of vitamin E to polyunsaturated fatty acids (PUFA) should be ≥0.6 mg of D-α-tocopherol (0.9 IU) per gram of PUFA
  - Recommended IV vitamin E is 2.8 IU/kg/day as α-tocopheryl acetate
- Vitamin K prevents hemorrhagic disease of the newborn in the first weeks of life
  - A single dose of intramuscular vitamin K (1.0 mg) is sufficient
  - Subsequent vitamin K supplementation helps prevent deficiency in critically ill infants who receive broad-spectrum antibiotics (reduces vitamin K synthesis by gut bacteria) and may have other abnormalities of hemostasis or hepatic function

POTENTIAL ADVERSE EFFECTS OF PHARMACOLOGIC USE OF FAT-SOLUBLE VITAMINS

- Vitamin A: acute toxicity can lead to liver damage and increased intracranial pressure (bulging fontanelle, vomiting, papilledema)
- Vitamin D: excessive dosing results in (infant discharged on high dose vitamin D)
  - Hypercalcemia, constipation, muscle weakness, and vomiting
    - Severe cases: damage the bones and kidneys
- Vitamin E: excessive dosing is associated with increased incidence of hemolytic anemia, ROP, BPD, and ICH
  - Increases risk of sepsis, necrotizing enterocolitis (NEC), and retinal hemorrhage in very low birth weight (VLBW) infants
- Vitamin K: excessive dosing causes hemolytic anemia (results in hyperbilirubinemia)
  - Blocks the effects of oral anticoagulants

Trace Minerals

- The content of trace minerals in human milk is the gold standard for requirements in term infants
  - Requirements for the preterm infant estimated from in utero accretion rates
  - Preterm infants are relatively lacking in some important minerals (e.g., iron, zinc)
    - Accumulation occurs mostly in the third trimester
- Trace mineral supplementation of human milk or use of an enriched preterm formula usually is necessary to achieve the recommended trace element requirements
- Trace mineral deficiencies: most common in those infants with excessive GI losses from ostomy/fistula output or diarrhea

IRON

- Iron intake: 2–4 mg/kg/day for both term and preterm enterally fed
  - Preterm infant with anemia of prematurity and on erythropoietin: 6 mg/kg/day
- Risks of iron overload and toxicity (e.g., possible increased risk of ROP) increase with red cell transfusions
- Iron supplementation often is delayed for 2 weeks after a transfusion
- Potential risks of IV iron in preterm infants include neonatal sepsis, iron overload, and anaphylaxis
- Formula-fed infants should receive only iron-fortified formula

OTHER TRACE MINERALS

- Zinc deficiency
  - Acrodermatitis enteropathica: inborn error of zinc (Zn) metabolism
    - Inherited as an autosomal recessive disorder
    - Characterized by growth impairment, periorofacial and acral dermatitis with perianal inflammation and excoriation
  - Acquired Zn deficiency: from prolonged maternal milk ingestion in mothers with low Zn levels
  - Preterm formulas and human milk fortifiers meet Zn requirements
  - Small for gestational age (SGA)/intrauterine growth restriction (IUGR) infants and infants with intestinal resection greater risk for Zn deficiency
  - Human milk Zn content declines over the early months of lactation
- Copper: copper (Cu) deficiency is rare, occurs when Cu is withheld from parenteral nutrition (PN) due to associated PN liver disease
  - Current recommendations: remove Cu only if evidence of toxicity is present
  - Deficiency signs in neonates: hypopigmentation of skin and hair, bone abnormalities, microcytic hypochromic anemia unresponsive to iron therapy, neutropenia, and leukopenia.
  - Cu dosage may be increased to 10–15 micrograms/kg/day in infants experiencing abnormally high biliary or enterostomy drainage
  - High doses of enteral Zn and iron intake can contribute to Cu deficiency
- Selenium: deficiency includes increased risk of sepsis, cardiac and skeletal muscle myopathies, abnormalities in hair and nails, microcytic anemia, and increased erythrocyte fragility
  - Selenium (Se) deficiency more likely in infants with SBS
- Manganese: a cofactor in numerous enzyme systems
  - Deficiency: rare, limited to mucopolysaccharide and lipopolysaccharide formation
- Chromium: deficiency includes neuropathy and hyperglycemia, rare in human infants
- Iodine deficiency: iodine is a major component of thyroid hormones triiodothyronine (T3) and thyroxine (T4)
  - Infants with high intestinal losses can develop hypothyroidism
  - Even with human milk fortification, iodine content remains below intake recommendations for preterm infants
  - Parenteral iodine intake of 1 micrograms/kg/day is recommended for preterm infants
  - The current US neonatal parenteral trace mineral product does not contain iodine

POTENTIAL TOXICITIES OF TRACE MINERAL SUPPLEMENTATION IN NEONATES

- Zinc toxicity: potential Cu and iron deficiency
- Cu toxicity: potential hepatotoxicity
  - Acute Cu toxicity in preterm infants is rare, even with cholestasis
  - Chronic excessive intake or reduced biliary excretion can result in hepatic cirrhosis and hepatotoxic cell injury (increased alanine aminotransferase)
- Manganese toxicity: potential neurotoxicity
  - Manganese (Mn) supplementation stopped with any signs of hepatic dysfunction or cholestasis
  - Mn toxicity can still occur without hepatic dysfunction, because Mn is a common contaminant in PN solutions

  - Parenteral calcium gluconate to prevent osteopenia contributes to Mn contamination and potential toxicity
- Chromium toxicity: potential nephropathy (reduced GFR), evidence of renal tubular damage
- Selenium toxicity: hair loss, weakness in older children
  - Toxicity in neonates is not documented

Suggested Readings

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Questions

1. Which of the following is TRUE about calcium and phosphorus supplements for preterm infants?
   a. Calcium and phosphorus are readily absorbed from the preterm infant GI tract and do not need to be supplemented.
   b. Calcium and phosphorus are easily soluble in IV nutrition solutions.
   c. Recommended intravenous intakes of calcium are higher than enteral requirements, ranging from 150 to 220 mg/kg/day for calcium.
   d. Risk factors in preterm infants for calcium and phosphorus deficiency and subsequent rickets include: gestational age <27 weeks or birth weight <1000 grams, long-term parenteral nutrition (>4–5 weeks), severe BPD requiring diuretics and fluid restriction, long-term steroid treatment, a history of necrotizing enterocolitis (NEC), and intolerance to enteral formula or human milk.

2. The following statement about potential manganese (Mn) toxicity is true:
   a. Potential nephrotoxicity.
   b. Mn supplementation should be stopped with any signs of hepatic dysfunction or cholestasis.
   c. The contaminant levels of Mn in parenteral nutrient solutions are too low to meet requirements without additional supplementation.
   d. Parenteral calcium gluconate to prevent osteopenia does not contribute to Mn contamination and potential toxicity.

25 Enteral Nutrition

WILLIAM W. HAY JR and KENDRA HENDRICKSON

Human Milk

- Ideal enteral diet for human neonates:
  - Human milk provides sufficient energy, protein, fat, carbohydrate, micronutrients, and water for normal metabolism, growth, and development in term infants.
    - Requires supplements of protein and certain minerals
- Contraindications to the use of human milk are rare.
  - Breastfeeding should be restricted in mothers with untreated maternal miliary tuberculosis or brucellosis; active herpes virus lesions on the breast; acute H1N1 pneumonia, acute varicella, or human immunodeficiency virus (HIV) infection; in infants with congenital galactosemia; and in infants whose mothers are taking antimetabolites.
  - Relative contraindications: breastfeeding in mothers with drug abuse (e.g., narcotics, phencyclidine, cocaine, cannabis, etc.).
    - Mothers who test positive for such drugs should be enrolled in drug reduction programs rather than stopping breastfeeding, particularly among mothers with preterm infants, in whom the advantages of mother's milk generally outweigh the risks of addiction and neurodevelopmental defects in the infant.
- The development of a beneficial gastrointestinal (GI) flora, characterized by a large prevalence of bifidobacteria and lactobacilli, is supported by human milk feedings.
- Human milk provides a variety of antimicrobial factors, such as secretory immunoglobulins (IgA), leukocytes, complement, lactoferrin, and lysozyme that protect against infections and Necrotizing Enterocolitis (NEC).
- Human milk contains hormones and growth factors such as epidermal and nerve growth factors, insulin-like growth factor (IGF) I and II, erythropoietin, prolactin, calcitonin, steroids, thyrotropin-releasing hormone (TRH), and thyroxine, which promote organ maturation, growth, and health.
- Several essential and conditionally essential amino acids (AAs) present in high concentrations in human milk promote gut growth and development.
- The protein and fat components of human milk are readily digestible, and human milk contains large numbers of enzymes that aid in nutrient digestion and processing (e.g., lipase).
- Exclusive human milk feeding of infants at high risk may reduce the risk for developing atopic disease or milk protein allergy in infancy.
- Human milk is advantageous for enhancing neurodevelopment, including vision, mental scales (particularly cognition), motor scales, behavior, and hearing.
- Preterm infants breastfed at discharge have less subnormal neurodevelopment at 2–5 years.
  - These effects last into infancy, childhood, and adolescence.
- There are psychological benefits to a mother who provides her own milk to her infant.

"Human milk is the recommended basis of nutrition for the preterm infant: all preterm infants should receive human milk; human milk should be fortified with protein, minerals, and vitamins to ensure optimal nutrient intake for infants weighing <1500 g at birth; and pasteurized donor human milk, appropriately fortified, should be used if mother's own milk is unavailable or its use is contraindicated."

AMERICAN ACADEMY OF PEDIATRICS (AAP)

COMPOSITION OF BREAST MILK: MOTHER OF PRETERM INFANT AND MOTHER OF FULL-TERM INFANT

- Preterm infant will not grow at the normal rate of fetal growth on human milk alone, because of the greater needs for protein and salts to promote growth at in utero rates.
- Protein content is higher in preterm mother's colostrum and milk right after birth, compared with term mother's milk.
- Milk from mothers of preterm infants has more sodium initially than milk obtained at term.
- Mother's milk can support adequate growth in larger and healthier preterm infants who have the capacity to take in larger volumes (usually >200 mL/kg/day).
  - Important when feeding preterm infants with donor human milk
    - Donor human milk has lower protein and salt concentrations than early preterm mother's milk

DIFFERENCES IN THE NUTRITIONAL COMPOSITION OF HUMAN MILK AND INFANT FORMULAS

- Unfortified mature preterm human milk is lower in nutrient density and protein content than commonly used preterm formulas.
- Major nutrient compositions for mature preterm milk and preterm formulas (Table 25.1).
- Preterm formulas are higher than mature, unfortified human milk for contents of calcium, phosphorus, sodium, potassium, chloride, iron, zinc, magnesium.
- Mature human milk and donor milk should be fortified with standard fortifiers to approximate the mineral compositions of preterm formulas to ensure adequate growth and development.

Table 25.1 Major Nutrient Composition of Mature Human Milk and Preterm Formulas

	Mature Preterm Human Milk (Unfortified)	Enfamil Premature	Similac Special Care
Nutrient density (kcal/oz)	19–21	24	24
Protein (g/100 kcal)	2.2	3.3	3
(% total calories)	8	13	12
Sources	Human milk	Bovine whey Protein concentrate Non fat milk	Bovine whey Protein concentrate Nonfat milk
Fat (g/100 kcal)	5.4	5	5.4
(% total calories)	44–52	44	47
Sources	Triglycerides	MCT oil, soy oil, high oleic, vegetable oil, DHA, ARA	MCT oil, soy oil, high oleic, vegetable oil, DHA, ARA
Carbohydrates (g/100 kcal)	10	11	10
(% total calories)	40–44	43	41
Sources	Lactose	Lactose Corn syrup Solids	Lactose Corn syrup Solids

ARA, Arachidonic acid; DHA, docosahexaenoic acid; MCT, medium-chain triglycerides.

- Preterm formulas are higher than mature, unfortified human milk for vitamins A, D, E, K, C, riboflavin, B_6, and folic acid.
- Standard multivitamin is used for preterm infants fed their own mother's milk or donor milk to ensure adequate metabolism, growth, and development.

IMMUNOLOGIC AND ANTI INFECTIVE CONSTITUENTS IN HUMAN MILK AND THEIR EFFECTS

- Lactoferrin (LF) and LF-iron-binding capacity:
  - LF has bacteriostatic function in the intestinal mucosa of the newborn:
    - Chelates iron and prevents growth of various pathogens
    - Direct cytotoxic effect against bacteria, viruses, and fungi
    - Immunomodulatory functions
      - Assists to limit excessive immune responses:
        - Inhibits inflammatory cytokines (IL-1β, IL6, IL8, Tumor Necrosis Factor [TNF]-α)
        - Stimulates activity and development of the immune system
  - Part of LF's activity attributed to the formation of lactoferricin:
    - Potent cationic peptide with bactericidal activity formed during the digestion of LF
- IgA is responsible for 80%–90% of total immunoglobulins in human milk.
  - IgA acts locally on the intestine as a first line of defense directed at foreign antigens, which include:
    - Commensal or pathogenic microorganisms
    - Toxins, viruses, and other antigenic materials (lipopolysaccharide)
      - Prevents their adherence and penetration into the epithelium without triggering inflammatory reactions that could be harmful to the newborn (immune exclusion)
    - High-affinity dimeric IgA antibodies inactivate viruses (e.g., rotavirus).
- IgM: high avidity IgM antibodies react with viruses and bacteria to protect the mucosal surfaces of infants.
  - Acts via agglutination and complement activation
- IgG is found at low concentrations in human milk.
  - Neutralizing and opsonizing activity
    - Activate the complement system and antibody-dependent cytotoxicity
  - IgG 1, 2, and 3 activate phagocytosis
  - IgG4 is anti inflammatory (responding to allergens)
- Lactoperoxidase: in the presence of hydrogen peroxide catalyzes the oxidation of thiocyanate (present in saliva), forming hypothiocyanite that can kill both gram-positive and gram-negative bacteria.
- Lysozyme enzyme activity: capable of degrading the outer wall of gram-positive bacteria.
  - Lysozyme ability to kill gram-negative bacteria in vitro (synergistically with LF).
  - Lysozyme may have antiviral activity.
- Human milk contains a variety of live cells including:
  - Macrophages, T cells, stem cells, lymphocytes with anti infective and immunologically protective functions
- Human milk contains large amounts of human milk oligosaccharides (HMOs).
  - HMOs: prebiotic agents encourage the growth of beneficial (probiotic) organisms
- Human milk contains many hundreds to thousands of distinct bioactive molecules that protect against infection and inflammation and contribute to immune maturation, organ development, and healthy microbial colonization.

HUMAN MILK: THE EFFECTS OF DIFFERENT PROCESSING METHODS

- Mother's own milk can be produced at home or produced in the Neonatal Intensive Care Unit (NICU) and stored.
  - Varying degrees of nutrient loss may occur with long-term storage.

- Depends on the nutrient and the storage methods
- For majority of human milk components: significant degradation occurs only with long-term storage and multiple freeze-thaw cycles (reduce bactericidal capacity).
- Vitamin C loss occurs rapidly.
  - Even in process of feeding freshly expressed human milk by bottle
- Donor milk.
  - Donated human breast milk can contain pathogenic microorganisms that could be transferred to the infants, requiring sterilization procedures to ensure its safety.
    - Such procedures diminish or destroy many nutritional and immunologic components of milk.
- Heat treatment (pasteurization) of human milk: the most common approach for sterilization.
  - May reduce concentration and functional capacity of many bioactive components.
  - Boiling is most damaging.
  - Holder pasteurization (62°C for 30 minutes).
    - Method used by the milk banks associated with the Human Milk Banking Association of North America.
    - Does not adversely affect the protein content of donor milk.
    - Flash-heat treatment may preserve bacteriostatic activity of donor milk more than the other methods.
  - Pasteurization significantly reduces all classes of immunoglobulin.
    - IgA, lysozyme, LF, Bile Salt Stimulated Lipase (BSSL), cytokines (most are antiinflammatory), lipases, macrophage inflammatory protein, TGF-b, and growth factor proteins (insulin, adiponectin, and erythropoietin).
  - Overall: considerable variability in the assessment of biologic activity both before and after pasteurization.
  - Total lipid generally is reduced (up to 60%), but Free Fatty Acids (FFAs) are increased.
    - Pasteurization is damaging to fat content of donor milk compared to multiple freeze-thaw cycles.
  - No significant reductions in lactose have been noted.
  - Higher heat sensitivity noted for water-soluble vitamins (vitamin C).
    - Less so for fat-soluble vitamins
  - Zinc concentrations unchanged: activity impaired by denaturation of zinc binding proteins.

HUMAN MILK FORTIFICATION

- Extremely-low-birth-weight (ELBW) infants require increased nutrient supplies than are provided with maternal or donor milk due to:
  - lower minimal energy reserves (carbohydrate stores in glycogen, fat in adipose tissue, protein in muscle);
  - intrinsically higher metabolic rate (greater relative mass of more metabolically active organs: brain, heart, liver);
  - higher protein turnover rates (especially when growing);
  - higher glucose needs for energy and brain metabolism;
  - higher lipid needs to match the in utero rate of fat deposition;
  - excessive evaporative rates (immature skin);
  - high urinary water and solute losses (depends on intake and renal maturation);
  - low rates of gastrointestinal peristalsis;
  - limited production of gut digestive enzymes and growth factors;
  - higher incidence of stressful events (hypoxemia, respiratory distress, sepsis);
  - metabolic effects of medications (steroids, antibiotics, sedatives, catecholamines);
  - abnormal neurologic outcome if not fed adequately.
- Recommended daily requirements for energy, protein, calcium, sodium, phosphorus, magnesium, iron, zinc, and several vitamins necessary to meet the normal rate of in utero growth usually not achieved in the growing "healthy" preterm infant, fed with unsupplemented human milk, unless feeding milk volume feeds >200–250 mL/kg/day.
  - Preterm infants with respiratory distress, infection, excessive heat losses, GI disorders, or surgery have even greater nutritional needs.
- Most new formulations of commercially available fortifiers use hydrolyzed cow's milk protein: may lead to less GI intolerance, less protein allergy (GI inflammation), and NEC.

PHYSIOLOGY AND PATHOPHYSIOLOGY OF HUMAN MILK PRODUCTION AND SECRETION

- Anatomy and function
  - Mammary tissue includes alveoli (small sacs made of milk-secreting cells) and excretory ducts
    - Milk collects in the lumen of the alveoli and ducts between feedings
  - The alveoli: surrounded by myoepithelial cells that contract in response to tactile stimulation (suckling, manual expression) and oxytocin to produce milk flow along the ducts
  - Each nipple has an average of nine milk ducts surrounded by muscle fibers and nerves
    - Montgomery glands within the pigmented areola surrounding the nipple secrete an oily fluid that protects the skin of the nipple and areola during lactation, and produce the mother's individual scent that attracts her baby to the breast
  - The ducts beneath the areola fill with milk and become wider during a feed (when the oxytocin reflex is active)
- Hormonal regulation of lactation
  - Prolactin secretion increases markedly during pregnancy and stimulates the growth and development of the mammary tissue
  - Milk secretion is suppressed during pregnancy by the pregnancy hormones (progesterone and estrogen)
  - After delivery: progesterone and estrogen decrease rapidly, allowing prolactin to stimulate milk secretion
  - Suckling by the infant increases prolactin secretion and its stimulation of milk production in the alveoli
  - Prolactin concentrations: highest about 30 minutes after suckling begins
  - Oxytocin is essential for establishing lactation by stimulating the myoepithelial cells around the alveoli to contract, thereby increasing milk flow through and out of the ducts

- The oxytocin reflex: called "letdown reflex" or the "milk ejection reflex"
- Oxytocin is produced more quickly than prolactin
- Increases flow of milk already in the breast alveoli and ducts, helps the infant to get the milk easily
- Oxytocin also stimulates uterine contractions (contributing to uterine pain during early suckling)
- Prolactin and oxytocin secretion increase in response to gentle areolar and nipple tactile stimulation, enhanced by skin-to-skin contact and promoting breastfeeding and emotional bonding
- A delay in breastfeeding of even 4 to 6 hours after birth may lead to breastfeeding failure, and early initiation of breast expression in mothers of preterm infants is equally important

- Preterm birth and milk production
  - Mammogenesis and lactogenesis are limited in mothers who deliver early.
    - *Lactogenesis I*: the development of the synthetic capability of the breast to produce milk-specific components (lactose, casein, and α-lactalbumin)
    - *Lactogenesis I:* begins by 22 weeks of pregnancy with production of unique milk components from the lactocytes
  - Milk production is limited immediately after birth (regardless of gestation).
  - First 48 hours after term birth: production of colostrum is 37 to 169 g/day.
    - *Lactogenesis II*: secretion of copious milk secretion, precedes the mother's sensation of milk coming into the breast (occurs between 24 to 102 hours after birth, average 59 to 64 hours)
    - *Lactogenesis II*: requires adequate levels of prolactin, insulin, and adrenocorticoid hormones, is triggered by withdrawal of progesterone following delivery of the placenta
  - Preterm infants can grasp the nipple with lips and tongue from 28 weeks' gestational age, and can suckle and remove some milk from nipple at 31 weeks.
    - Coordination of suckling, swallowing, and breathing develops between 32 to 35 weeks
    - Most preterm infants can breastfeed fully by 36 weeks
  - Preterm birth is stressful and may lead to unsuccessful milk production if supportive nursing care, lactation counseling, encouragement by physicians, and provision of a calm, quiet, private environment are not provided.
    - Many mothers delivering preterm infants have not breastfed previously and are not familiar with the sensations caused by the release of oxytocin
    - Inadequate milk production in some stressed mothers of very preterm infants could be caused by failure of milk ejection

PROBLEMS ASSOCIATED WITH BREAST MILK PRODUCTION IN THE NICU

Common Problems and Strategies to Acquire and Feed Mother's Own Milk (MOM) in the NICU

- Establishing a milk-friendly environment that promotes breast milk and breastfeeding.
- Assuring access to effective and efficient hospital-grade electric pumps, double collection kits, and customized breast shield sizing.
- Implementing breast pump use within 1 hour after birth.
- Avoidance of exclusive hand expression in the early days after birth.
- Monitoring pumped milk volume during the critical first 2 weeks after birth when breast-pump dependent mothers are at risk for long-lasting milk volume problems.
- Integrating NICU-based breastfeeding peer counselors as direct lactation care providers.
- Incorporating tested lactation technologies (milk analysis and test-weighing) to objectively manage growth on MOM feedings.
- Promoting breastfeeding and milk production right after birth of a preterm, sick infant.
- Promoting donor milk when MOM is not available and formula is not desired.
- Optimizing counseling of mothers, avoiding problems such as promoting discharge at the expense of breastfeeding and pumping breast milk emphasized over breastfeeding.
- Promoting kangaroo mother care and prenatal education to encourage breastfeeding and to enhance knowledge and perception of providing appropriate volumes.

ADVANTAGES AND DISADVANTAGES OF THE USE OF DONOR HUMAN MILK

- Donor human milk is a pasteurized product from accredited milk banks and used when maternal milk is insufficient or unavailable.
- Donor milk is pasteurized to prevent infections in the infant. Pasteurization removes most of the antiinfective properties of milk, reduces lipase activity, the content of live cells and microbes, and CMV virus.
- Infection rates and NEC rates are much lower with MOM and pasteurized donor milk than formulas.
- Donor milk in the United States is low in Docosahexaenoic Acid (DHA) content.
- Donor milk is an appropriate choice for Extremely Low Birth Weight (ELBW)/Very Low Birth Weight (VLBW) preterm infants whose mother's milk is unavailable.
- Donor milk has >75% improvement in feeding tolerance compared with formulas.
- Rates of NEC and related sepsis may be lowest among very preterm infants fed with an exclusive human milk diet (compared with formula fed infants).

Formulas

DISTRIBUTION OF NUTRIENTS IN INFANT FORMULAS

- Formulas for term infants contain 20 kcal/ounce (oz) and are adequate to meet the needs of term infants with an intact GI tract and "normal" fluid requirements
- Preterm formulas are available in 20, 24, and 30 kcal/oz preparations, with similar osmolalities and renal solute loads
  - Newer generations of high-protein preterm formulas containing ~2.8 grams/100 mL may be indicated for VLBW preterm infants, who are not growing well (in

length and/or head circumference), or who are fluid/volume restricted
- Preterm formulas contain whey:casein ratios of 60:40 and have higher protein contents than those of term formulas (2.4 grams/100 mL in preterm formula versus 2 grams/100 mL in term formula or human milk)
- Preterm formulas
  - Contain less lactose as a carbohydrate source
  - Substitute glucose polymers or corn syrup solids for lactose to provide ~42%–44% of the calories derived from this carbohydrate
- Preterm formulas provide some fat in the form of Medium Chain Triglycerides (MCTs) (ease of digestion and absorption)
- Calcium (Ca) and phosphorus (P) content is increased, with a Ca:P ratio of 1.8–2:1, provides for improved bone mineralization
- Other minerals and vitamins also present in higher concentrations in preterm formulas
  - Mineral and vitamin content of preterm infant formulas (Table 25.2)

BENEFITS AND RISKS OF FORMULAS THAT CONTAIN NONSTANDARD SOY PROTEINS

- Soy protein formulas reserved for term infants:
  - With galactosemia, have severe lactose intolerance, have hereditary lactase deficiency
  - Who are of vegan families (counseled on need for a balanced protein diet in their infant)
  - With an IgE-mediated cow's milk protein allergy
- Soy-derived formulas are not used for preterm infants due to poor quality of protein, lower digestibility and bioavailability, and lower calcium and zinc accretion rates
- There are concerns for all infants about the concentrations of phytates, aluminum, and phytoestrogens that are in soy formulas
- For term infants: formulas derived from protein hydrolysates are reserved for infants who are allergic to cow's milk proteins and are not breastfed, or do not tolerate soy-derived formulas
- Soy formulas have no role in the prevention of atopic disease
- Extensively hydrolyzed formulas may delay or prevent atopic dermatitis in infants at high risk and who are not breastfed
- Families with a strong history of cow milk protein allergy
  - Encouraged to breastfeed
  - Appropriate counseling of mother in avoiding cow milk products in her diet

MEDICAL INDICATIONS FOR NONSTANDARD INFANT FORMULAS

- Elemental and extensively hydrolyzed formulas
  - Used in infants with malabsorption, severe liver disease, Short Bowel Syndrome (SBS), dysmotility syndromes (e.g., in gastroschisis), or severe protein allergy
  - The protein source: derived from free AAs
  - Fat source: derived from MCT oil (0%–55%)
  - Many are lactose free
- Elemental or hydrolyzed formulas: may be useful after a severe episode of infectious gastroenteritis with mucosal injury and resulting protein or lactose intolerance
- Preterm infants fed partially hydrolyzed whey preterm infant formula
  - No benefit in feeding tolerance, enteral intake, or growth
- Modified formulas are available for infants with special nutritional needs due to inherited enzyme deficiencies
  - Lactose intolerance from congenital lactase deficiency, galactosemia, and PKU
  - These formulas require multivitamin and mineral supplements (if used for preterm infants)
- Some preterm infants have apparent cow milk protein "allergy" (feeding intolerance, intestinal dilation, hematochezia without other signs of illness or NEC)
  - These infants may benefit from reduction in maternal cow milk protein diet or use of hydrolyzed cow milk protein fortifiers (mother is breastfeeding) or use of hydrolyzed cow milk protein formulas

Table 25.2 Mineral and Vitamin Contents of Preterm Infant Formulas per 100 kcal (Based on Similac Special Care Premature and Enfamil Premature)

Minerals (per 100 kcal)		Vitamins: Fat Soluble (per 100 kcal)		Vitamins: Water Soluble	
Calcium	165–180 mg	Vitamin A (IU)	1250–1350	Vitamin B_6 (mcg)	150–250
Phosphorus	90–100 mg	Vitamin D (IU)	150–300	Vitamin B_{12} (mcg)	0.25–0.55
Sodium	43–70 mg	Vitamin E (IU)	4–6.3	Vitamin C (mg)	20–37
Potassium	98–129 mg	Vitamin K (mcg)	9–12	Biotin (mcg)	4–37
Chloride	81–106 mg			Niacin (mcg)	4000–5000
Magnesium	9–12 mcg			Pantothenic acid (mg)	1.2–1.9
Manganese	6–12 mcg			B_2 riboflavin (mcg)	300–620
Zinc	1.5 mg			B_1 thiamine (mcg)	200–250
Copper	120–250 mcg			Folic acid (mcg)	37–40
Iodine	6–25 mcg				
Iron	1.8 mg				
Selenium	2–2.8 mcg				

STANDARD INFANT FORMULA MODIFICATIONS FOR USE IN PRETERM INFANTS

- Preterm formulas are developed to meet the unique nutritional needs of preterm infants (though most were not specifically tested in ELBW infants)
- Indications for use of high protein preterm formulas include
  - Birth weight <1500 g
  - Infants who are fluid/volume restricted (congenital heart disease and Bronchopulmonary Dysplasia [BPD])
  - Promotion of wound healing (postoperative)
  - Cumulative deficit of protein intake (early Total Parenteral Nutrition (TPN) weaning before full enteral feeding established)
  - Inadequate growth in length and/or head circumference (treated with liquid protein supplements)
  - Unfortified human milk feeds (e.g., direct breastfeeding or use of donor milk)
- Lactose usually is reduced due to concern for early lactase deficiency
- The remaining carbohydrate is provided by glucose polymers (easily digested) and provide a lower osmolality (~300 mOsm/L)
- Fat blends include 20% to 50% MCTs to compensate for lower bile salts and lipases
- Protein concentrations are increased to 2.7–3.3 g/100 kcal and are whey predominant
- Calcium and phosphorus vitamins and other minerals are increased
- Carnitine commonly added to aid in lipid oxidation
- Increasing caloric density or goal volumes addresses most growth concerns, but it may also be necessary to provide additional individual nutrients (protein, minerals, zinc, sodium)

Suggested Readings

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Questions

1. Which of the following is a TRUE statement regarding human milk being the ideal enteral diet for human neonates?
   a. It provides sufficient energy, protein, fat, carbohydrate, micronutrients, and water for normal metabolism, growth, and development in term infants.
   b. It does not require supplements of protein and certain minerals.
   c. It is enriched in nutrients when it comes from a milk bank as mature donor milk.
   d. It is associated with delayed neurodevelopmental outcomes compared with term formulas.

2. Which of the following about mother's own milk produced at home or in the NICU and stored is TRUE?
   a. Varying degrees of nutrient loss may occur with long-term storage, particularly in frozen conditions.
   b. Vitamin C loss does not occur, even during the process of feeding freshly expressed human milk by bottle.
   c. For multiple human milk components, significant degradation generally occurs with even very short-term storage and multiple freeze-thaw cycles.
   d. Donated human breast milk does not contain pathogenic microorganisms that could be transferred to the infants who consume it.

3. Which of the following statements about heat treatment (pasteurization) of human milk are FALSE?
   a. Heat treatment (pasteurization) of human milk may reduce the concentration and functional capacity of many bioactive components.
   b. Holder pasteurization does not adversely affect the protein content of donor milk (average value of about −4%).
   c. Total lipid generally is increased (as much as by 60%), but free fatty acids are reduced, which might increase their nutritive potential.
   d. No significant reductions in lactose have been noted, both as free molecules and as part of biologically active compounds such as oligosaccharides.

26 Parenteral Nutrition

WILLIAM W. HAY JR and KENDRA HENDRICKSON

Indications of Parenteral Nutrition

- The more preterm and less developed the infant, the less body stores (protein, fat, glycogen) are available to provide nutrients for metabolic needs.
- Intravenous feeding is always indicated when normal metabolic needs are not met by normal enteral feeding.
- The metabolic and nutrient requirements of the newborn are equal to or greater than those of the fetus of the same gestational age.
- Intravenous feeding is essential, but it should not be a sole substitute for enteral nutrition unless the infant has absolutely no capacity for enteral feedings.
  - These conditions are rare (usually short-term) and include:
    - Intestinal obstructions (atresia or totally obstructing bands), malformations (gastroschisis, severe omphalocele), or early gut infarctions and perforations.
      - These infants may be able to feed enterally in small amounts.
- Parenteral nutrition is important to ensure full protein and energy supplies to maintain neuronal development.
  - In the first week of life: protein and energy intakes are associated with improved developmental outcomes in preterm infants at 18 months of age.
  - In the first three weeks of life: protein and energy intakes are associated with greater adult lean body mass and higher resting energy expenditure.

Composition and Energy Content

NUTRITIONAL COMPOSITION OF PARENTERAL SOLUTIONS

- Parenteral nutrition (PN) is a combination of nutrients: dextrose, crystalline amino acids, fat emulsion, sterile water, electrolytes, vitamins, and minerals administered intravenously.
  - In neonates, fat emulsion is administered in a separate syringe in a two-in-one formulation.
- PN calories are increased as tolerated to a goal caloric intake of 90–115 kcal/kg/day as a combination of macronutrient components.
  - Dextrose solutions are usually 5% or 10% dextrose weight/volume in solution, with other concentrations added as needed with average glucose infusion rate of 5–10 mg/kg/min.
  - Crystalline amino acids (AAs) are provided in stock solutions ranging from 3% to 20%, (i.e., a 3% amino acid solution has 3 grams of total amino acids in 100 mL of solution).
    - Average daily AA 3–4 g/kg/day.
    - Pediatric formulations contain higher concentrations of branched-chain AAs (leucine, isoleucine, valine) and decreased amounts of methionine and phenylalanine.
    - Neonates have additional AAs that are considered conditionally essential (tyrosine, glutamine, arginine, cysteine, glycine, proline).
    - Cysteine added at the time of compounding due to stability issues.
  - Intravenous fat emulsion is used to provide energy and essential fatty acids for total parenteral nutrition (TPN) formulations.
    - Lipid emulsions should be 20% solutions (20 g/100 mL) to minimize phospholipid content and improve clearance.
    - In the United States 100% soybean oil or a combination product using several oil sources is available for use in TPN, with a fish oil product being recently FDA approved.
- Electrolytes are added based on fluid status and laboratory values as salts that also provide acetate, chloride, and phosphorus.
  - Calcium is provided in the form of calcium gluconate.
- Cysteine, carnitine, and some medications may also be added.
- PN can contain up to 40 different nutrient components that impact stability and compatibility.

IMPORTANCE OF PROTEIN AND NONPROTEIN NUTRIENTS TO ACHIEVE OPTIMAL ENERGY

- Even at standard infusion rates, protein accretion rates with current TPN solutions with lower concentrations of certain essential amino acids (e.g., leucine, isoleucine, threonine, lysine) limit protein accretion.
- The amino acid composition of current neonatal parenteral amino acid solutions is based on providing plasma concentrations similar to those of term, fully breastfed infants.
  - Preterm infants require considerably greater amounts of amino acids to achieve their higher gestational age-appropriate protein accretion rates.
- At lower, nonprotein calorie intakes (<60–70 kcal/kg/day), increasing energy intakes promote net protein accretion rates.

- Energy intake >60–70 kcal/kg/day produces fat gain but not protein accretion.
- The relationship between energy intake and protein accretion is curvilinear.
  - In contrast, protein accretion at any caloric (energy) intake is directly dependent on protein intake (either as intact protein in enteral diets or as amino acids in TPN solutions).

CALCULATE THE CALORIC CONTENT OF PARENTERAL NUTRITION SOLUTIONS

- Protein concentrations in parenteral nutrition are ordered as g/kg/day.
  - Amino acids produce about 4 kcal/g of energy if totally oxidized.
  - Therefore the amount of amino acids g/kg/day received can be multiplied by 4 to determine kcal/kg/day.
  - Glucose produces about 4 kcal/g of energy if totally oxidized; therefore the total: g/kg/day × 4 will provide the calories/kg/day.
- Lipids emulsions are usually infused separately and ordered as g/kg/day.
  - Lipids produce about 10 kcal/g of energy if totally oxidized.
    - The ordered amount of g/kg/day × 10 provides the kcal/kg/day from fat.
- A standard parenteral infusion of 3 g/kg/day amino acids and 10% dextrose at 100 mL/kg/day would provide:
  - Total energy intake of 82 kcal/kg/day
    - 52 kcal/kg/day
      - 3 grams amino acids × 4 kcal/gram = 12 kcal
      - 10 grams of dextrose × 4 kcal/gram = 40 kcal
    - 30 kcal/kg/day: 3 grams/kg/day of lipid

Complications of Parenteral Nutrition

RELATIONSHIP BETWEEN THE CALCIUM AND PHOSPHORUS CONTENT OF PN SOLUTIONS AND OSTEOPENIA

- Intravenous calcium and phosphorus supplementation should be started in high-risk infants soon after birth.
- The usual dosing range of parenteral calcium in the form of calcium gluconate is 0.6–2.5 mmol/kg/day (25–100 mg/kg/day of elemental calcium), and the dose is titrated based on either the total serum calcium level or ionized calcium level.
- Phosphorus is given as sodium phosphate with a dosing range of 0.75 to 2.5 mmol/kg/day (25–80 mg/kg/day of phosphate).
- The Ca/P ratio should preferentially be kept at 11.3-1:1 on a molar basis and 1.3 to 1.7/1 on a mg/mg basis to maximize accretion of both minerals.
- The solubility of calcium and phosphorus in TPN solutions depends on temperature (better at higher temperatures), amino acid concentrations (better with higher concentration), glucose concentration, pH, type of calcium salt, sequence of addition of calcium and phosphorus to the solution, the calcium and phosphorus ratio, and the presence of lipid.
- Adding cysteine to enhance protein balance lowers the pH and improves calcium and phosphorus solubility.
- Caution should be taken if calcium is infused into a peripheral IV catheter, as severe tissue necrosis and sloughing can occur with extravasations and even minor leaks.
  - Some intensive care units avoid peripheral calcium administration entirely except in emergencies, such as hypocalcemic seizures or shock.
- Magnesium supplementation ranges from 0.12–0.4 mmol/kg/day (3–10 mg/kg/day).

ASSOCIATION OF CHOLESTASIS WITH TPN NUTRITION

- Cholestasis or parenteral nutrition associated liver disease (PNALD) more common in:
  - Extremely preterm infants
  - Infant with short gut syndromes (receive parenteral nutrition exclusively and for prolonged periods)
- PNALD is first noticed by increased direct (conjugated) bilirubin concentrations, which should be measured at least weekly.
- PNALD is reduced by any enteral nutrition.
- PNALD is markedly reduced in frequency with use of newer lipid emulsions that contain less soybean oil and can be reversed with lipid emulsions that contain fish oil or a combination of omega-3 rich oils.
  - These emulsions also have antiinflammatory DHA and vitamin E.
  - Phytosterols that are high in soybean oils have been shown independently to cause or worsen liver inflammation and cholestatic disease.

CAUSES AND CLINICAL MANIFESTATION OF CATHETER COMPLICATIONS OF PARENTERAL NUTRITION

- Peripheral IV lines: can be used for parenteral nutrition, although usually are limited in both dextrose (12.5%) and amino acid concentrations (3%) to prevent local skin and subcutaneous skin inflammation and necrosis with common extravasations.
  - Adding heparin to these catheters limits clotting and prolongs catheter lifetime.
- Umbilical vein catheters are associated with air embolism during placement (rare), sepsis (if kept in >5–7 days), and hemorrhage (can dislodge).
- Percutaneously inserted central catheters (PICC) are commonly used for long-term central venous access.
  - Major risk factors involve thrombosis and erosion of the catheter tips extravascularly, producing complications of pleural effusion with lung collapse and pericardial effusions with cardiac tamponade.
- Any prolonged IV line (>5–7 days), more commonly with central lines, increases the risk of invasive bacterial infection and systemic sepsis.
  - Sepsis can be reduced by a common insertion and management protocol by only highly skilled and practiced caregivers with use of meticulous sterile precautions for insertion and care.
  - These lines should not be used for blood sampling or other drug infusions except during major life-threatening crises.

CAUSES AND CLINICAL MANIFESTATIONS OF METABOLIC COMPLICATIONS OF PARENTERAL NUTRITION

- The principal metabolic complication of parenteral nutrition is hyperglycemia.
  - This problem has increased in recent years and has been associated with increased rates of morbidity and mortality.
  - Most preterm infants as well as term infants continue to produce glucose from their livers at about 2–3 mg/kg/min.
  - If the parenteral dextrose infusion rate is >7–9 mg/kg/min, then total glucose utilization capacity will be exceeded, resulting in progressively increasing glucose concentrations.
- Hyperglycemia from excessive dextrose infusion is compounded by stress with increased production of cate cholamines, glucagon, and cortisol, which suppress or limit insulin secretion and action and increase hepatic glucose production.
- Excessive dosing of IV lipids also aggravates hyperglycemia by providing competitive lipid carbon for oxidation, and by producing co-factors in the liver from beta-oxidation of fatty acids that promote the regulatory enzymes in the gluconeogenic pathway.
- Preterm infants also often develop hypertriglyceridemia (150 to 200 mg/dL).
  - Hypertriglyceridemia is increased by maturational deficiency of lipases (inversely related to gestational age), low levels of carnitine palmitoyltransferase (CPT, the protein necessary for transfer of longer chain fatty acids into the mitochondria for oxidation and energy production), and competition from glucose carbon (commonly associated hyperglycemic conditions).
  - Risks of hypertriglyceridemia can be diminished significantly by enteral feeding of milk or preterm formulas, which have natural or added carnitine as well as lipases in human milk.
- The principal metabolic complication of IV amino acid solutions is lower than needed plasma concentrations of essential and some conditionally essential amino acids.
- High amino acid concentrations generally are the result of excessive and unnecessary infusion rates (>4.0 g/kg/day) and limited urinary excretion, although caution should be used in giving high infusion rates to infants with clearly damaged liver function from hypoxic-ischemic injury.
- Blood urea nitrogen concentrations and ammonia concentrations should increase by small amounts with increased amino acid infusion rates if the amino acids are appropriately oxidized producing ammonia and the liver is functioning well to remove ammonia through the urea cycle.

POTENTIAL TOXICITIES ASSOCIATED WITH THE USE OF PARENTERAL NUTRITION

- Manganese (Mn) can produce potential neurotoxicity, as Mn is a common contaminant in PN solutions.
  - Mn supplementation stopped with any signs of hepatic dysfunction or cholestasis
  - Parenteral calcium gluconate to prevent osteopenia contributes to Mn contamination and potential toxicity
- Phytosterols and low antioxidant factors (e.g., DHA and vitamin E) can lead to cholestasis.
- There is significant aluminum contamination in albumin, blood products, certain medications, and TPN components.
  - Premature infants are at high risk of aluminum accumulation and toxicity as they often require PN for many days and have immature kidneys incapable of excreting aluminum efficiently.
  - Calcium gluconate and phosphate salts are high in aluminum content and are required by premature infants in substantial amounts to promote bone mineralization.
  - The Food and Drug Administration (FDA) has set limits for aluminum content of TPN components, but manufacturers are often unable to meet these restrictions and health care providers should make a concerted effort to use the least contaminated products.
  - A readily available substitution is using sodium phosphate in preference to potassium phosphate.

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Questions

1. Which of the following statements regarding TPN and enteral neonatal nutrition is FALSE?
   a. Normal fetal metabolic and growth rates and nutritional requirements stop with birth, precluding routine use of IV nutrition.
   b. The smaller and more preterm and less developed the infant, the less body stores (protein, fat, glycogen) are available to provide nutrients for metabolic needs.
   c. The metabolic and thus nutrient requirements of the newborn are equal to or greater than those of the fetus of the same gestational age.
   d. First-week protein and energy intakes are associated with improved 18-month developmental outcomes in preterm infants.

2. Which of the following statements regarding TPN is FALSE?
   a. The amino acid composition of current neonatal parenteral amino acid solutions is based on providing plasma concentrations similar to those of term, fully breastfed infants, which is appropriate for preterm infants who are growing at much faster rates than term infants.
   b. A standard parenteral infusion of 3 g/kg/day amino acids, 10% dextrose, and 3 grams/kg/day lipid at 100 mL/kg/day would provide 82 kcal/kg/day, according to the following calculations: 3 grams amino acids × 4 kcal/gram = 12 kcal; 10 grams of dextrose × 4 kcal/gram = 40 kcal; 3 grams/kg/day of lipid would add 30 kcal/kg/day.
   c. Cholestasis or parenteral nutrition associated liver disease (PNALD) is more common in infants (extremely preterm infants, and those with short gut syndromes such as gastroschisis or those with severe enteral feeding intolerance) who receive parenteral nutrition exclusively and for prolonged periods (weeks, vs. days).
   d. The principal metabolic complication of parenteral nutrition is hyperglycemia.

SECTION 7

Renal/ Fluids/ Electrolytes

ERIN RADEMACHER

27 Water-Electrolyte Metabolism and Acid-Base Balance

ERIN RADEMACHER

Water Metabolism

- Total body water (TBW) is expressed as a percentage of body weight in kg. It decreases from ~95% of total weight at 16 weeks' gestation to 75% total weight at 40 weeks (Fig. 27.1).
- TBW is divided into intracellular water and extracellular water (ECW). ECW is further divided into interstitial space and intravascular space. The percentage of TBW contained in the ECW declines with gestational age (GA). At term birth, almost 50% of TBW is intracellular.
- ECW decreases after birth. Term infants typically lose ~5%–10% of birth weight over the first 4–7 days. Preterm infants can lose 15% over the first 5–10 days. Failure to lose ECW is associated with increased risk of PDA (patent ductus arteriosus), NEC (necrotizing enterocolitis), and BPD (bronchopulmonary dysplasia).
  - Before delivery, fluid shifts from intravascular to interstitial space.
  - After birth, fluid shifts back into intravascular space over the first few days resulting in release of ANP (atrial natriuretic peptide) with resulting loss of water and sodium from kidney and loss of TBW.
- Maintenance water requirement = urine volume + other losses (stool typically 5–10 mL/kg/day, emesis, drains) + insensible water loss + amount needed for tissue generation (10–15 mL/kg/d).
- The best indicators of appropriate fluid prescription are stable sodium levels and appropriate weight gain (or loss in the first week).
- See Table 27.1 for guidelines for water needs for different GA/postnatal ages.
- Insensible water losses (IWL) = water lost through skin (two-thirds total) and respiration (one-third total).
- Preterm infants have increased skin losses due to an immature epithelial layer, increased body surface area:body weight ratio, and increased skin vascularity. Administration of steroids prenatally accelerates skin maturation and can decrease skin losses.
- IWL will be increased/decreased under different conditions (Table 27.2).
- Arginine vasopressin (AVP, ADH, vasopressin) is the major effector involved in water metabolism. It is synthesized in hypothalamus and stored in posterior pituitary gland.
- A rise in plasma osmolality (sensed by osmoreceptors in hypothalamus) or a fall in intravascular volume (detected by baroreceptors in the heart) leads to release of AVP.
- Intravascular volume depletion trumps plasma osmolality if the two stimuli are in opposing directions.
- AVP acts on its receptor, vasopressin 2 receptor (V2R), which is located on the basolateral (blood side) of distal tubules and collecting duct cells in the nephron.
- Binding of AVP to V2R stimulates adenylate cyclase leading to increased levels of cAMP and eventually fusion of vesicles containing the water channel aquaporin (AQP2) to the apical membrane (urine side), which allows water to move from the urinary space into the cell.
- When AVP levels fall, the AQP2 is recycled back out of the apical membrane into vesicles.
- Two other effectors of water metabolism: thirst and angiotensin II (which stimulates thirst).
- Maximal urine concentrating ability is ~600 mOsm/kg in preterm, 800 mOsm/kg in term, and reaches adult levels of 1200 mOsm/kg by 6–12 months.
- Preterm infants are unable to generate/maintain the countercurrent mechanism critical to concentrating urine due to immature tubules and short loops of Henle that do not reach the inner medulla.
- Full-term infants can maximally dilute urine (50 mOsm/kg). Preterm have slightly impaired dilution ability (70 mOsm/kg).

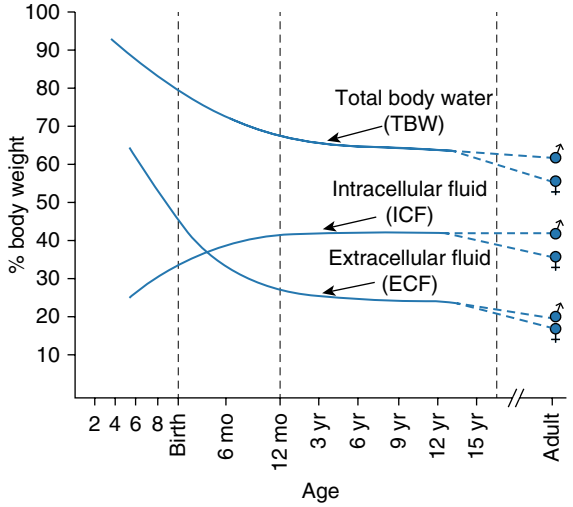

Fig. 27.1 Changes in total body water and its components with increasing age. (From Martin RJ. *Fanaroff and Martin's Neonatal-Perinatal Medicine*. 10th ed. Philadelphia: Elsevier/Saunders; 2015 [p. 614, Fig. 44.1].)

Table 27.1 Fluid Requirements by GA

BirthWeight (g)	Insensible Water Loss (mL/kg/day)	TOTAL WATER REQUIREMENTS BY AGE (ML/KG/D) Day 1–2	Day 3–7	Day 8–30
<750	100+	100–200	120–200	120–180
750–1000	60–70	80–150	100–150	120–180
1001–1500	30–65	60–100	80–150	120–180
>1500	15–30	60–80	100–150	120–180

From Martin RJ. *Fanaroff and Martin's Neonatal-Perinatal Medicine.* 10th ed. Philadelphia: Elsevier/Saunders; 2015 [p. 615, Table 44.1].

Table 27.2 Factors That Affect Insensible Fluid Loss

Factors That Increase Losses[a]	% Increase	Factors That Decrease Losses[a]	% Decrease
Prematurity	100–300 depending on how low the GA is	Incubator	25–50
Radiant warmer	50–100	Humidified air	15–30
Phototherapy	25–50 depending on equipment[b]	Sedation	5–25
Increased activity	5–25	Decreased activity	5–25
Hyperventilation	20–30	Increased ambient humidity	25–50
Hyperthermia	>10% per °C	Plastic blanket, chamber, or heat shield[c]	30–70
Loss of skin integrity	Varies with extent of lesion		

[a]Factors are additive in each column.
[b]Effect of fiberoptic blankets/pads not known. LED phototherapy does not change IWL.
[c]Plexiglass heat shield is not effective under radiant warmer.

Disorders of Water Metabolism

SYNDROME OF INAPPROPRIATE ANTIDIURETIC HORMONE (SIADH)

Basic Information

- ADH release triggered by nonphysiologic mechanism: perinatal asphyxia, pneumothorax, intraventricular hemorrhage, drugs (morphine, barbiturates, carbamazepine).

Clinical Presentation

- Hyponatremia with mild/moderate expansion of ECV.

Diagnosis/Evaluation

- Urine osmolality > serum osmolality.
- Urine sodium >20 mEq/L.
- Normal thyroid, kidney, adrenal function.

Treatment

- Fluid restriction is of primary importance.
- Remove the stimulus to ADH release.
- Lasix 1–2 mg/kg/day + NaCl if first two measures not successful.

CONGENITAL NEPHROGENIC DIABETES INSIPIDUS (CNDI)

Basic Information

- X-linked: mutation of V2R renders receptor unable to bind AVP; 90% of cases.
- Autosomal (usually recessive): mutation of AQP2.

Clinical Presentation

- Polyuria, polydipsia, recurrent dehydration episodes, fevers, constipation, failure to thrive (FTT).

Diagnosis/Evaluation

- Hypernatremia.
- Urine Osm < serum Osm.
- No response to DDAVP (desmopressin).
- Genetic testing available.

Treatment

- Adequate water intake to normalize sodium (Na): may require nasogastric or gastrostomy tube for overnight fluid.
- Decrease solute load: low Na diet (low protein also when growth completed).
- Thiazides: induction of intravascular depletion leads to increased reabsorption Na/water in proximal nephron.
- Amiloride may augment thiazide effect and prevent hypokalemia.
- Nonsteroidal antiinflammatory drugs (NSAIDs).

SECONDARY NEPHROGENIC DIABETES INSIPIDUS

Basic Information

- Kidney response to AVP reduced but no mutation in V2R or AQP2.
- Seen with: hypokalemia, hypercalcemia, post urinary obstruction, CKD.

SODIUM METABOLISM

- Positive Na balance is required for growth.
- After first 24–48 hours, Na requirement generally 1–2 mEq/kg/d for days of life 3–7 then increases after first week to 2–3 mEq/kg/d.
- Premature infants (GA <28 weeks) may require much higher Na intake (4–10 mEq/kg/d) due to immature tubules leading to renal Na wasting.
- Fractional excretion of sodium (FENa) in term infant <1% while FENa of preterm (<30 week GA) may be >5%.
- Some trials suggest Na supplementation associated with better long-term neurodevelopment in preterm infants.
- Na reabsorbed from tubular lumen via transporters or channels in the apical membrane (urine side) throughout the nephron and then pumped out of the cell via the Na-K ATPase on the basolateral membrane (blood side). Na-K ATPase critical to this process. Activity is lower in neonates than adults (Fig. 27.2).
- In neonates, the proximal tubule reabsorbs ~50%–60% (similar to adult capacity) of the filtered Na via Na/H exchanger or Na-X cotransporter (X = glucose, amino acid, or phosphate). Na/H exchanger activity is lower in neonates than adults.
- Thick ascending limb of loop of Henle (LoH) reabsorbs Na via Na-K-2Cl channel (furosemide sensitive).
- Distal convoluted tubule (DCT) reabsorbs Na via Na-Cl cotransporter (thiazide sensitive).
- Cortical collecting duct (CCD) reabsorbs Na via ENaC (epithelial Na channel) under control of aldosterone.
- Maturation of the nephron during fetal development and after birth allows increased reabsorption of Na from the distal LoH and distal segments.
  - Na-K ATPase and the proximal tubule Na transporters increased by thyroid hormone and glucocorticoid.
  - LoH's Na-K-2Cl channel and DCT's Na-Cl increased by glucocorticoids.

DISORDERS OF SODIUM METABOLISM

Hyponatremia

- Usually defined as Na <130 mEq/L.
- Occurs in 30% of VLBW in 1st week, 25%–65% develop later.
- Three mechanisms lead to hyponatremia (Fig. 27.3):
  - Inability to excrete water load most common cause. This may be due to a decrease in effective blood volume providing a stimulus for ADH release. May also be due to decreased fluid delivery to distal nephron either from decreased glomerular filtration rate (GFR) in acute kidney injury (AKI) or from increased proximal Na and water reabsorption in volume-depletion states.
  - Excessive Na loss.
    - May be physiologic (i.e., high FENa in preterm).
    - Pathologic causes: see sections on congenital adrenal hyperplasia, pseudohypoaldosteronism, and Bartter syndrome.
  - Inadequate intake.
- High maternal water intake during labor or oxytocin use may cause hyponatremia in the neonate.
- Correction estimated by: Na^+ deficit (mEq) = 0.7 × body weight (kg) × ($Na_{desired} - Na_{current}$).
  - Usually replaced as 2/3 in first 24 hours, remainder over next 24 hours.
  - If Na <120 mEq/L, consider using 3% saline (513 mEq Na/L) to correct serum Na to 120 mEq/L over 4–6 hours, then replace remainder over 48 hours.

HYPERNATREMIA

- Usually defined as Na >150 mEq/L.
- Occurs in 40% of preterm infants < 29 weeks.
- Mechanisms (Fig. 27.4).
  - Increased water loss most common etiology. Often due to underestimated IWL. Inadequate breastfeeding and diarrhea other common causes.
  - Excessive Na administration from medications or improperly prepared formula or TPN.
- Therapy.
  - H_2O deficit (L) = 0.7 × weight (kg) × ([Na current/Na desired]−1).
  - Correction should be slow (0.5 mEq/hr) in cases of chronic or unknown duration to avoid cerebral edema.
  - With Na >175 mEq/L, may need to add 3% saline to IVF to make a fluid with Na 10–15 mEq/L less than the current serum Na.

POTASSIUM METABOLISM

- Transported actively across placenta from mother to fetus.
- Positive balance required for growth. Typically 1–2 mEq/kg/d after the first 48 hours of life; start supplementation after urine output well established.
- Infants have higher plasma levels than adults (average 5 versus 4 mEq/L).
- Potassium (K) shifts into/out of cells under certain conditions.
  - Into cell: insulin, β2 agonists, metabolic alkalosis.
  - Out of cell: α-adrenergic agonists, metabolic acidosis, hyperosmolality.
- Metabolic acidosis caused by mineral acid (HCl or $NH4^+Cl$) causes much larger shifts than organic anion acidosis (lactic acid, acetoacetic and β-hydroxybutyrate acids).
- Excretion mainly via kidneys; GI tract provides lesser mechanism.
- K freely filtered at glomerulus but then reabsorbed along the tubule.
- Renal excretion is by secretion in the distal nephron, mainly cortical collecting duct (Fig. 27.5). K enters cells via Na-K ATPase then exits to urine space via K channels.
- Secretion is affected by:
  - Rate of distal Na delivery and the transepithelial voltage:
    - When Na is avidly reabsorbed in proximal nephron due to intravascular volume depletion, less Na reaches the distal tubule. This results in deceased Na reabsorption via ENaC, which diminishes the electrochemical gradient that would favor K secretion into urine.
  - Tubular flow rate: high flow rate stimulates K secretion in a mature kidney, but neonates lack these maxi-K channels.

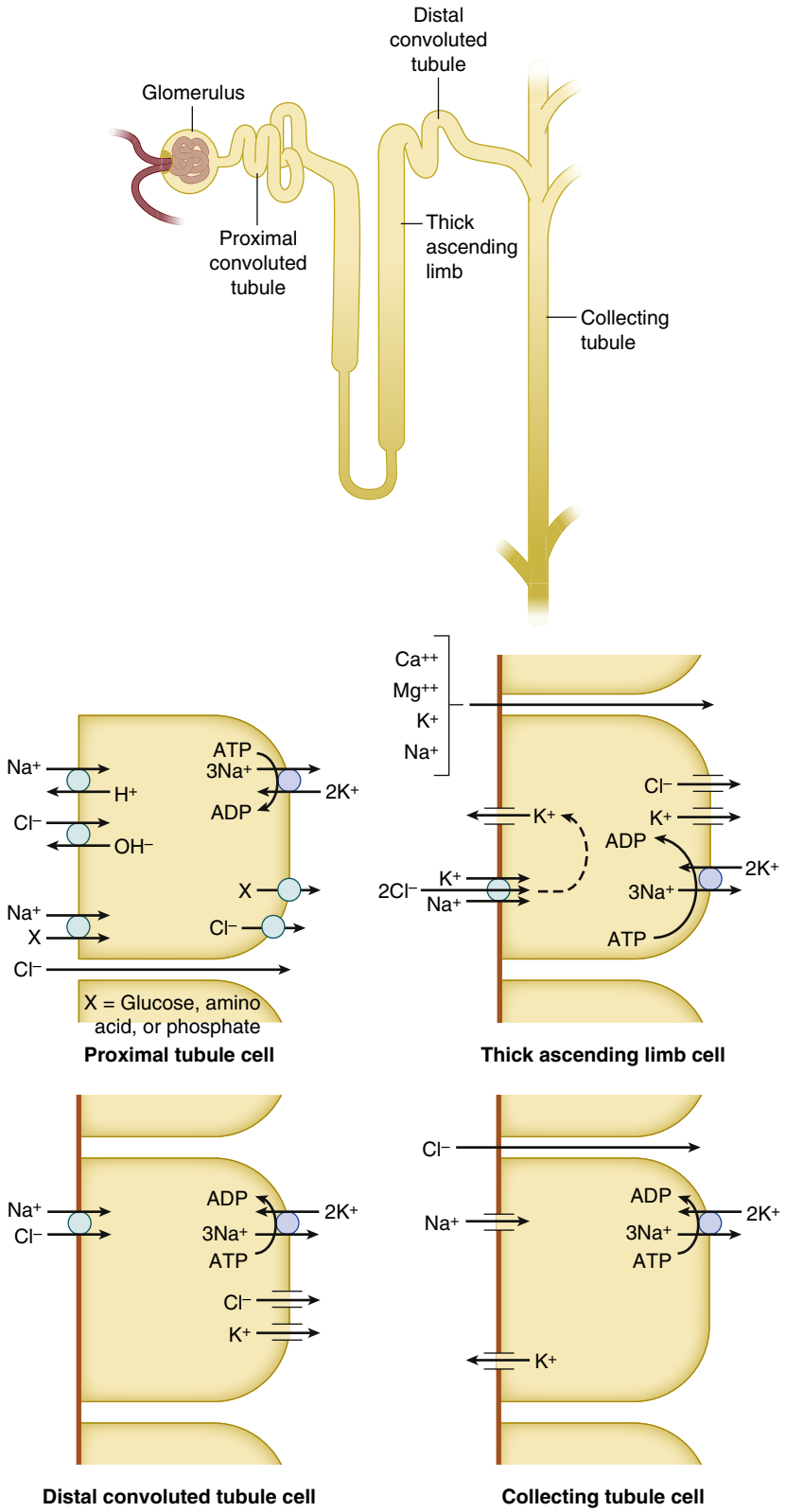

Fig. 27.2 Na transport along the tubule. (From Polin R. *Fetal and Neonatal Physiology*. 5th ed. Philadelphia: Elsevier; 2016 [p. 1004, Fig. 104.3].)

- Plasma K level: higher plasma levels allow steeper gradient favoring entry from blood into distal tubule cells and subsequently secretion into lumen.
- Aldosterone stimulates epithelial sodium channels (ENaC) and Na-K ATPase to reabsorb Na thus making lumen more negative, which favors K secretion from cell. Neonates are relatively insensitive to aldosterone.
- Acid-base balance.
  - Alkalosis stimulates K secretion via two mechanisms:

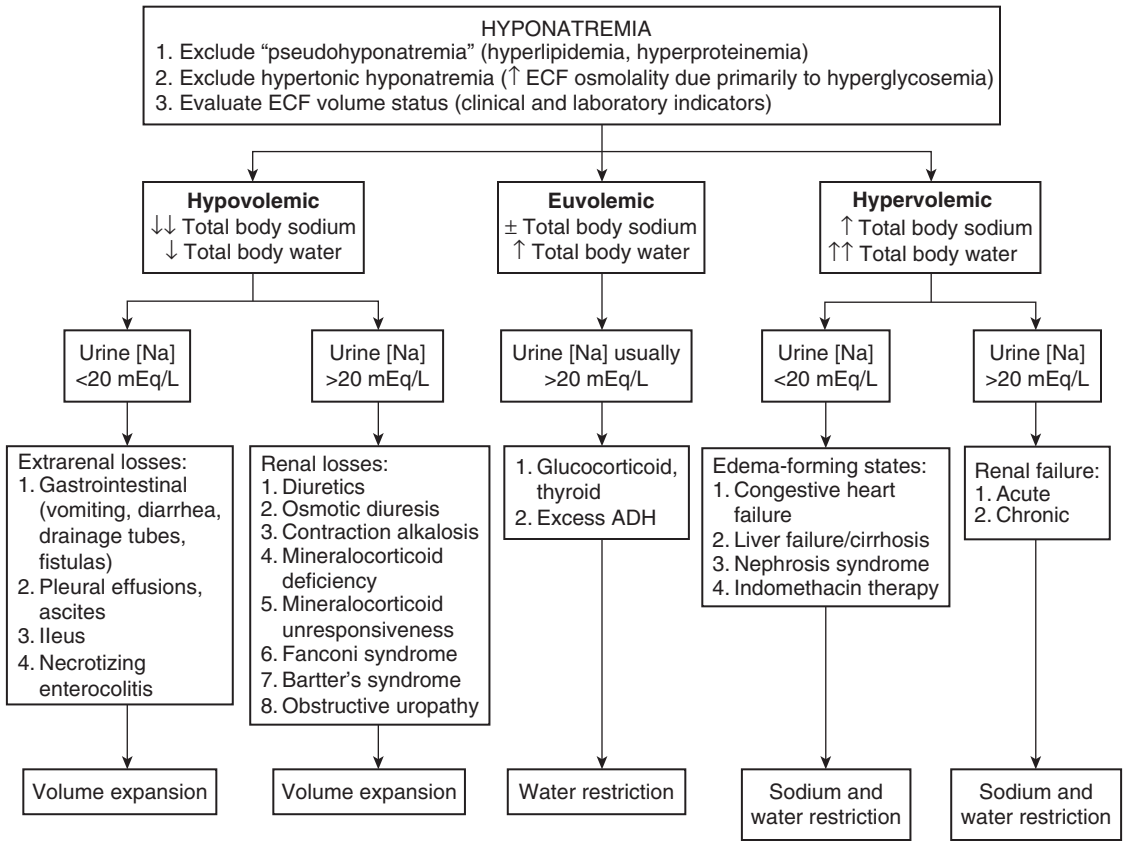

Fig. 27.3 Algorithm for evaluation and treatment of neonatal hyponatremia. *ECF,* Extracellular fluid. (From Gleason C. *Avery's Diseases of the Newborn.* 9th ed. Philadelphia: Elsevier; 2012 [p. 376, Fig. 31.5].)

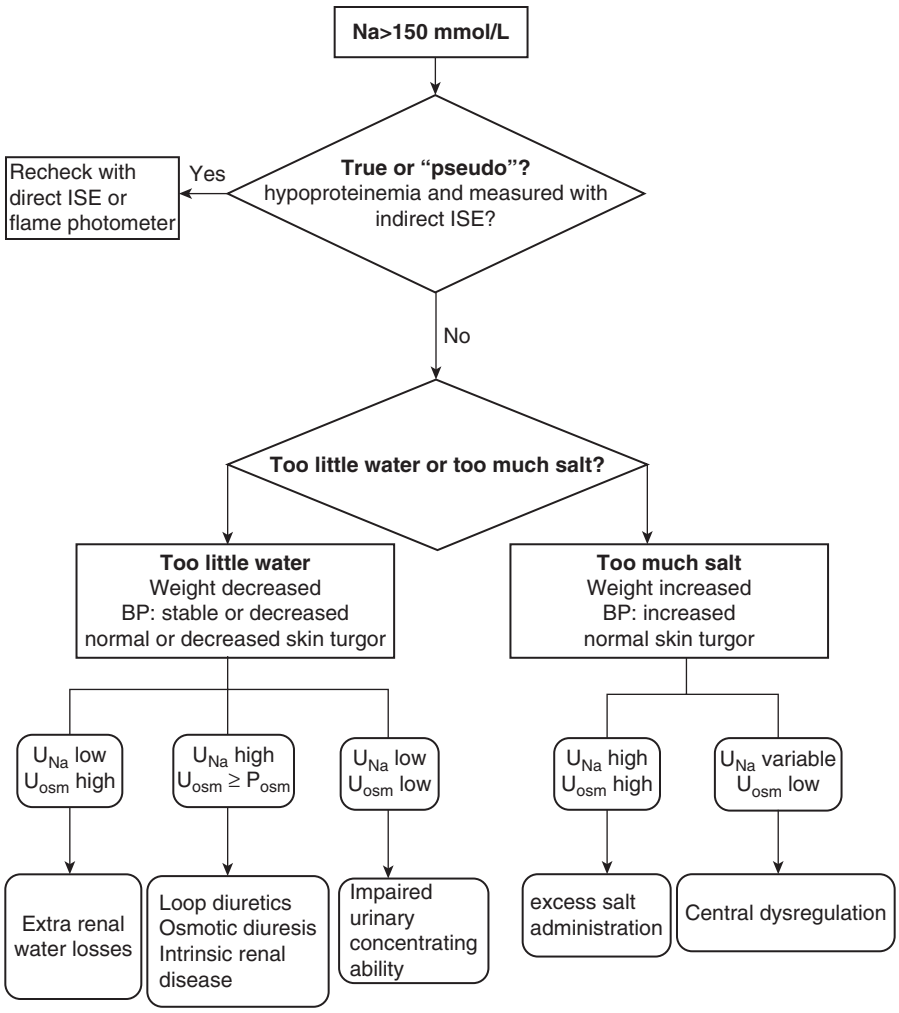

Fig. 27.4 Algorithm to determine causes of hypernatremia. *BP,* Blood pressure; *ISE,* Ion selective electrode; P_{Osm}, Plasma osmolality; U_{Na}, Urine sodium; U_{Osm}, Urine osmolality. (From Bockenhauer D, Zieg J. Electrolyte disorders. *Clin. Perinatology*. 2014;41:575–590, Fig. 27.2.)

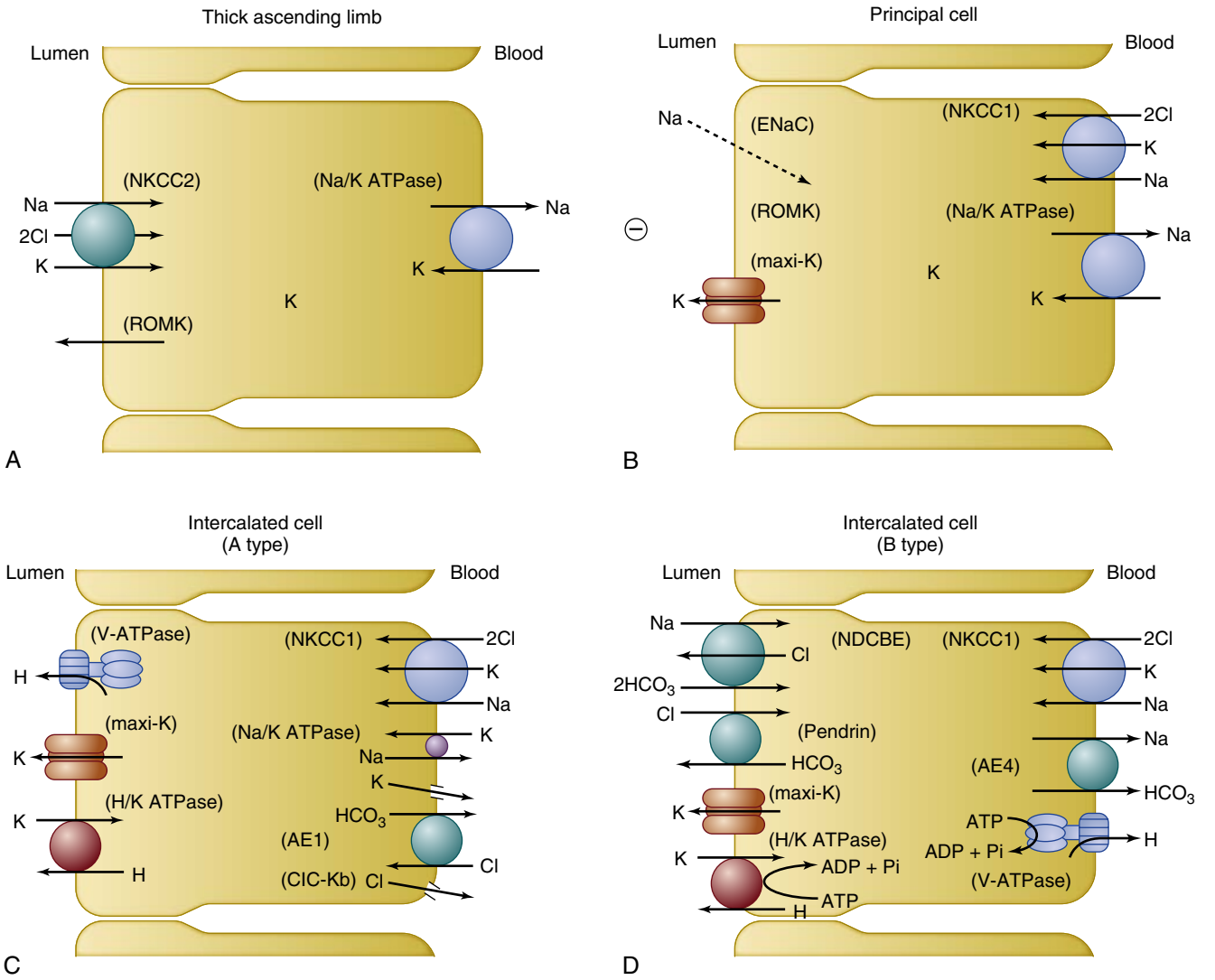

Fig. 27.5 (A–D) Potassium handling along the nephron. (From Polin R. *Fetal and Neonatal Physiology.* 5th ed. Philadelphia: Elsevier; 2016 [p. 1016, Fig. 105.4].)

- Stimulation of Na-K ATPase and therefore K uptake into cell.
- Increases length of time K channels open on apical membrane to allow exit into urine.
  - Acute metabolic acidosis inhibits K secretion by inhibiting apical K channel (ROMK).
  - Chronic metabolic acidosis has variable effects on secretion.
- Hypokalemia: <3.5 mEq/L.
  - Seen with diuretics, diarrhea, renal dysfunction, NG drainage, alkalosis.
  - EKG changes: flattened T waves, prolonged QT interval, U waves.
- Hyperkalemia: K >6.5 mEq/L.
  - Seen with renal dysfunction, metabolic acidosis, cell breakdown.
  - EKG changes: peaked T waves, wide QRS, bradycardia, tachycardia, supraventricular tachycardia, ventricular tachycardia, ventricular fibrillation.
  - Therapy centers on shifting K into cells and stabilizing the myocardium as acute temporizing measures and elimination from body (see Table 27.3).

ACID-BASE BALANCE

- Normal pH ranges between 7.35–7.45.
- Growth and development depend on acid-base balance.
- Mechanisms to keep pH in normal range include buffering systems that act acutely and compensatory systems to maintain balance chronically.
- Extracellular buffering system: carbonic acid-bicarbonate system most important. Carbonic anhydrase (CA) catalyzes the following reaction:

$$H^+ + HCO_3^- \leftrightarrow H_2CO_3 \leftrightarrow H_2O + CO_2$$

- Intracellular buffering systems:
  - Hemoglobin, intracellular proteins, intracellular phosphate.
  - Requires several hours to reach maximum capacity.
  - Much of buffering is done in bones: chronic acidosis leads to increased bone resorption.

Table 27.3 Therapy of Hyperkalemia

Medication	Dosage	Onset	Length of Effects	Mechanism of Action	Comments and Cautions
Calcium gluconate	100 mg/kg IV over 2–5 minutes	Immediate	30 min	Protects the myocardium from toxic effects of potassium; no effect on total body potassium	Can worsen digitalis toxicity
Sodium bicarbonate	1–2 mEq/kg	Immediate	Variable	Shifts potassium intracellularly; no effect on total body potassium	Maximum infusion: mEq/min in emergency situations
Tromethamine	3–5 mL/kg	Immediate	Variable	Shifts potassium intracellularly; no effect on total body potassium	—
Insulin plus dextrose	Insulin 0.1–0.15 U/kg IV plus dextrose 0.5 g/kg IV	15–30 min	2–3 h	Shifts potassium intracellularly; no effect on total body potassium	Monitor for hypoglycemia
Albuterol	0.15 mg/kg every 20 min for three doses then 0.15–0.3 mg/kg	15–30 min	2–3 h	Shifts potassium intracellularly; no effect on total body potassium	Minimum dose, 2.5 mg
Furosemide	PO: 1–4 mg/kg/dose 1–2 times/day IV: 1–2 mg/kg/dose given every 12–24 hours	15 min to 1 h	4 h	Increases renal excretion of potassium	—
Kayexalate	1 g/kg PO/PR every 6 hours	1–2 h (rectal route faster)	4–6 h	Removes potassium from the gut in exchange for sodium	Use with extreme caution in neonates, especially preterm; contains sorbitol; may be associated with bowel necrosis and sodium retention

From Gleason CA. *Avery's Diseases of the Newborn.* 9th ed. Philadelphia: Elsevier; 2012 [p. 379, Table 31.4].

- Respiratory compensatory mechanism:
  - Immediate regulator of homeostasis by maintaining normal $PaCO_2$ (arterial partial pressure of carbon dioxide).
  - Chemoreceptors (central more than peripheral) activated by change in pH or $PaCO_2$.
  - Develops within minutes for respiratory acidosis but takes several hours to develop for metabolic acidosis.
  - Compensation for metabolic process is incomplete: pH does not normalize.
  - Winters formula predicts the respiratory response to a primary metabolic acidosis:
    - $pCO_2 = (1.5 \times HCO_3^-) + 8 \pm 2$
- Renal compensatory mechanism:
  - Starts within hours but takes days to reach its maximal effect.
  - Secretion of H^+ is the primary mechanism of urine acidification.
  - Filtered bicarbonate is recycled back into cells as CO_2 where it is reformed into bicarbonate and transported back into blood.
- Urinary acidification process:
  - Proximal tubule:
    - Adults reabsorb 70%–90% of the filtered bicarbonate; neonates less.
    - H^+ is secreted into lumen via Na/H exchanger and H^+ ATPase where it combines with the filtered bicarbonate via action of luminal CA to form CO_2, which then diffuses back into cell. Cellular CA uses this CO_2 to regenerate bicarbonate that is transported to blood along with Na (Fig. 27.6).
  - Ammoniagenesis: results in net acid secretion via generation of NH_4^+.
    - Glutamine → NH_4^+ + α-ketoglutarate.
    - NH_4^+ secreted into lumen via Na/NH_4^+ exchanger.
    - α-ketoglutarate buffers intracellular H^+ and results in HCO_3^- that is transported to blood via Na HCO_3^- transporter.
  - The fully mature tubule's response to systemic acidosis is to:
    - Increase proximal tubule cells, uptake of glutamine.
    - Increase the number of Na/H exchangers on apical surface.
    - Increase citrate reabsorption from lumen.
    - Decrease phosphate reabsorption.
  - Thick ascending limb (TAL) and distal tubule:
    - Reabsorbs 20% of the filtered bicarbonate.
    - TAL takes up secreted NH_4^+ by proximal tubule to store in medullary interstitium where it can be secreted by collecting duct.
  - Collecting duct (Fig. 27.7):
    - Type A intercalated cells have H^+ ATPase on apical membrane to secrete H^+ into the lumen where it combines with filtered anions (PO_4^- and sulfates) to form titratable acids.
    - Metabolic acidosis leads to increased insertion of preformed H^+ ATPase.
    - Also secretes NH_3 from medullary interstitium, which combines with secreted H^+ to form NH_4^+.
    - Type B intercalated cells secrete HCO_3^- via Cl^-/HCO_3^- exchanger.

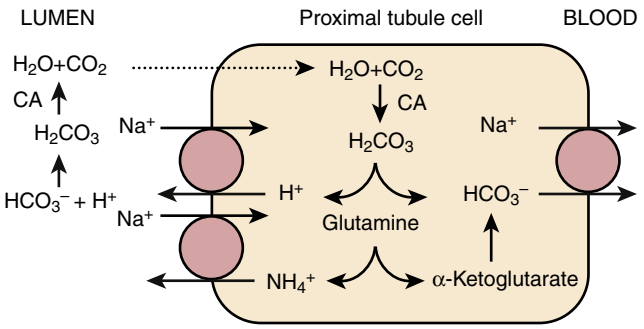

Fig. 27.6 Proximal tubule reabsorption of bicarbonate and secretion of ammonium. (From Martin RJ. *Fanaroff and Martin's Neonatal-Perinatal Medicine*. 10th ed. Philadelphia: Elsevier/Saunders; 2015 [p. 622, Fig. 44.4].)

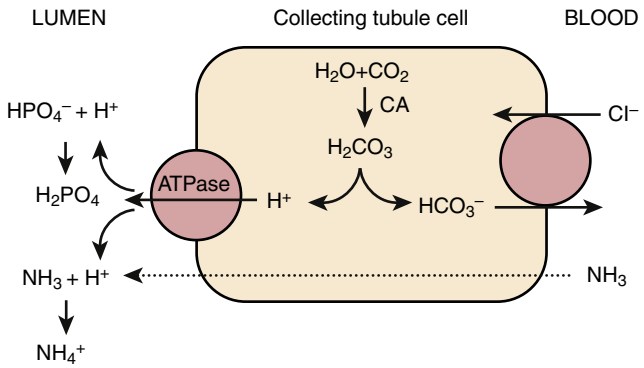

Fig. 27.7 Cortical collecting duct acid secretion. (From Martin RJ. *Fanaroff and Martin's Neonatal-Perinatal Medicine*. 10th ed. Philadelphia: Elsevier/Saunders; 2015 [p. 623, Fig. 44.5].)

- Maximal urinary acidification in mature kidney results in a urine pH of 4.5–5; preterm kidney can only reach a urine pH of 6.
- Regulation of acid-base in neonate:
  - Mild metabolic acidosis is normal shortly after birth, due to maternal respiratory alkalosis (hyperventilation of pregnancy), which stimulates a compensatory metabolic acidosis in mother.
  - Growing children produce 1–2 mEq/kg/day of nonvolatile acid.
  - Respiratory compensation: effectiveness depends on maturity of central respiratory control system and lung function. Preterm infants have decreased sensitivity to changes in CO_2.
  - Renal compensation:
    - Immature tubules result in decreased ability to reclaim the filtered bicarbonate, which contributes to the lower serum bicarbonate levels seen in neonates.
    - Urinary excretion of titratable acid and NH_4^+ also increases with GA.
    - By 1 month after delivery, regardless of GA, distal tubular H^+ secretion present.
  - Neonatal metabolic acidosis:
    - Causes: increased nonvolatile acid or decreased HCO_3 in extracellular fluid (ECF) (Box 27.1).
    - Categorized by high or normal anion gap (AG).
- AG = Na – (Cl + HCO_3^-)
  - Normal value varies with lab, usually 8–16.
  - For every decrease by 1 g/dL albumin, AG decreases by 2.5 mEq/L.
  - Increased AG may not be present in neonates with lactic acidosis.
  - Treatment.
    - Removing inciting event.
    - Alkali (Na bicarbonate) use is controversial. Requires adequate ventilation; other complications include fluid overload, hypernatremia, cerebral vasoconstriction, decreased O_2 delivery to brain due to shift in oxyhemoglobin dissociation curve, intracellular acidosis due to CO_2 diffusion into cells.
  - Full correction = base deficit (mEq/L) × body weight (kg) × 0.3. Usually give 50% of calculated dose and reassess.

Box 27.1 Causes of Metabolic Acidosis in Neonates

Increased Anion Gap

Lactic Acidosis

- Hypoxemia, shock, sepsis
- Inborn errors of carbohydrate or pyruvate metabolism
- Pyruvate dehydrogenase deficiency
- Pyruvate carboxylase deficiency
- Mitochondrial respiratory chain defects
- Renal failure

Ketoacidosis

- Glycogen storage disease (type I)
- Inborn errors of amino acid or organic acid metabolism

Normal Anion Gap

- Bicarbonate loss: acute diarrhea; drainage from small bowel, biliary, or pancreatic tube; fistula drainage; bowel augmentation cystoplasty; ureteral diversion with bowel
- Renal tubular acidosis
- Mineralocorticoid deficiency
- Administration of Cl^--containing compounds: arginine HCl, HCl, $CaCl_2$, $MgCl_2$, NH_4Cl hyperalimentation, high-protein formula
- Carbonic anhydrase inhibitors
- Dilution of extracellular fluid compartment

From Martin RJ. *Fanaroff and Martin's Neonatal-Perinatal Medicine*. 10th ed. Philadelphia: Elsevier/Saunders: 2015 [p. 624, Box 44.1]. Adapted from Brewer E. Disorders of acid-base balance. *Pediatr Clin North Am*. 1990;37:429.

  - Na or K acetate may be used to treat chronic acidosis, can be added to TPN.
- Neonatal respiratory acidosis:
  - Results from decreased excretion of CO_2 due to primary lung disease and V/Q mismatch; may require mechanical ventilation to increase excretion of CO_2.
  - Preterm infants respond with increased respiratory rate with only small increase in tidal volume; term infants respond with increased tidal volume.
  - Renal compensation is limited by immature tubules' inability to reclaim more filtered bicarbonate.

Box 27.2 Common Causes of Metabolic Alkalosis in Neonates

- Acid loss: vomiting (e.g., pyloric stenosis), nasogastric suction
- Diuretics
- Chloride deficiency: chronic chloride-losing diarrhea, Bartter syndrome, low-chloride formula, loss via skin secondary to cystic fibrosis
- Administration of alkali: bicarbonate, lactate, acetate, citrate

From Martin RJ. *Fanaroff and Martin's Neonatal-Perinatal Medicine*. 10th ed. Philadelphia: Elsevier/Saunders; 2015 [p. 625, Box 44.2].

  - Administration of alkali not indicated as increased serum HCO_3^- stimulates hypoventilation.
- Neonatal metabolic alkalosis (Box 27.2):
  - Most commonly seen in neonatal intensive care unit with prolonged diuretic use.
  - Other causes: loss of H^+ from GI tract (vomiting, NG suction) or kidneys, exogenous bicarbonate, contraction of extracellular fluid volume (ECFV) around a fixed amount of HCO_3^- (have lost more Cl^- than HCO_3^-).
  - May be maintained by continued decrease in ECV, which:
    - Leads to decrease in GFR and less filtered bicarbonate.
    - Stimulates avid proximal Na reabsorption, which leads to HCO_3^- reabsorption.
    - Stimulates renin-angiotensin system (RAS) resulting in increased aldosterone, increased distal Na reabsorption, and excretion of H^+ and K^+.
  - K depletion stimulates renal ammoniagenesis and inhibits shift of H^+ out of the cell.
  - Respiratory response: decrease rate and tidal volume.
  - Renal response: decrease in absorption of filtered HCO_3^- and distal net acid excretion.
  - Therapy: remove inciting condition, restore ECV, correct low K^+ and Cl^-.
  - Prolonged pH >7.6 may increase risk of sensorineural deafness.
- Neonatal respiratory alkalosis:
  - Results from increased excretion of CO_2. Typically secondary to fever or iatrogenic hyperventilation.
  - Rare cause: urea cycle defect–increased NH_4^+ may stimulate central respiratory center.

PSEUDOHYPOALDOSTERNONISM (PHA)

Basic Information

- Kidney is unresponsive to aldosterone.
- Autosomal dominant (AD) form = mutation in aldosterone receptor.
- Autosomal recessive (AR) form = mutation in subunit of epithelial Na channel (ENaC).

Clinical Presentation

- Polyuria, dehydration, vomiting, FTT.
- AR type is systemic, more severe, and lifelong (renal, sweat glands, salivary glands, nasal mucosa, lung, colon involved).
  - Respiratory symptoms (cough, wheezing, tachypnea) from impaired mucociliary clearance; may mimic cystic fibrosis.
  - Eczema/skin lesions.
- AD type is renal limited and symptoms usually resolve by age 2.
- Secondary or transient forms:
  - Medications:
    - Amiloride, triamterene, trimethoprim, pentamidine: block ENaC
    - Spironolactone: mineralocorticoid antagonist
    - Cyclosporine, ACE inhibitor, NSAIDs, β-blockers
  - UTIs and obstructive uropathy.
  - Rare: medullary necrosis and renal vein thrombosis.

Diagnosis/Evaluation

- Hyponatremia, hyperkalemia, metabolic acidosis with high renin and aldosterone levels.
- High urine Na.
- AR form has high sweat and salivary NaCl.
- Genetic testing available.

Treatment

- Salt supplements, may require up to 10–15 mEq/kg/day.
- K restriction, K binder (Kayexalate), alkali (Bicitra or $NaHCO_3^-$) may be required, especially for AR form.

BARTTER SYNDROME

Basic Information

- Results from autosomal recessive defects in Na, K, or Cl tubular transport proteins.
- Multiple types (Table 27.4) classified by which transport protein is defective:
  - Type 1: Na-K-2Cl channel.
  - Type II: ROMK.
  - Type III: CLC-Kb (basolateral Cl channel).
  - Type IVa: barttin, a subunit of basolateral Cl channel.
  - Type IVb: CLC-Kb and CLC-Ka.

Clinical Presentation

- Neonatal and infant forms present with FTT.
- Types I, II, and IV have severe polyhydramnios resulting in preterm delivery and continued significant polyuria.
- Type IV presents with deafness.
- Type III usually presents later in infancy.

Diagnosis/Evaluation

- All forms have hyponatremia, hypokalemia, and metabolic alkalosis.
- Type II will have an initial transient hyperkalemia before developing hypokalemia.
- Hypomagnesemia can be seen in type III and IV.
- Genetic testing available.

Treatment

- Indomethacin helpful except in type IV (for unknown reason).
- Na and water supplementation for all.
- Potassium and magnesium supplements may be required.

RENAL TUBULAR ACIDOSIS

- All forms characterized by normal AG metabolic acidosis in absence of GI loss of $NaHCO_3^-$ or cysteine Cl supplementation in TPN.
- Results from either inadequate renal acidification or renal bicarbonate wasting.

Table 27.4 Subtypes of Bartter Syndrome

Type	Synonyms	Diuretic Mimic	Sx/Signs[a]	Transporter Affected
Type I	Antenatal Bartter syndrome Hyperprostaglandin E syndrome	Furosemide	Polyuria (severe) Preterm High urine Ca Medullary nephrocalcinosis	NKCC2
Type II	Same as type I	Furosemide + amiloride	Same as type I Transient hyperkalemia followed by hypokalemia	ROMK
Type III	Classic Bartter syndrome	Thiazide + furosemide	FTT as infant Mild polyhydramnios Mild hypo Mg	ClC-Kb
Type IV	Antenatal Bartter syndrome with sensorineural deafness	Furosemide-thiazide	Polyhydramnios Preterm Polyuria Hypo Mg sensorineural deafness May proceed to end stage renal disease	CLC-Ka + ClC-Kb or barttin

[a]All forms have hyponatremia, hypokalemia, and metabolic alkalosis.

PROXIMAL RTA/TYPE II

Basic Information

- Impaired capacity to reabsorb HCO_3^- by proximal tubule.
- Reabsorption does not occur until serum HCO_3^- falls below tubular threshold.
- Ability to secrete H^+ distally is intact so can maximally acidify urine when serum HCO_3^- is below threshold.
- Isolated form is rare, usually part of generalized proximal tubular dysfunction (Fanconi syndrome).
- Genetic causes exist.
  - AR defect in Na- HCO_3^- cotransporter: associated with eye problems.
  - Rare AD form without identified gene thus far.

Clinical Presentation

- FTT, polyuria.

Diagnosis/Evaluation

- Urine pH variable:
  - If serum HCO_3^- is below the tubular threshold, urine pH will be maximally acidified (<5.5).
  - If treated to raise serum HCO_3^- above threshold, urine pH will be high.
- If present with Fanconi syndrome, will also have phosphate wasting, renal glucosuria, aminoaciduria, tubular proteinuria.

Treatment

- Administer alkali: typically requires 5–10 mEq/kg/d or more.
- If part of generalized proximal dysfunction, will need supplements of affected electrolytes.

DISTAL RTA/TYPE I

Basic Information

- Inability to properly acidify the urine.
- In children usually an isolated entity.
- Genetic causes:
  - AD or AR mutation in Cl^-/ HCO_3^- exchanger (AE1)
  - AR mutation in B1 subunit of H^+ ATPase; associated with early onset deafness
  - AR mutation in A4 subunit of H^+ ATPase; variably associated with later onset deafness
- Drugs: classically amphotericin.
- Congenital lesions causing tubular dysfunction such as obstructive lesions.

Clinical Presentation

- FTT, lethargy, polyuria, vomiting, dehydration.
- May have kidney stones or nephrocalcinosis.

Diagnosis/Evaluation

- Urine pH <5.5 rules out.
- Urine pH >6.5 with non-AG metabolic acidosis is suggestive.
- Typically diagnosed by positive urine AG but this is not reliable in neonates due to their high urine anions.
- Can use urine pCO_2–blood pCO_2 gradient:
  - Administer alkali to raise serum HCO_3^- to slightly above normal.
  - Measure pCO_2 from urine and blood.
  - Difference should be >20 with normal function.
- Hypercalciuria, hypocitraturia, hypokalemia typical.

Treatment

- Alkali: amount required decreases with age; typically requires less than proximal RTA (2–3 mEq/kg/d).

HYPERKALEMIA RTA/TYPE IV

Basic Information

- Impaired potassium and hydrogen secretion in collecting duct.
- Rare in children.
- May be from drugs that impair release or action of aldosterone.
- Also seen in genetic conditions that result in decreased production (CAH) or resistance to aldosterone (PHA type 1).

Clinical Presentation

- Acidosis typically less severe than other forms: bicarb in high teens.
- Hyperkalemia.

Table 27.5 Normal Values for Renal Indices in Neonate

Age	GFR (mL/min/1.73 m²)	RBF (mL/min/1.73 m²)	Maximum Urine Osm (mOsm/kg)	Serum Creatinine (mg/dL)	Fe_{Na} (%)
Premature	14±3	40±6	480	0.6–1.3	2–6
Term	21±4	88±4	800	0.6–1	<1
1–2 weeks	50±10	220±40	900	0.27–0.5	<1
6 months–1 year	77±14	352±73	1200	0.18–0.29	<1
1–3 years	96±12	540±118	1400	0.24–0.43	<1
Adult	118±18	620±92	1400	0.6–1.3	<1

From Martin RJ. *Fanaroff and Martin's Neonatal-Perinatal Medicine.* 10th ed. Philadelphia: Elsevier/Saunders; 2015 [p. 1680, Table 101.3].

Diagnosis/Evaluation

- Hyperkalemia.
- High urine sodium.
- Low urine potassium.

Treatment

- If due to low aldosterone production, mineralocorticoid replacement.
- Low potassium intake.
- Potassium binding resins.
- Alkali.

MIXED RTA/TYPE III

Basic Information

- Defect in both proximal and distal tubule.
- Common in VLBW infants in first few weeks.
- Genetic form results from defect in carbonic anhydrase II: presents with mixed RTA and osteopetrosis, growth restriction, mental retardation, cerebral calcifications.

HORMONAL CONTROL OF RENAL FUNCTION

- Renin-angiotensin system (RAS).
  - Angiotensinogen is produced in liver.
  - Renin produced by juxtaglomerular apparatus of afferent arterioles converts angiotensinogen to angiotensin I (ang I).
  - Angiotensin converting enzyme (ACE) converts ang I to angiotensin II (ang II)
  - Ang II via its AT1 receptor subtype constricts efferent arteriole > afferent resulting in increase in GFR.
  - Ang II also promotes Na, HCO_3^-, and water reabsorption along nephron.
  - Ang II via AT2 receptor subtype important in nephrogenesis.
  - Pharmacologic RAS inhibition during pregnancy or mutation in genes involved in RAS can result in hypotension, hypocalvaria, IUGR, pulmonary hypoplasia, oligohydramnios, anuria, and fetal/neonatal death.
- Prostaglandins:
  - Synthesized in kidney via cyclooxygenase pathway.
  - Important in maintaining GFR when renal perfusion is low or vasoconstrictive state activated.
  - Exposure to NSAIDs in utero results in transient decrease in GFR.
  - Use of indomethacin for PDA therapy associated with decrease in GFR and AKI.
- Atrial natriuretic peptide (ANP):
  - Released from atrial myocytes when stretched.
  - Causes afferent arteriole vasodilation and efferent arteriole constriction: increase GFR.
  - Inhibits renin production, and aldosterone release stimulates natriuresis.
- Nitric oxide (NO): potent vasodilator synthesized by endothelial cells.
- Dopamine:
  - Increases renal blood flow and GFR.
  - Inhibits Na reabsorption by inhibiting Na-K ATPase.
- Sympathetic nervous system:
  - Low level activation results in equal constriction of afferent and efferent arterioles: decrease renal blood flow with no effect on GFR.
  - Higher degree of activation results in constriction of mesangial cells and decreases GFR.
  - Stimulates renin release: activates RAS.

EVALUATION OF RENAL FUNCTION

- See Table 27.5 for normal values of renal indices for term and preterm infants.
- Creatinine most commonly used to assess renal function. Falls to 0.4 mg/dL by 2 weeks after term birth. Preterm infants may have a rise in creatinine over several days then slow fall to 0.4 mg/dL over next month.
- Creatinine clearance:
  - GFR = (U_{Cr} × Urine volume in L)/S_{Cr} = X L/day
  - Requires 24-hour urine collection.
  - Provides estimate of GFR but since creatinine secreted by tubules may overestimate; also, immature tubules reabsorb creatinine thus further complicating interpretation of the result.
- Cystatin C has been proposed as alternate estimate of GFR but is not nearly as widely available as serum creatinine measurements.
- Urinalysis:
  - Proteinuria: best assessed by spot urine protein/creatinine ratios. Preterm normal <0.7 mg/mg, term <0.5 mg/mg. May be seen with ATN, fever, dehydration, heart failure, nephrotic syndrome.
  - Hematuria: >5 RBC/hpf by microscopic exam. May be seen with ATN, renal vein thrombosis, urine infection, trauma from catheter.
- FENa = (U_{Na} (Urine sodium) × S_{Cr} (Serum creatinine))/(S_{Na} (Serum sodium) × U_{Cr} (Urine creatinine))
- Calculated serum osmolality: (2 × S_{Na} in mmol/L) + (glucose in mg/dL/18) + (BUN in mg/dL/2.8)

Suggested Readings

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Questions

1. A 24-week, 600 gm infant is admitted to the NICU. The baby is intubated and sedated. Due to being quite unstable and requiring frequent hands-on care, she is under a radiant warmer. You estimate her baseline insensible fluid loss as 100 mL/kg/d. Based on the above information, what will you write her total fluids for the next 24 hours?
   a. 75 mL/kg/d
   b. 110 mL/kg/d
   c. 140 mL/kg/d
   d. 175 mL/kg/d
   e. 200 mL/kg/d

2. A full-term infant is being cared for in your NICU following a difficult delivery. He was initially prescribed D5W at 70 mL/kg/d for dol 0–2. On dol 3 he is noted to have a sodium of 130, a potassium of 4.8, and a creatinine of 0.7. His weight has been stable since birth. He appears euvolemic on exam. Urine lytes show a sodium of 40 mEq/L. What is the most likely etiology of the hyponatremia?
   a. AKI
   b. Bartter syndrome
   c. Inadequate intake of sodium
   d. SIADH
   e. Pseudohypoaldosteronism

3. An ex-25-week-old infant is now 11 days old. Her serum sodium has trended down from 137 to 126. Her creatinine is 0.8. Her TF are written as 130 mL/kg/d. Her TPN has 3 mEq/kg/d of sodium with an additional 1 mEq/kg/d provided in her carrier fluids. You obtain urine lytes that show a sodium of 80 and a creatinine of 10. What is her FENa and how does it explain her serum sodium?
   a. 12.6%, tubular wasting from immature tubule
   b. 7.9%, tubular wasting from acute tubular necrosis
   c. 5%, tubular wasting from prematurity
   d. 2.5%, prerenal AKI
   e. 0.05%, inadequate Na intake

4. The lab calls with a critical potassium value of 7.2 in a 4-day-old ex-26-week infant. His weight is 15% below birth weight. The rest of the chemistry panel shows a Na of 151 and a bicarbonate of 10. Which of the following mechanisms would not perpetuate hyperkalemia?
   a. Avid sodium reabsorption by the proximal tubule secondary to volume depletion
   b. Lack of Maxi-K channels in neonates
   c. Inhibition of ROMK channels by acidosis
   d. Neonates' blunted response to aldosterone
   e. Acidosis stimulating Na-K ATPase, which increases the intracellular to urine gradient.

5. A 33-week cGA infant has been on thiazides for about 6 weeks for CLD. She develops acute vomiting. A chemistry panel shows a bicarbonate of 32 with potassium of 3.0 and creatinine of 1.1. A blood gas confirms metabolic alkalosis. What mechanism is not involved in stimulating or maintaining the alkalosis?
   a. Vomiting leads to loss of protons.
   b. Vomiting leads to decrease in intravascular volume, which results in a decrease in GFR.
   c. Hypokalemia limits the shift of H+ out of cells.
   d. Intravascular depletion stimulates proximal Na reabsorption, which leads to increased distal H+ secretion.
   e. Intravascular depletion stimulates RAS driving further potassium loss.

6. A 1-week-old ex-37-week infant is admitted with the following chemistry: Na 127, K 7.3, bicarbonate 15. His mother reports he is not very interested in feeding but has been making a normal amount of wet diapers. His weight is 12% below his birth weight. His father reports that he has been told he was often admitted to the hospital as a baby but he doesn't know any details. He is currently well and not on any medications. What advice could be given to the family about what to expect as their child grows up?
   a. Resolution of symptoms by age 2
   b. A chronic cough
   c. Persistent rashes
   d. Growth failure
   e. A need for salt supplementation throughout life

7. A 950-gram infant is noted to have a 6% loss of weight from birth weight. His UOP has increased from dol 1 to 2. His electrolytes and creatinine are normal for age. So far, he has been on 90 mL/kg/d TF without any Na or K in the TPN. Which statement below regarding his fluid/electrolytes management is correct?
   a. Increase TF to 130 mL/kg/d since he is losing too much weight.
   b. He is at a decreased risk of a PDA based on the numbers above.
   c. His risk of NEC is higher than an infant of similar BW who did not lose weight.
   d. Adding 1 mEq/kg/d potassium to the TPN would be dangerous.
   e. Your management has increased his risk of chronic lung disease.

8. A FT infant with bilateral pneumothoraces develops respiratory acidosis. Regarding neonatal respiratory acidosis, which statement is true?
   a. Preterm infants can respond to respiratory acidosis by increasing their tidal volume.
   b. Providing a dose of bicarbonate using the following formula is helpful: base deficit × BW × 0.3.
   c. Renal compensation is as efficient as in older children.
   d. Intubation may be needed.
   e. Administered bicarbonate stimulates hyperventilation.

9. A 1-month-old ex-33-week infant has been having difficulty gaining weight. Her feeds have been fortified to 28 kcal/oz but she still gains <5 g/d. Her mother reports her son had a similar issue with weight gain. You obtain a chemistry panel that shows: Na 137, K 4.1, bicarbonate 12, BUN 14, creatinine 0.3, glucose 85, Ca 9.4, phosphorus 6.0. A urine sample has a specific gravity of 1.010, pH 5.4, and is negative for blood, protein, LE, or nitrates. What is the baby's diagnosis?
   a. Distal RTA
   b. Type IV RTA
   c. Hemolyzed blood sample
   d. Proximal RTA
   e. Pseudohypoaldosteronism

10. You are treating an ex-27-week infant for a moderate sized PDA. The baby has developed worsening pulmonary edema despite restricting fluids. You start indomethacin. After the second dose, the baby's urine output is noted to drop from 1 to 0.6 mL/kg/hr. Which statement explains the drop in UOP?
   a. Release of ANP has caused dilation of the efferent arteriole.
   b. Indomethacin has disrupted the intrarenal production of prostaglandins.
   c. Ang II is constricting the afferent arteriole only.
   d. The indomethacin has closed the PDA resulting in shunting of blood away from the kidneys.
   e. Dopamine is stimulating NA-K ATPase.

28 Abnormal Renal Development

ERIN RADEMACHER

Prenatal Ultrasound (U/S) of Kidneys and the Bladder

- Should evaluate kidney size, shape, echogenicity; amniotic fluid volume; bladder size/shape. See Box 28.1 for potential etiologies of different U/S findings.
  - Fetal kidneys can be visualized at 9–12 weeks; Average length: 1 cm at 12 weeks and 2.7 cm at 20 weeks; the bladder can be seen by the 15th week
- Abnormal findings in renal/urinary system account for 20%–30% of anomalies detected on prenatal ultrasound.
- Risk of renal tract malformations is increased by maternal diabetes mellitus and certain drug exposures. Cocaine and alcohol have also been reported to increase risk.

Prenatal Diagnosis: Hydronephrosis

- Hydronephrosis is defined as significant dilatation of upper tract involving dilatation of the calyces.
  - Pelviectasis or pyelectasis usually refers to dilatation of the renal pelvis only.
- Hydronephrosis or pelviectasis seen in ~1%–5% of pregnancies
- Definition depends on which classification system used
  - Measurement of the anterior-posterior diameter of the renal pelvis most common
  - > 4 mm if < 33 weeks, or > 7 mm at > 33 weeks predictive of postnatal problems
  - > 15 mm is highly predictive of ureteropelvic junction (UPJ) obstruction
- Presence of oligohydramnios is predictive of long-term renal impairment. Other predictors: lack of reniform shape of kidney, presence of cysts, and increased echogenicity
- 50%–70% of prenatally detected hydronephrosis cases are physiologic/idiopathic (no obstruction or reflux); most resolve over the first 2 years of life
- Other causes of prenatal hydronephrosis:
  - Ureteropelvic junction (UPJ) obstruction: 10%–30%
    - Most common cause of severe hydronephrosis
    - More common in males
    - May be part of syndrome
  - Vesicoureteral reflux (VUR): 10%–40%
    - Caused by ectopic insertion of the ureter resulting in shortened intravesicular segment
    - One-third have affected first-degree relative
  - Ureterovesical junction (UVJ) obstruction: 5%–15%
    - Usually isolated
    - Hydroureter seen on U/S
  - Multicystic dysplastic kidney (MCDK): 2%–5%
  - Posterior urethral valve (PUV): 1%–5%
  - Ureterocele: 1%–3%
    - Usually from duplex collection system upper pole ureter
  - Eagle-Barrett syndrome, aka "prune belly syndrome": <1%

POSTNATAL EVALUATION OF PRENATAL HYDRONEPHROSIS

- U/S in first 1–2 days of life indicated for severe prenatal hydronephrosis, bilateral hydronephrosis, oligohydramnios, concern of bladder obstruction
- If initial early U/S is normal, follow-up in 1–2 weeks when urine output is well established
- Unilateral hydronephrosis: U/S at ~2 weeks of life
- Follow-up U/S done 4–6 weeks of life
- If U/S at 1–2 weeks and 4–6 weeks are both normal, no further follow-up needed
- If severe hydronephrosis present on postnatal U/S, baby should be placed on antibiotic prophylaxis and VCUG (voiding cystourethrogram) obtained

Prenatal Treatment of Suspected Bladder Outlet Obstruction With Oligohydramnios

- Controversial: intervention has not been shown to reliably improve renal or pulmonary function
- Most common intervention is a vesicoamniotic shunt placed in second trimester in fetus thought to have preserved renal function
- Fetal renal function assessed by fetal urine indices on serial bladder taps (need to empty the bladder to obtain fresh urine for analysis)
- Findings thought to predict good renal function
  - Urine Na < 100 mEq/L
  - Urine Ca < 8 mg/dL
  - Urine Osm < 200 mOsm/L
  - Urine β_2 microglobulin < 4 mg/L
  - Urine protein < 40 mg/dL

Oligohydramnios Sequence (Potter Syndrome) (Fig. 28.1)

- Seen in babies with oligohydramnios or anhydramnios of any cause
- Characteristic facies: wide-set eyes, depressed nasal bridge, beaked nose, receding chin, posteriorly rotated and low-set ears

Box 28.1 Abnormal Findings of Urinary Tract Seen by Prenatal Ultrasound

Kidneys

- Dilated renal pelvis/hydronephrosis: physiologic vesicoureteral reflux, obstruction
- Cystic kidney: multicystic dysplastic kidney (MCDK), cystic dysplasia, autosomal dominant polycystic kidney disease (ADPKD), severe obstruction
- Echogenic kidney: renal dysplasia, ARPKD
- Structural abnormalities: renal duplication, malposition (e.g., horseshoe, crossed fused ectopia)
- Lack of visualization: renal agenesis, hypoplasia, malposition
- Enlarged kidneys: ARPKD, obstruction, overgrowth syndromes (Simpson-Golabi-Behmel, Perlman, Beckwith-Wiedemann)
- Renal mass

Ureter

- Hydroureter
- Ureterocele

Bladder

- Dilation
  - With thickened wall: posterior urethral valves
  - Without thickened wall: megaureter-megacystis syndrome, neurogenic bladder, EBS
- Bladder exstrophy, cloacal exstrophy
- Lack of visualization: minimal or absent fetal urine production; obstructive uropathy

Ascites

- Urinary ascites (typically associated with thickened bladder wall and/or abnormal kidneys)

Hydrops Fetalis

- Most often owing to nonrenal causes; occasionally caused by bilateral renal cystic disease, urinary tract obstruction, congenital nephrotic syndrome

Oligohydramnios

- Bilateral renal malformations, ARPKD, urinary tract obstruction
- Rupture of membranes, postmaturity, subacute fetal distress

Polyhydramnios

- Renal tubular disorder with urinary concentrating defect (NDI, Bartter syndrome)
- Multiple gestation, upper gastrointestinal tract obstruction, neurologic disorders, maternal diabetes, fetal hydrops

Placental Edema

- Congenital nephrotic syndrome

ADPKD, autosomal dominant polycystic kidney disease; *ARPKD,* autosomal recessive polycystic kidney disease; *EBS,* Eagle-Barrett syndrome; *MCDK,* multicystic dysplastic kidney; *NDI,* nephrogenic diabetes insipidus.

From Martin RJ. *Fanaroff and Martin's Neonatal-Perinatal Medicine.* 10th ed. Philadelphia: Elsevier/Saunders; 2015:1681, Box 101.1.

- Other features: small chest, arthrogryposis, hip dislocation, club feet
- Respiratory failure secondary to pulmonary hypoplasia

Posterior Urethral Valves

- Occurs in 1/5000–1/8000 live birth males/year
- U/S show hydronephrosis with hydroureter and thickened, trabeculated bladder
- VCUG shows narrowing of urethra (Fig. 28.2)
- PE: palpable bladder with poor urine stream
- Treatment: place urethral catheter to relieve obstruction, followed by valve ablation
- Prognosis: prone to dehydration due to poor concentrating ability, 12%–15% progress to renal failure by adolescence

Eagle-Barrett Syndrome (Fig. 28.3)

- Full syndrome has triad of findings:
  - Poorly contractile, markedly enlarged bladder without urethral obstruction plus megaureters plus renal dysplasia
  - Deficient abdominal wall musculature
  - Cryptorchidism
- Can be incomplete and only display some of the features of the classic triad
- 1/35,000–1/50,000, nearly all males
- May have abnormalities of other organs
- Should be on UTI prophylaxis due to poorly functioning bladder

Fig. 28.1 Oligohydramnios sequence typical facial appearance. (From Martin RJ. *Fanaroff and Martin's Neonatal-Perinatal Medicine.* 10th ed. Philadelphia: Elsevier/Saunders; 2015 [p. 1682, Fig. 101.4].)

Renal Agenesis

- Unilateral absence of kidney: incidence 1/500–1/3200 live births/year
  - Expect compensatory hypertrophy of contralateral kidney (often seen in utero)

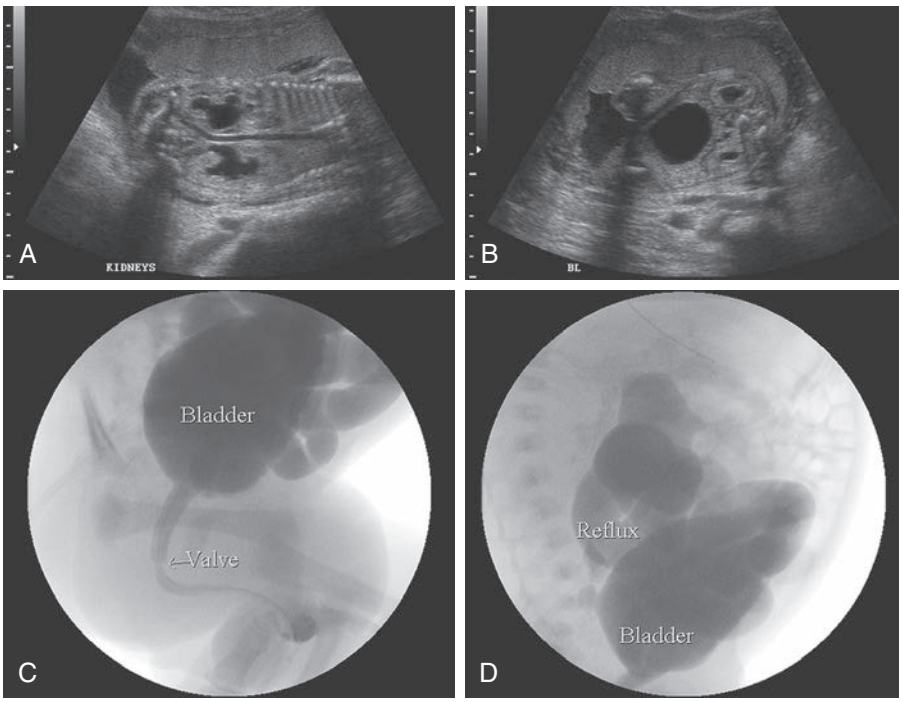

Fig. 28.2 Posterior urethral valve imaging. (A) Prenatal ultrasound (U/S) showing bilateral hydronephrosis. (B) Prenatal U/S showing dilated bladder. (C) VCUG (Voiding Cystourethrogram) showing narrowing in posterior urethral (D) VCUG showing reflux into dilated ureter. (From Clayton DB, Brock JW. Lower urinary tract obstruction in the fetus and neonate. *Clin Perinatol*. 2014;41:643–659, Fig. 2.)

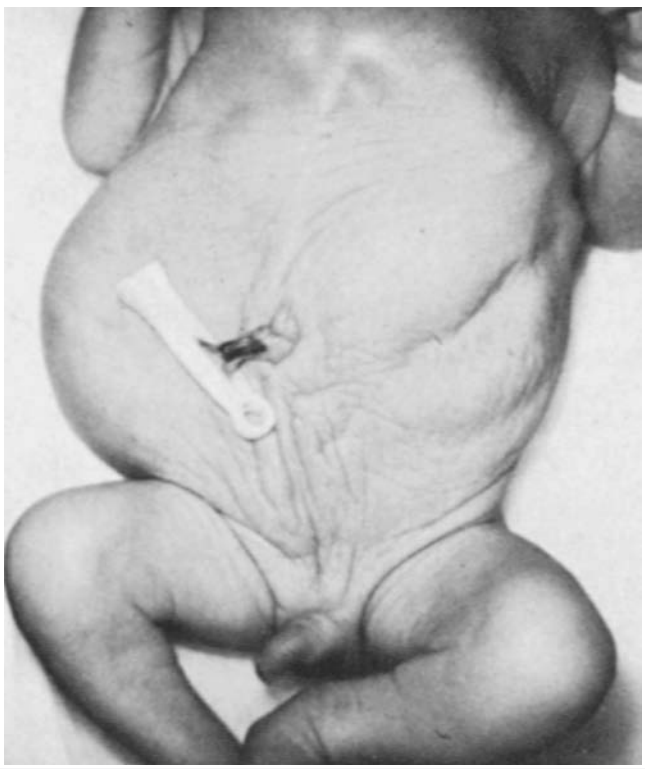

Fig. 28.3 Eagle-Barrett syndrome. (From Martin RJ. Fanaroff and Martin's Neonatal-Perinatal Medicine. 10th ed. Philadelphia: Elsevier/Saunders; 2015 [p. 1694, Fig. 101.8].)

  - One-third will have abnormality in contralateral kidney: VUR, UPJ, dysplasia, ureterocele
  - Can be associated with defects in müllerian ducts
- Bilateral: 1/4000–1/10,000 /year, fatal in neonatal period due to pulmonary hypoplasia
- May be associated with syndromes: VACTERL, caudal regression syndrome, branchio-oto-renal syndrome, chromosomal defects

Renal Dysplasia

- Abnormal development of kidney resulting in disorganized structure and presence of cartilage
- Can be caused by genetic mutation, obstruction, toxin/medication exposure
- Associated with syndromes: VACTERL, CHARGE, Jeune syndrome, trisomies 13, 18, and 21
- Bilateral dysplasia usually results in chronic kidney disease

Multicystic Dysplastic Kidney (MCDK)

- Nonfunctional kidney
- Normal architecture replaced by "cluster of grapes" cysts (Fig. 28.4)
- 1/4300 live births
- Twice as common on the left side
- Most involute over time
- No increased risk of tumor or hypertension

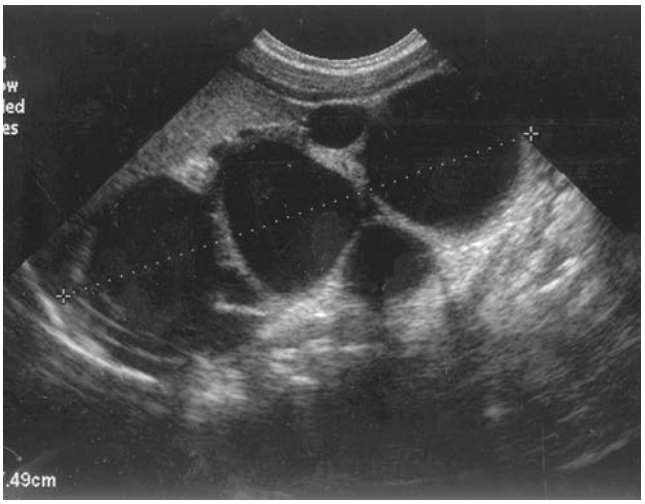

Fig. 28.4 Ultrasound appearance of multicystic dysplastic kidney showing the "bunch of grapes" appearance: multiple cysts that do not communicate with each other. (From Gleason CA. *Avery's Diseases of the Newborn*. 9th ed. Philadelphia: Elsevier; 2012:1193, Fig. 84.4.)

- One-third have abnormal contralateral kidney (agenesis, dysplasia, VUR, ectopia)
- Should have VCUG if contralateral kidney or bladder has abnormal U/S appearance or if cryptorchidism present
- If opposite kidney is normal, should see compensatory hypertrophy

Autosomal Recessive Polycystic Kidney (ARPKD)

- Polycystic kidney disease with congenital hepatic fibrosis
- 1/40,000 incidence
- Autosomal recessive: mutation in *PKHD1* gene. Genetic testing available but only detects 85% of cases. Expression is variable within a family
- Prenatal U/S shows enlarged, echogenic kidneys; cysts are usually too small to be detected
- May develop oligohydramnios in second trimester
- After birth may have respiratory failure secondary to oligohydramnios and/or abdominal distention from large kidneys
- May have severe hypertension
- Hyponatremia is common
- Nutrition may be compromised by large kidneys limiting intake
- 70% survive neonatal period, 80% of these will survive to age 10
- 50% develop renal failure in first decade

Autosomal Dominant Polycystic Kidney Disease (ADPKD)

- 1/1000 live births carry mutation but rarely manifests clinically until adulthood
- May have visible cysts at birth
- Rarely has severe presentation similar to ARPKD
- 10% have a new mutation

Box 28.2 Presenting Signs of Aortic and Renal Artery Thromboembolism

- Signs of congestive heart failure
- Hypertension
- Oliguria
- Renal failure
- Bowel ischemia or frank necrotizing enterocolitis secondary to superior or inferior mesenteric artery
- Decreased femoral pulses with lower limb ischemia
- Thrombocytopenia, hypofibrinogenemia, elevated fibrin split products, variable prothrombin and thromboplastin times
- Conjugated hyperbilirubinemia
- Elevated blood urea nitrogen and creatinine
- Hyperreninemia
- Hematuria

From Gleason CA. *Avery's Diseases of the Newborn.* 9th ed. Philadelphia: Elsevier; 2012:1236, Box 88.2.

Renal Artery Thrombosis

- Major risk factor: presence of umbilical artery catheter (UAC)
- Presumed cause is endothelial injury after insertion of UAC
- High UAC (T6–T10) has decreased incidence
- Heparinized fluid also associated with decreased incidence
- Other risk factors: shock, coagulopathy, congestive heart failure
- Incidence varies with modality used to detect:
  - U/S with Doppler: 14%–35%
  - Angiography: 64%
  - Autopsy: 9%–28%
- Symptomatic in 1%–3%
- Presents within first few days in term infant but delayed in preterm (~8 days)
- Signs (Box 28.2)
  - Minor clot: mildly decreased lower extremity perfusion, hypertension, hematuria
  - Moderate clot: decrease lower extremity perfusion, hypertension, oliguria, congestive heart failure
  - Major clot: multi-organ failure
- Prognosis
  - 9%–20% mortality with clot involving both aorta and renal artery
  - Renovascular hypertension most common long-term complication but often resolves
  - Chronic kidney disease not common but always present if clot affected both renal arteries
- Diagnosis
  - Thrombocytopenia, low fibrinogen, increase fibrin split products, variable prothrombin and thromboplastic times, conjugated hyperbilirubinemia, increased BUN and creatinine, hematuria
  - Diagnostic imaging: Doppler U/S or angiography
- Treatment
  - Asymptomatic/minor symptoms: removal of UAC and supportive care
  - More severe symptoms: systemic heparinization
  - Life-threatening: thrombolytic agents have been used but few data on dosing, safety, or efficacy

Renal Vein Thrombosis

- Most common blood clot in infancy: reported incidence has varied from 2.2/100,000 live births (symptomatic clot) to 0.5/1000 NICU (neonatal intensive care unit) admissions;
- More common in males (2/3)
- Left renal vein more common than right (60%)
- Unilateral in 70%
- IVC (inferior vena cava) involved in 40%
- Adrenal hemorrhage in 15%
- Risk factors (Box 28.3)
  - Prothrombotic factors play significant role
  - Maternal diabetes
  - Most do not involve an umbilical venous catheter
- Clinical presentation
  - Classic triad: gross hematuria, decreased platelets, flank/abdominal mass (all three seen in only 13%–22% cases)
  - Decreased urine output
- Prognosis
  - Scarring and atrophy of affected kidney common
  - 20% have hypertension
  - Mortality ~3%, usually relating to underlying cause of the renal vein thrombosis (RVT)
- Diagnosis and evaluation
  - Labs: low platelets, hemolytic anemia, metabolic acidosis, increased BUN/Cr, variable prothrombin and partial thromboplastic times
  - Renal ultrasound with Dopplers: appearance of U/S changes with time (Box 28.4), Clot in small intrarenal veins can cause increased resistance in renal artery
  - Angiography and MRI are used in selected circumstances

Box 28.3 Risk Factors for Renal Vein Thrombosis

Inherited

- Lupus anticoagulant
- Protein C and protein S deficiency
- Plasma antithrombin III activity
- Elevated lipoprotein (a)
- Factor V Leiden mutation
- Prothrombin gene mutation
- Methylenetetrahydrofolate (MTHFR) thermolabile mutation

Acquired

- Maternal diabetes
- Traumatic delivery
- Prematurity
- Hyperviscosity
- Hypovolemia
- Hemoconcentration
- Sepsis
- Birth asphyxia
- Cyanotic congenital cardiac disease
- Congenital renal vein defects
- An indwelling umbilical venous catheter

From Gleason CA. *Avery's Diseases of the Newborn.* 9th ed. Philadelphia: Elsevier; 2012:1237, Box 88.2.

- Treatment
  - Correct any fluid, electrolyte, or acid-base issues in all cases
  - Avoid hypertonic solutions, nephrotoxins, hyperosmotic radiocontrast material, diuretics
  - Unclear if heparinization leads to differences in long-term outcomes but usually recommended in unilateral cases with IVC involvement
  - Fibrinolysis only considered in bilateral cases

Acute Kidney Injury (AKI)

- Can be defined as sudden decline in GFR or tubular function
- Currently used neonatal AKI definition defines AKI into stages based on rise in creatinine or drop in urine output (Table 28.1)

Box 28.4 Ultrasound Changes in Kidney Affected by Renal Vein Thrombosis

Early (first week)

Globular enlargement of kidney
Increase in echogenicity
Loss of corticomedullary boundary
Echogenic streaks
Loss of normal sinus echoes

Intermediate (second week)

More prominent and diffuse renal enlargement
Diffuse "snowstorm" pattern of echogenicity
Loss of corticomedullary differentiation
May see coexisting hyperechoic (hemorrhagic) areas and hypoechoic (edema/resolving hemorrhagic) areas
May see thrombus extension in renal veins and inferior vena cava

Late (after second week)

May be normal in appearance
May become atrophic
May see calcifications in either or both kidneys and within the vascular system

From Brandão LR, Simpson EA, Lau KK. Neonatal renal vein thrombosis. *Semin Fetal Neonatal Med.* 2011;16:323–328, Box 1.

Table 28.1 Neonatal KDIGO (Kidney Disease Improving Global Outcomes) Acute Kidney Injury Definitions

Stage	Serum Creatinine (SCr)	Urine Output Over 24 hours
0	No change in serum creatinine or rise < 0.3 mg/dL	> 1 mL/kg/hour
1	SCr rise ≥0.3 mg/dL within 48 h or SCr rise ≥ 1.5 to 1.9× reference SCr[a] within 7 days	> 0.5 and ≤ 1 mL/kg/hour
2	SCr rise ≥ 2 to 2.9× reference SCr	> 0.3 and ≤ 0.5 mL/kg/hour
3	SCr rise ≥ 3× reference SCr or SCr ≥ 2.5 mg/dL or receipt of dialysis	≤ 0.3 mL/kg/hour

[a]Reference SCr is the lowest prior SCr measurement.
From Nada A, Bonachea EM, Askenazi DJ. Acute kidney injury in the fetus and neonate. *Semin Fetal Neonatal Med.* 2017;22:90–97, Table 1.

- Problems with creatinine-based definitions in neonates: creatinine may not change until 25%–50% GFR lost. Creatinine may rise in preterm over the first few days of life, then plateau for several days before falling
- Most neonatal AKI does not involve oliguria
- Rates of AKI in NICU vary with population studied
  - Very low birthweight: 18%–40%
  - Extracorporeal membrane oxygenation (ECMO): as high as 70%
  - Cooling protocol for HIE (hypoxic ischemic encephalopathy): 40%
- Often divided into prerenal, intrinsic, postrenal causes (Box 28.5)
- Prerenal AKI
  - Most common type in NICU
  - Results from short period of decreased perfusion of the kidneys
  - Typically reversible
  - If intact tubular function, increased reabsorption of sodium and urea
    - FENa < 1%
    - FEUrea < 35%
    - BUN/Cr ratio increased
  - Interpretation of above tests can be difficult in preterm, salt-wasting states, or chronic kidney disease
  - Treatment: address underlying cause of poor blood flow to kidneys, fluid boluses, colloid such as blood products
- Intrinsic AKI
  - Prerenal AKI can progress to ischemic AKI if prolonged hypoperfusion to the kidneys results in cellular damage. Severity ranges from mild tubular dysfunction to acute tubular necrosis (ATN) to renal infarction to corticomedullary necrosis

Box 28.5 Causes of Acute Kidney Injury in the Neonate

Prerenal

- Volume depletion
- Hypotension
- Hemorrhage
- Sepsis
- Necrotizing enterocolitis
- Congestive heart failure
- Drugs: angiotensin-converting enzyme inhibitors, angiotensin-receptor blockers, indomethacin, ibuprofen, amphotericin

Renal

- Acute tubular necrosis
- Renal dysplasia
- Polycystic kidney disease
- Renal venous thrombosis
- Uric acid nephropathy
- Transient acute renal insufficiency of the newborn

Postrenal

- Posterior urethral valves
- Bilateral ureteropelvic junction obstruction
- Bilateral ureterovesical junction obstruction
- Neurogenic bladder
- Obstructive nephrolithiasis

From Martin RJ. *Fanaroff and Martin's Neonatal-Perinatal Medicine*. 10th ed. Philadelphia: Elsevier/Saunders; 2015:1684, Box 101.2.

- Nephrotoxic AKI results from drugs or endogenous substances
  - Aminoglycosides, cephalosporins, amphotericin B, rifampin, vancomycin, nonsteroidal antiinflammatory drugs (NSAIDs), IV contrast, myoglobin, hemoglobin all cause direct tubular injury
  - Acyclovir, uric acid: cause tubular obstruction
- Obstructive AKI
  - Results from congenital malformation, neurogenic bladder, extrinsic compression, fungal ball, stone
- Evaluation of AKI
  - History: maternal medical history/drug exposures, birth history, coexistent conditions (cardiac or liver issues, sepsis, NEC, etc.), intake, output, weights, BP, drug exposures
  - Exam: assessment of fluid status (hypovolemic, euvolemic, hypervolemic), vital signs, fontanelle, skin turgor, mucus membranes, edema, crackles, murmurs/rubs, color, capillary refill
  - Labs: electrolytes, BUN, creatinine, albumin, U/A (urinalysis), urinary electrolytes
  - Diagnostic imaging: renal/bladder U/S, CXR (chest x-ray)
- Treatment of AKI
  - Remove inciting factors if possible: restore perfusion via bolus, pressors if needed to support blood pressure, remove nephrotoxic drugs
  - Specific therapy for AKI limited:
    - Theophylline may have protective effect as it was shown to decrease AKI rates in asphyxiated infants in one small study
    - "Renal dose dopamine" has not shown decreased rates of AKI in metaanalysis
  - Manage consequences of AKI (impaired homeostasis)
    - Hyperkalemia (refer to Table 27.3 in Chapter 27):
      - Remove sources of potassium (TPN, feeds, medications such as potassium-sparing diuretic)
      - Correct hypovolemia if present with normal saline to deliver Na to distal nephron to aid in potassium secretion
      - Stabilize myocardium (calcium)
      - Shift into cells (insulin, sodium bicarbonate, albuterol)
      - Remove from body: Lasix, binding resin (Kayexalate), dialysis
    - Metabolic acidosis
      - $NaHCO_3$ bolus, repeated dosing may make hypernatremic
      - Use acetate in TPN
    - Hypocalcemia: replete
    - Hyperphosphatemia: decrease intake: remove from TPN, use low phosphorus formulas, use phosphate binders with feeds
    - Hypermagnesemia: limit intake
    - Fluid status
      - Needs to be tailored to individual patient needs
      - Fluid-overloaded patient: restrict intake to be less than output; careful use of diuretics may help with volume overload but will not hasten recovery from AKI; for severe overload, may need dialysis for fluid removal
      - Euvolemic: keep intake = output + insensible losses

- Hypovolemic: use boluses or increased total daily fluids to restore normal blood volume
- Postobstructive AKI may have polyuria when obstruction relieved

- Dialysis
  - Peritoneal dialysis (PD): instillation of dialysate through catheter placed through abdominal wall into the peritoneal space
    - Advantages
      - Insertion of PD catheter may be easier than obtaining vascular access for hemodialysis (HD) or continuous renal replacement therapy (CRRT)
      - Can be done by NICU nurses
      - No anticoagulation needed
      - For infants who will be expected to need a renal transplant, involves less blood exposure
    - Disadvantages
      - Less efficient than HD or CRRT: not ideal for intoxications, tumor lysis, or severe hyperkalemia
      - Contraindicated in abdominal wall defects, ventriculoperitoneal shunts, presence of abdominal adhesions
      - Peritonitis possible complication
      - May lose immunoglobulins into dialysate
  - Hemodialysis (HD)
    - Advantage: rapid clearance of solutes
    - Disadvantages:
      - Technically challenging, requires dialysis nursing support
      - Requires reliable vascular access: minimum 7Fr dual lumen or two 5Fr single lumen catheters
      - Rapid volume shifts
      - Anticoagulation
  - Continuous renal replacement therapy (CRRT)
    - Advantages:
      - Able to be used in hemodynamically unstable patients
      - Allows fluid removal to be adjusted hourly
      - Can be hooked into ECMO circuit
    - Disadvantages
      - Requires reliable vascular access
      - Requires skilled nursing personnel
      - Anticoagulation

Diuretics

- Loop diuretics (furosemide and bumetanide)
  - Highly protein bound so must be secreted into tubular lumen where they act on thick ascending limb of loop of Henle's Na-K-2Cl transporter
  - Half-life is much longer in preterm compared to term infants
  - With repeated doses, develop tolerance to its effect likely due to compensatory increase in Na reabsorption in other parts of the nephron
  - Adverse effects: hypokalemia, hypomagnesemia, hypocalcemia, hyponatremia, hypercalciuria, nephrocalcinosis, decreased bone density, deafness
- Thiazide diuretics (hydrochlorothiazide, chlorothiazide, metolazone)
  - Secreted into lumen then binds the Na-Cl cotransporter in the distal tubule
  - Less potent than loop diuretics but can be added to loop diuretic; particularly useful when desire increased diuretic effect and tolerance to loop has developed
  - Adverse effects: hypokalemia, hyponatremia
  - Unlike loop diuretic, lead to increased calcium reabsorption
- Aldosterone receptor antagonist (spironolactone)
  - Weak diuretic
  - Primary use in neonate is as potassium-sparing agent in combination with thiazide
- Other diuretics not commonly used in the NICU
  - Mannitol: osmotic diuretic
  - Carbonic anhydrase inhibitor (acetazolamide): mild diuretic acting on proximal tubule
  - Amiloride: blocks epithelial sodium channel in collecting duct; potassium sparing diuretic

Suggested Readings

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Questions

1. You are asked to consult on a woman at 21 weeks of her pregnancy for an abnormal prenatal U/S at 20 weeks. The ultrasound showed kidneys measuring 3.4 cm each with increased echogenicity. The bladder was not able to be seen. There is no family history of kidney disease. What is the likely cause of these findings?
   a. ADPKD
   b. MCDK
   c. Renal dysplasia
   d. ARPKD
   e. Beckwith-Wiedemann

2. You are asked to do another prenatal consult on a woman who was noted at her 20-week U/S to be carrying a fetus with abnormal kidneys. The left kidney has multiple cysts of similar size and is of normal size. The right kidney is of normal echogenicity and shape with good corticomedullary differentiation and no cysts. It measures 3 cm. No hydronephrosis or hydroureter is seen. The amniotic fluid volume is normal. Family history is negative for renal disease. What is the MOST likely diagnosis?
   a. MCDK
   b. ADPKD
   c. Left-sided UPJ
   d. Left UVJ obstruction
   e. ARPKD

3. You provide a prenatal consult to a couple with a baby suspected to have a posterior urethral valve who are considering prenatal intervention. Which of these statements regarding prenatal intervention for suspected bladder obstruction is false?
   a. The most common intervention performed is a vesicoamniotic shunt.
   b. Urine Na < 100 mEq/L on serial taps suggests a good renal prognosis.
   c. Intervention has been shown to improve both renal and lung function long term.
   d. Serial bladder taps are preferred when assessing fetal renal function.
   e. Urine Osm < 200 mOsm/L predicts good renal function.

4. A 6-day-old ex-24 week infant is noted by his bedside nurse to have decreased pulses in his lower extremities. His blood pressure is also noted to be trending up. His urine has a pink tinge. Urine output is normal. His respiratory status is unchanged. He has a UAC in place. U/S shows a small unilateral renal artery clot. What is the most likely long-term outcome?
   a. End stage renal disease as an infant
   b. Necrosis of toes bilaterally
   c. Persistent hematuria
   d. Hypertension
   e. Small bowel necrosis

5. A 4-week-old ex-30 week infant undergoes a renal ultrasound for work-up of UTI. The U/S shows a small left kidney with some echogenic spots. His past medical history includes treatment for culture-negative sepsis with ampicillin and gentamicin for which he had a UVC (umbilical venous catheter) in place. He was noted to have a transient drop in platelets shortly before his antibiotics finished. What is the most likely etiology of the U/S findings?
   a. Kidney stones
   b. Dysplasia
   c. ARPKD
   d. Old renal vein thrombosis
   e. Nephrocalcinosis

6. A full-term baby with congestive heart failure is noted to have a rise in creatinine from a baseline of 0.7 to 1.6 by day of life 3. Urine output remains more than 1 mL/kg/hour. What stage of AKI is the baby in using the KDIGO system?
   a. Stage 0
   b. Stage 1
   c. Stage 2
   d. Stage 3

7. A 5-day-old full term infant is admitted to the NICU after seeing his pediatrician for a weight check. He was noted in the office to have a 15% decrease in weight since birth. On exam he has dry mucus membranes, a sunken fontanelle, and capillary refill of 3 seconds. His creatinine is 1.6. He receives fluid resuscitation with significant clinical improvement. Over the next 2 days his creatinine falls to 1.2. His vitals are normal for age. He appears euvolemic on exam. His renal U/S is normal. His urine output is 1.1 mL/kg/hour. What should be your next step in management?
   a. NS (normal saline) bolus
   b. Start renal dose dopamine
   c. Kidney biopsy
   d. Insert a bladder catheter
   e. Observation

8. A cGA 30-week infant weighing 1340 gm develops stage 3 AKI using the neonatal KDIGO definition. His daily fluid intake has been severely restricted due to oliguria and thus he is receiving next to no nutrition. His potassium is 6.2, bicarbonate 15, BUN 42, phosphorus 8. Which statement is incorrect regarding dialysis options for this baby?
   a. PD can be performed by his NICU nurses.
   b. PD does not require any anticoagulation.
   c. PD removes immunoglobulins.
   d. HD involves rapid volume shifts that may not be tolerated.
   e. CRRT fluid goals are set on the machine once every 24 hours and cannot be adjusted in between.

9. A 28-week-old infant is receiving daily Lasix for fluid overload. His response to the Lasix dose seems to be decreasing despite increasing from 1 to 2 mg/kg/day. What strategy can be used next to optimize diuresis?
   a. Increase the frequency to q8 dosing
   b. Add spironolactone
   c. Increase the dose to 3 mg/kg
   d. Add a thiazide diuretic
   e. Space dosing to q48 hours

10. The parents of a 10-week-old ex-24 week infant are nervous about his medications causing long-term damage. They ask what the side effects of his diuretics may be. Which of these is a true statement?
   a. Long-term use of thiazides is linked to bone fractures.
   b. Lasix has not been associated with hearing loss.
   c. Loop diuretics can lead to nephrocalcinosis.
   d. Thiazides are associated with increased numbers of kidney stones.
   e. Spironolactone causes hypokalemia.

SECTION 8

Endocrine

DAVID R. WEBER and ALISON FALCK

29 Normal and Abnormal Sexual Differentiation

DAVID R. WEBER

Normal Sexual Differentiation

BASIC INFORMATION

- Sexual differentiation: process by which male or female phenotype develops
  - Begins early in fetal development (Fig. 29.1)
- Chromosomal sexual determination: formation of XY (male) or XX (female) zygote via fertilization between spermatocyte (X or Y) and oocyte (X)
- Gonadal differentiation
  - Differentiation of the bipotential gonad into testes (male) or ovaries (female)
    - Migration of germ cells to genital ridge
    - Begins at week 6
  - Testicular development
    - Initiated by expression of the *SRY* gene
- Induces differentiation of Sertoli and Leydig cells
  - Ovarian development
    - Proceeds in the absence of *SRY* expression
- Differentiation of granulosa and theca cells
- Genital differentiation
  - Differentiation of internal genital structures from wolffian ducts (male) or müllerian ducts (female)
    - Male:
      - Anti-müllerian hormone (AMH) secretion by Sertoli cells causes regression of müllerian ducts
      - Testosterone secretion by Leydig cells induce wolffian ducts to differentiate into epididymis, vas deferens, seminal vesicle
        - Begins at 8 weeks
    - Female: absence of AMH and testosterone results in persistence of müllerian ducts and regression of wolffian ducts
- Müllerian ducts differentiate into fallopian tubes, uterus, cervix, upper vagina
  - Differentiation of external genital structures from the bipotential urethral folds, genital tubercle, and labioscrotal swellings
    - Males: virilization under the action of dihydrotestosterone (DHT)
- Genital tubercle elongates into penis, urethral folds fuse into urethra, labioscrotal swellings fuse into scrotum, urogenital sinus closes
- Begins at week 8, virilization complete by week 12–14
- Testes begin descent into scrotum at week 28
  - Females: external genitalia development proceeds in absence of androgens
- Genital tubercle forms clitoris and urethral folds; labioscrotal swellings form labia minora and majora; urogenital sinus forms vagina

Ambiguous Genitalia

BASIC INFORMATION

- Disorder of sexual development (DSD): discordance in chromosomal, gonadal, and/or genital sex that develops as a result of genetic mutation or environmental exposure

CLINICAL PRESENTATION

46 XY DSD: Undervirilized internal and/or external genitalia in a chromosomal male due to impaired androgen production/function

- Gonadal dysgenesis (partial or complete; symmetric or asymmetric)
  - Mutation affecting early differentiation of bipotential gonad into testis
- Yp deletion; mutations in SRY, SOX9, others
- Denys-Drash syndrome: gonadal dysgenesis, nephropathy, Wilms tumor due to *WT1* mutation
  - Phenotype varies from complete sex reversal to mild undervirilization
- Internal structures and external genitalia can be undervirilized
  - Low testosterone and AMH
  - Defective testicular hormone production
  - Defective Leydig cell differentiation
- Mutations in LH/hCG receptor result in Leydig cell hypoplasia/aplasia
- Variable internal/external undervirilization based on receptor activity
- AMH not affected; regression of müllerian ducts occurs
- Labs: elevated luteinizing hormone (LH), low testosterone, no response to hCG stimulation
  - Testosterone biosynthetic defect: mutations affecting dehydrocholesterol reductase (DHCR), StAR, P450 side-chain cleavage, P450 oxidoreductase, 3β-hydroxysteroid dehydrogenase (3β-HSD), 17α-hydroxylase/17,20 lyase deficiency, 17β-hydroxysteroid dehydrogenase (17β-HSD)
- Variable internal/external undervirilization based on enzymatic activity
- AMH not affected; regression of müllerian ducts occurs
- DHCR mutation (Smith-Lemli-Opitz syndrome) associated with multiple congenital anomalies
- All but 17,20 lyase and 17β-HSD deficiency can cause adrenal insufficiency

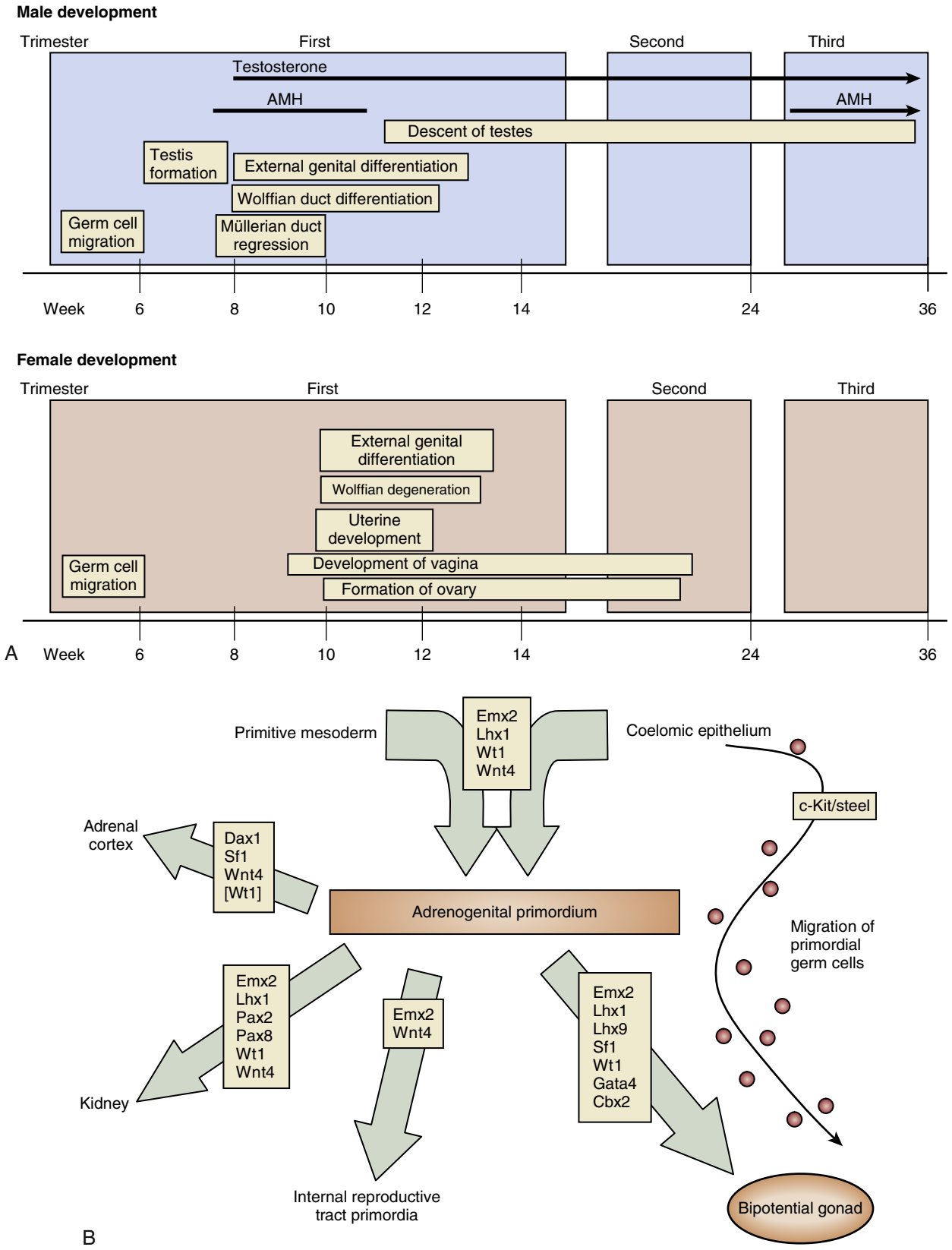

Fig. 29.1 Time line of sexual differentiation . (A) Timetable of gonadal and genital differentiation. (B) Genetic determinants of gonadal development. (From Jameson JL and Dulop RG. *Endocrinology: Adult and Pediatric*. 7th ed. Philadelphia: Elsevier; 2016:2051–2085.)

- Labs show elevated steroid hormone precursors upstream of defect
  - 5α-reductase deficiency: low/absent conversion of testosterone to DHT
- AMH and testosterone unaffected; internal structures are normal male
- External genitalia undervirilized to a variable degree
  - Virilization will occur at puberty as a result of increased testosterone
- Labs show elevated testosterone: DHT ratio
  - Defective androgen receptor
    - Partial/complete androgen insensitivity (AIS): androgen receptor mutation
- Variable undervirilization of external genitalia and internal structures
- Complete AIS presents as primary amenorrhea in phenotypic female
- Labs during infancy may show normal or elevated testosterone
- 46 XX DSD: Virilized chromosomal female due to excess androgen production or phenotypically normal female with absent development of secondary sex characteristic due to impaired estrogen synthesis or action
  - Excessive androgen production due to congenital adrenal hyperplasia (CAH): mutations in p450 oxidoreductase, 3β-HSD, 11β-hydroxylase, 21-hydroxylase
    - Degree of virilization determined by magnitude of androgen production
    - May be associated with adrenal insufficiency, salt wasting
    - See "Adrenal Disorders" Chapter 30 for details
  - Gonadal dysgenesis
    - Mutation affecting early differentiation of bipotential gonad into ovary
    - Normal female internal/external genitalia, present in adolescence with primary amenorrhea, absent breast development because of absent ovaries and estrogen

Other DSD

- Sex chromosome DSD
  - Turner syndrome (45 X)
- Atrophic gonads, normal female external genitalia
  - Klinefelter syndrome (47 XXY)
- Normal male external genitalia at birth
  - Mixed gonadal dysgenesis (45 X/46 XY)
- Phenotype varies from that of Turner syndrome to virilized female based on extent/timing of androgen production
  - Ovitesticular DSD: presence of both ovarian and testicular tissue
    - Usually undervirilized XY, depends upon extent of androgen production
    - Can be XX with translocation of *SRY* or mosaicism of sex chromosomes
  - Environmental exposures
    - Endocrine hormone disrupters
- Concern about possible estrogenic/antiandrogenic effects of numerous chemicals and potential contribution to undervirilization of XY males
  - Placental aromatase deficiency
- Excess androgens cross placenta; virilization of XX female
  - Maternal androgen/exposure
- Endogenous/exogenous androgens can cross placenta; virilization of XX female

DIAGNOSIS AND EVALUATION

- Diagnosis and evaluation of DSD require early involvement of multidisciplinary team
  - Neonatologist, endocrinologist, urologic/gynecologic surgeon, psychologist, others
- An algorithm for the work-up of an infant with ambiguous genitalia is shown in Fig. 29.2
- Initial work-up must include clinical evaluation for signs of adrenal insufficiency and assessment of electrolytes/glucose
  - Higher likelihood of adrenal insufficiency if infant has nonpalpable gonads
- Karyotype should be obtained shortly after birth
  - Chromosomal sex will guide differential diagnosis and further testing
- Ultrasound, MRI, and/or genitogram can identify presence of gonads and internal genital structures
- Hormone studies may include gonadotropins, androgens, androgen precursors, and AMH
  - Assessment of androgen levels after hCG stimulation may aid in diagnosis of Leydig cell hypoplasia, testosterone biosynthesis defect, and 5α-reductase deficiency

TREATMENT

- Specific medical and surgical management depends upon disorder
  - Hydrocortisone ± mineralocorticoid replacement is life-sustaining in CAH with adrenal insufficiency (see "Adrenal Disorders" Chapter 30)
  - Feminizing or virilizing genitoplasty as needed for ambiguous external genitalia
  - Gonadectomy in cases of atrophic/dysplastic gonads due to increased risk of malignancy
  - Sex hormone replacement may be needed at time of puberty to develop secondary sex characteristics concordant with gender
- Gender assignment
  - Current practice is to assign gender as soon as possible (allowing for completion of diagnostic work-up)
    - Values regarding the timing of this decision may vary based upon personal/cultural perspective
  - Gender assignment is based upon numerous factors, including:
    - Consideration of sex steroid exposure in utero and anticipated future sex steroid production
    - Likelihood of adequate functional and cosmetic outcomes of virilizing versus feminizing surgery
    - Potential for future fertility
    - Individual cultural perspectives
  - Female gender is typically assigned to
    - Virilized XX infants with CAH
    - Nonvirilized XX infants with gonadal dysgenesis.
    - XY infants with complete AIS

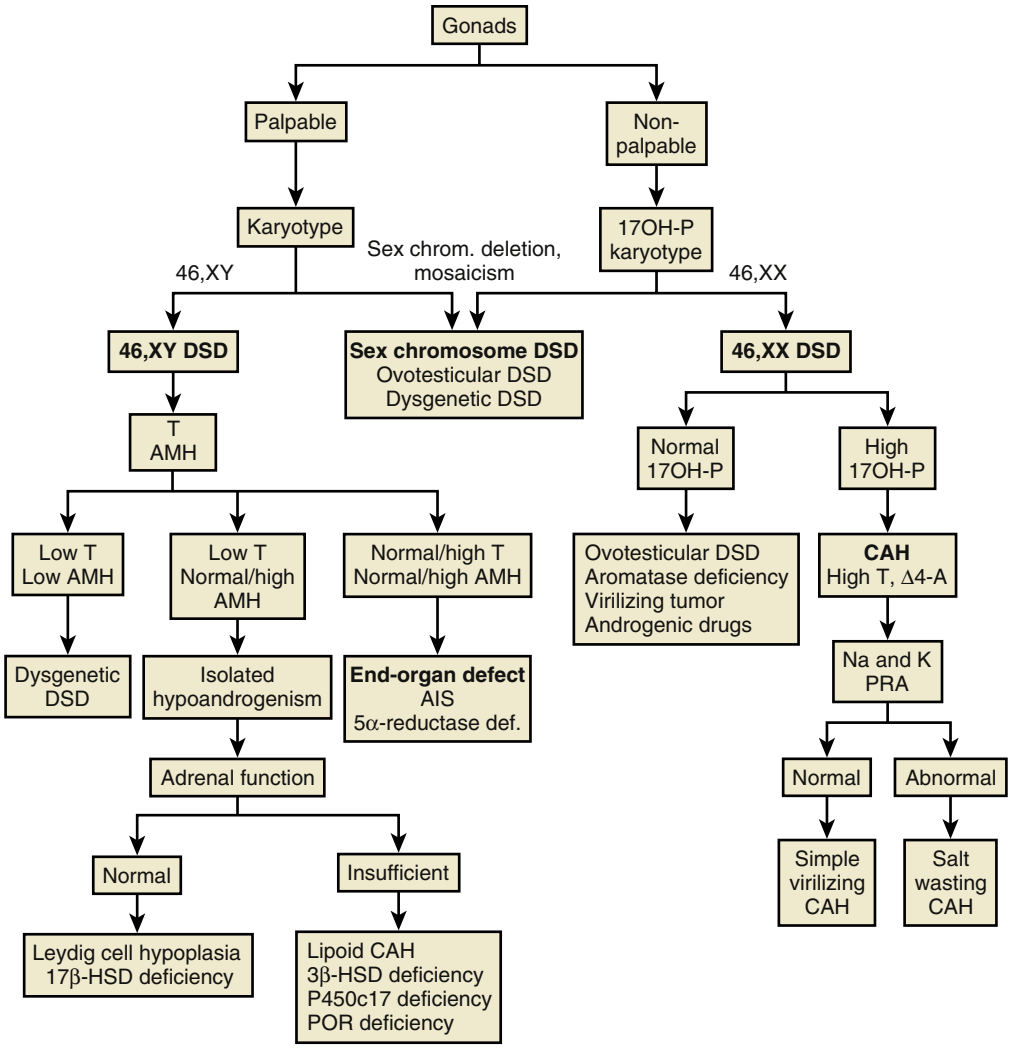

Fig. 29.2 Diagnostic work-up of suspected disorder of sexual development. *AMH,* Anti-müllerian hormone; *CAH,* congenital adrenal hyperplasia; *DSD,* disorders of sexual development. (From Jameson JL and Dulop RG. *Endocrinology: Adult and Pediatric.* 7th ed. Philadelphia: Elsevier; 2016:2086–2118.)

  - Male gender is typically assigned to undervirilized XY infants when virilizing genitoplasty is expected to be adequate or significant virilization is expected during puberty (as in 5α-reductase deficiency)
  - Incompletely virilized infants with XX or XY gonadal dysgenesis or sex chromosome mosaicism may be assigned male or female gender based upon degree of virilization of internal/external structures
- In many instances, long-term data on patient satisfaction with gender assignment are incomplete or inadequate
  - Parents should be allowed to make final decision of gender assignment

Developmental Anomalies of the Penis, Urethra, and Testicles

BASIC INFORMATION

- Hypospadias: urethral opening is located on ventral shaft of penis
  - Locations: glanular, coronal, subcoronal, midpenile, penoscrotal, scrotal, perineal
- Epispadias: urethral opening on the dorsal shaft of the penis
- Chordee: ventral curvature of penis
- Micropenis: Morphologically normal penis more than 2.5 SD below mean for size
  - Stretched penile length < 2 cm in term infants, cut-off depends on gestational age
- Aphallia: congenital absence of penis
- Cryptorchidism: undescended testes
  - Relatively common: ~4% of term males and ~30% of preterm males
    - ~10% of cases are bilateral
  - Location: abdominal, inguinal, gliding (can be pulled down), ectopic

CLINICAL PRESENTATION

- Typically present at birth
- May be seen in association with congenital syndromes with multiple midline defects

DIAGNOSIS AND EVALUATION

- Bilateral nonpalpable testes, or presence of severe hypospadias in association with cryptorchidism should be evaluated for DSD as described above

- Micropenis can be the result of hypothalamic/pituitary dysfunction (growth hormone, gonadotropins); pituitary function should be tested

TREATMENT

- Hypospadias/epispadias
  - Avoid circumcision in newborn period
  - Typical age of surgical repair is between 6–12 months
- Micropenis
  - Recombinant human growth hormone if deficient
  - A short course of testosterone (25 mg IM testosterone every 3–4 weeks over 3–4 months) can be given to increase penile size during infancy
- Cryptorchidism
  - Spontaneous descent unlikely after 4 months of age (corrected for gestational age)
  - Orchiopexy between 6–15 months of age
    - Orchiectomy if testis atrophic

Suggested Readings

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Krishnan S, Wisniewski AB. Ambiguous genitalia in the newborn. In: DeGroot LJ, Chrousos G, Dungan K, et al., eds. Endotext. South Dartmouth, MA: MDText.com, Inc. Available online: <https://www.ncbi.nlm.nih.gov/books/NB 68/> Accessed 21.8.2017.

Questions

1. A term infant is noted to have bilateral (BL) undescended testes palpable in the inguinal canal. Penis is morphologically normal with stretched penile length of 3.2 cm. Which of the following is true about the management of this condition?
   a. Immediate surgical consultation is necessary because this infant is at increased risk of germ cell malignancy
   b. Immediate endocrinologist evaluation is necessary because this infant likely has a disorder of sexual development
   c. Spontaneous descent is likely; surgery should be delayed until after mini-puberty of infancy
   d. Spontaneous descent is likely; surgery should be delayed until after onset of puberty

2. A term infant born with cleft palate and large atrial septal defect has a morphologically normal penis with stretched penile length of 1.5 cm. Which of the following hormone defects is the most likely cause of his micropenis?
   a. Hypothyroidism due to impaired synthesis of thyroid-stimulating hormone
   b. Growth hormone deficiency
   c. Testosterone deficiency due to 17β hydroxysteroid deficiency
   d. Dihydrotestosterone deficiency due to 5α-reductase deficiency

3. Which of the following conditions is typically associated with significant clinical virilization at the time of puberty?
   a. XY with 5α-reductase deficiency
   b. XY with complete androgen insensitivity
   c. XX with 21-hydroxylase CAH
   d. XY with 17β-HSD CAH

4. Who should make the final decision regarding gender assignment for an infant with ambiguous genitalia?
   a. The surgeon, who can best discuss functional and cosmetic outcomes of genitoplasty
   b. The endocrinologist, who can best discuss past and future hormone exposure and will be guiding any sex-hormone replacement at the time of puberty
   c. The neonatologist, after reviewing the consults from the surgeon, endocrinologist, geneticist, and psychologist
   d. The family, after hearing recommendations of the full multidisciplinary team

5. Which of the following statements regarding hormones and their actions in sexual differentiation is not correct?
   a. The production of estrogen by granulosa cells in an XX female causes regression of the primordial male internal genitalia structures.
   b. The production of anti-müllerian hormone by Sertoli cells in an XY male causes regression of the primordial female internal genitalia structures.
   c. The production of testosterone by Leydig cells in an XY male results in differentiation of internal structures into the epididymis, vas deferens, and seminal vesicle.
   d. The conversion of testosterone into dihydrotestosterone results in the virilization of external genitalia in an XY male.

6. Which of the following clinical presentations of ambiguous genitalia is associated with high risk of adrenal insufficiency?
   a. Testes palpable in a normally formed scrotum BL, microphallus with stretched penile length of 1 cm
   b. Testes palpable in a bifid scrotum BL, urethral opening at the ventral penile-scrotum junction
   c. Partially fused scrotum, phallic structure 1.5 cm in length, no palpable gonads
   d. Testis palpable on one side of scrotum, stretched penile length of 2.7 cm

7. A term infant is noted to have ambiguous genitalia. Karyotype was found to be XY, labs drawn on DOL 2 showed undetectable testosterone, normal AMH, normal androgen precursors including androstenedione and dehydroepiandrosterone (DHEA). HCG stimulation test showed no increase in testosterone levels. What is the most likely diagnosis?
   a. 17β-HSD deficiency
   b. Androgen insensitivity syndrome
   c. Leydig cell hypoplasia
   d. 5α-reductase deficiency

8. A term infant is found to have ambiguous genitalia. Rapid karyotype is XX, repeated androgen precursor hormones including 17-hydroxyprogesterone are normal. All of the following are appropriate next steps in the evaluation, except
   a. Questioning of mother to determine if any performance enhancing drugs used during early phases of pregnancy
   b. Questioning/examination of mother for new-onset hirsutism
   c. Genetic testing for presence of *SRY*
   d. Whole exome sequencing

9. Which of the following statements is true regarding gonadal dysgenesis?
   a. A karyotype showing XY sex chromosomes rules out gonadal dysgenesis
   b. Patients with gonadal dysgenesis are at increased risk of gonadoblastoma

c. All patients with XY gonadal dysgenesis should be assigned male gender at birth
d. Wolffian duct differentiation is unaffected in patients with XY gonadal dysgenesis

10. An infant with ambiguous genitalia has been found to have an XY karyotype. At which of the following time-points will a serum testosterone level be informative?
a. 1 day of life
b. 1 week of life
c. 2 months of age
d. 6 months of age
e. 16 years of age
f. a, b, c
g. a, c, e
h. All of the above

30 Adrenal Disorders

DAVID R. WEBER

Adrenal Hormone Physiology

BASIC INFORMATION

- Anatomy/histology (Fig. 30.1): adrenal glands, located superior to kidneys, composed of two distinct endocrine hormone producing regions: adrenal medulla and adrenal cortex
  - The adrenal medulla secretes catecholamine hormones (epinephrine, norepinephrine, dopamine), which are synthesized in chromaffin cells
  - The fully developed adrenal cortex is organized into three different zones that synthesize and secrete steroid hormones
    - Zona glomerulosa, which secretes mineralocorticoids (aldosterone)
    - Zona fasciculata, which secretes glucocorticoids (cortisol)
    - Zona reticularis, which secretes adrenal androgens (androstenedione and dehydroepiandrosterone [DHEA])
  - Fetal adrenal steroid hormone production occurs in a transient fetal zone
- Embryology/fetal development: the hormone secreting cells of the medulla are derived from the neuroectoderm; those of the cortex are derived from the mesoderm
  - The adrenal gland is formed and begins to secrete steroid hormones by weeks 8–10
  - The timing, location, and magnitude of steroid hormone synthesis after week 8 is regulated by the fetoplacental unit
    - Mother provides cholesterol for steroid hormone synthesis and receives progesterone and estrogens at levels necessary to maintain pregnancy
    - The placenta expresses enzymes (3β-hydroxysteroid dehydrogenase [3β-HSD], aromatase) necessary for the conversion of cholesterol into steroid hormone precursors and androgens into estrogens
    - The fetus receives steroid hormone precursors for glucocorticoid and androgen hormone synthesis; provides androgens to the placenta; receives estrogens necessary for organ/tissue development
  - The fetal zone of the adrenal cortex involutes rapidly following birth and is largely undetectable by 6–12 months
- Steroid hormone synthesis: steroid hormones are synthesized from cholesterol through a sequential series of enzymatic reactions (Fig. 30.2)
  - Steroid acute regulatory protein (StAR) is required for cholesterol transport to the inner mitochondrial membrane
  - Conversion of cholesterol into pregnenolone is the rate limiting step
  - Six enzymes expressed in the adrenal gland are responsible for steroidogenesis
    - Five members of the cytochrome P450 family (CYP11A1, CYP17, CYP21, CYP11B1, CYP11B2)
    - One additional steroid dehydrogenase (3β-HSD)
  - The final steps of androgen conversion from DHEA and androstenedione into testosterone and estrogen occur only outside of the adrenal glands (gonads and some peripheral tissues)

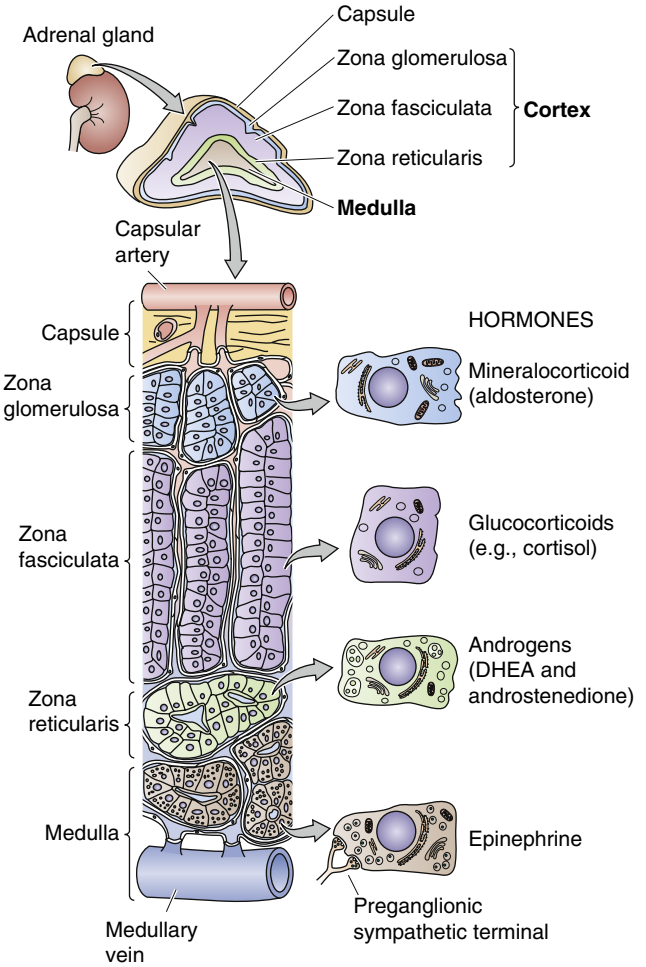

Fig. 30.1 The adrenal gland. Anatomy and organization of the adrenal gland. Catecholamine hormones are synthesized and secreted by the adrenal medulla; steroid hormones are synthesized and secreted by the adrenal cortex. (From Barrett EJ. *Medical Physiology.* 3rd ed. Philadelphia: Elsevier; 2016:1018–1034.)

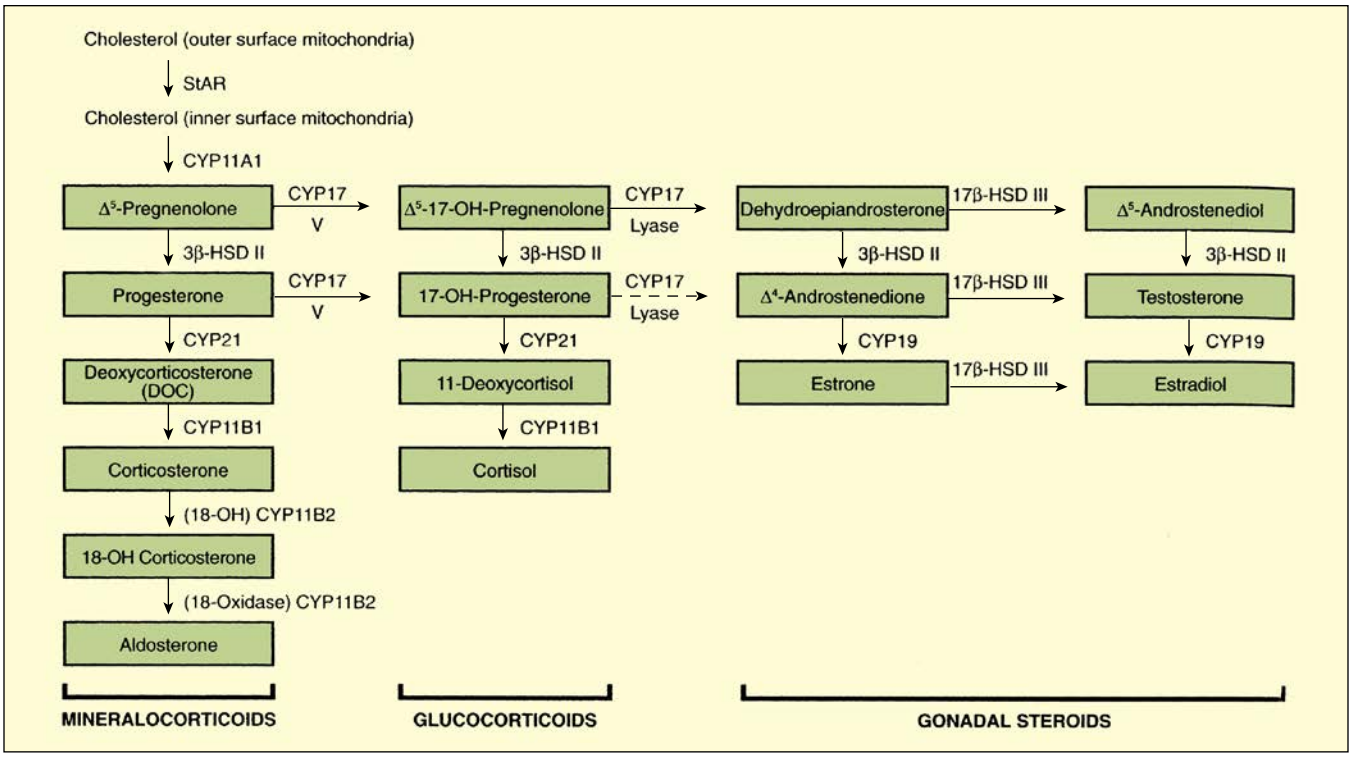

Fig. 30.2 Steroidogenesis. Diagram of the steroid synthesis pathway. Steroid hormones and precursors are shown in *boxes*, enzymes are shown next to *arrows*. *CYP11A1,* Cholesterol side chain cleavage enzyme; *CYP11B1,* 11β-hydroxylase; *CYP11B2,* 18-hydroxylase and 18-oxidase, also known as aldosterone synthetase; *CYP17,* 17α-hydroxylase and 17,20-lyase; *CYP19,* aromatase; *CYP21,* 21-hydroxylase. (From Marcdante KJ, Kliegman RM. *Nelson Essentials of Pediatrics*. 7th ed. Philadelphia: Elsevier; 2015:607–611.)

- Pathophysiology: steroid hormones exert their action through nuclear hormone receptors
  - Aldosterone functions to promote sodium and water retention, raise blood pressure, and lower potassium
    - It is regulated by the renin-angiotensin system, potassium concentration, and the pituitary hormone adrenocorticotropic hormone (ACTH)
  - Cortisol regulates both resting physiology and the stress response
    - The glucocorticoid receptor is expressed in most cells
    - Glucocorticoids affect cellular action via regulation of gene transcription
    - Key physiologic actions of glucocorticoids include regulation of glucose homeostasis; fat metabolism; cardiovascular reactivity and blood pressure; sodium and potassium balance; and mood and appetite
    - At high levels, glucocorticoids cause immunosuppression, inhibit growth
    - Cortisol secretion is under hypothalamic-pituitary control via the actions of corticotropin releasing hormone (hypothalamus) and ACTH (pituitary)
  - Adrenal androgens (androstenedione and DHEA) are sex steroids essential to the function of the fetoplacental unit as above and contribute to the development of secondary sex characteristics in puberty
    - The synthesis and secretion of adrenal androgens falls after birth and remains low until puberty
    - Increased production at puberty contributes to physical signs of adrenarche (acne, body odor, pubic/axillary hair)
    - Sustained elevations of ACTH increase androgen production with physiologic consequences in congenital adrenal hyperplasia (CAH)

Congenital Adrenal Hyperplasia

BASIC INFORMATION

- Inherited disease from a defect in one of the enzymes necessary for steroidogenesis
- All forms are autosomal recessive
- Incidence from 1:10,000–1:20,000 live births
- Mutations in CYP21 (21-hydroxylase) account for ~95% of all cases of CAH
  - 75% also have salt wasting due to aldosterone deficiency "classic salt wasting"
  - The remainder have aldosterone synthesis preserved "simple virilizing"
  - "Nonclassic 21 hydroxylase deficiency" is a mild form with preserved cortisol and aldosterone synthesis; typically presenting later in life with androgen excess
- Pathophysiology
  - Enzymatic defect results in decreased cortisol production
  - ACTH levels increase in response to low cortisol
  - High ACTH leads to excess stimulation of adrenal cortex and increased production of steroid hormone precursors
  - Steroid hormone precursors are shunted into the androgen synthesis pathway leading to increased production of sex steroids

Table 30.1 Identifying Features of Different Forms of Congenital Adrenal Hyperplasia Presenting in Infancy

CAH Form	Ambiguous Genitalia	Salt Wasting	Steroid Hormone Abnormalities	Other Notable Clinical Features
3β-HSD				
- Classical	M ± F	Yes	↑ *Δ⁵P, Δ⁵17-OHP, DHEA*	
- Nonclassical	F only	No	↑ PRA	
CYP11B1 (11β-hydroxylase CAH)				
- Classical	F only	Yes	↑ *11-DOC,11-deoxycortisol,* 17-OHP	▪ Hypertension
- Nonclassical	None	No	↓ PRA, aldosterone	▪ Infantile gynecomastia
CYP17 (17-hydroxylase/17,20 lysase CAH)	M only	No	↑ *11-DOC, corticosterone,* 18-hydroxycorticosterone ↓ PRA, aldosterone	▪ Low potassium hypertension
CYP21 (21-hydoxylase CAH)				
- Classical	F only	Yes	↑ *17-OHP*, Δ⁵P, Δ⁵17-OHP, DHEA, Δ⁵ –A	▪ Cause of >90% of all CAH
- Simple virilizing	F only	No[a]		
- Nonclassical	None	No	↑ PRA	
P450 oxidoreductase (POR deficiency)	M and F	No	↓ levels of all CYP dependent hormones ↑ progesterone, 17-OHP	▪ Skeletal and cranio/facial anomalies ▪ Maternal virilization
StAR / CYP11A1 (congenitial lipoid hyperplasia)	M only	Yes	↓/undetectable levels of all steroids ↑ PRA, ACTH	▪ Fatty infiltration adrenal glands ▪ Often fatal in infancy

3β-HSD, 3β-hydroxysteroid dehydrogenase; *11-DOC,* 11-deoxycorticosterone; *17-OHP,* 17-hydroxyprogesterone; *Δ⁵ –A,* androstenedione; *17-Δ⁵P,* pregnenolone; *Δ⁵17-OHP,* 17-hydrodxypregnenolone; *CAH,* congenital adrenal hyperplasia; *DHEA,* dehydroepiandrosterone; *PRA,* plasmin renin activity; *StAR,* steroidogenic acute regulatory protein.

[a]Elevated PRA and some degree of salt wasting may be present in infancy.

- Excess androgens/sex steroids result in virilization, rapid growth, early skeletal maturation, precocious puberty

CLINICAL PRESENTATION

- Clinical presentation in infancy varies based upon sex, genotype, and residual enzymatic activity (Table 30.1)
  - Cortisol deficiency
    - Hypoglycemia
    - Hypotension
    - Hyponatremia/hyperkalemia
    - Poor feeding/vomiting
    - Poor weight gain
    - Typically manifests 7–10 days after birth
  - Aldosterone deficiency (if present)
    - Salt wasting with hyponatremia, hyperkalemia
    - In combination with cortisol deficiency can lead to hypovolemic shock
    - Typically manifests 7–10 days after birth
  - Androgen excess
    - Virilization manifested as ambiguous genitalia at birth in females
    - Hyperpigmentation and/or penile enlargement may be present in males
    - Progressive androgen excess postnatally in males and females if untreated
  - Androgen deficiency
    - Mutations blocking androgen synthesis (StAR, CYP11A1, 3β-HSD, CYP17) may manifest as ambiguous genitalia in males

DIAGNOSIS AND EVALUATION

- Newborn screening for 21-hydroxylase CAH
  - Measure of 17-hydroxyprogesterone (17-OHP) in capillary blood on DOL 2
  - Levels drawn in the first 24 hours may be falsely elevated
  - 17-OHP levels are higher in premature infants and must be interpreted against local lab reference ranges according to gestational age and/or weight
  - Classic CAH is typically associated with 17-OHP levels >10,000 ng/dL (300 nmol/L), unaffected individuals typically have values <100 ng/dL (3 nmol/L)
  - Elevated or borderline levels should be repeated with venous blood sample
  - Diagnosis can be confirmed with ACTH stimulation testing or CYP21 sequencing
    - ACTH stimulation: measure serum 17-OHP at times 0 and 60 minutes after injection of 125 micrograms or 250 micrograms cosyntropin (Cortrosyn)
    - Stimulated 17-OHP >10,000 ng/dL c/w classic CAH
    - Stimulated 17-OHP <1000 ng/dL is normal
    - Stimulated 17-OHP between 1000–10,000 may represent nonclassic 21-hydroxylase CAH or another form of CAH (11β-hydroxylase)
  - Treatment should not be delayed while awaiting confirmation if clinical evidence of adrenal insufficiency or salt wasting
  - Diagnosis of salt wasting
    - Low sodium, high potassium
    - Elevated plasma renin activity (PRA)

- Low aldosterone
- Low aldosterone/PRA ratio

- Testing for other forms of CAH (non-21-hydroxylase disease)
  - Basal steroid profile: 17-OH pregnenolone, 17-OH progesterone, 11-deoxycorticosterone (DOC), 11-deoxycortisol, androstenedione, DHEA, cortisol
  - ACTH stimulation as described above, with additional steroids from above list added based upon clinical suspicion (see Table 30.1)

TREATMENT

- Goal of treatment for all forms of CAH is physiologic glucocorticoid and mineralocorticoid (if necessary) replacement
- Hydrocortisone 10–15 mg/m^2 of body surface area/day divided into three daily doses
  - Follow 17-OHP, androstenedione, testosterone, growth, physical exam for signs of androgen excess to evaluate treatment
  - ACTH is not a reliable marker of treatment adequacy
  - 17-OHP levels in the normal range typically indicate overtreatment
  - Overtreatment results in poor growth, obesity
- Stress dosing with hydrocortisone 50–100 mg/m^2 of body surface area/day
  - Fever, acute illness
  - Surgery requiring general anesthesia
  - Trauma
- Treatment of salt wasting (if present)
  - Infants typically require higher doses of fludrocortisone and salt supplements then older children
    - Low sodium content of breast milk/formula
    - Immaturity of kidneys to reabsorb sodium
  - Fludrocortisone 0.05–0.2 mg/day divided into one to two daily doses
  - NaCl supplements 1–2 g/day mixed into two to three feedings per day
  - Follow potassium, plasma renin activity, blood pressure to evaluate treatment
    - High potassium, PRA = increase fludrocortisone and/or NaCl dose
    - Suppressed PRA, hypertensive = decrease doses
- Prenatal treatment of affected fetuses remains experimental
  - Goal of treatment is to suppress adrenal androgen production and minimize prenatal virilization of affected females
  - Dexamethasone is used because it is not inactivated by placenta
  - Treatment instituted by 6–8 weeks in potentially affected fetuses
    - Prior to age when genetic confirmation/sex determination can be made
    - Therefore seven out of eight fetuses will be exposed to therapy with no potential benefit

Suggested Readings

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Questions

1. Which of the following hormones is not produced in the adrenal cortex?
   a. Cortisol
   b. Dopamine
   c. Aldosterone
   d. Dehydroepiandrosterone
   e. All of the above are produced in the adrenal cortex

2. Which of the following statements is true regarding fetal adrenal steroid hormone production?
   a. The adrenal glands develop and begin secreting hormones at 12 weeks.
   b. The histopathologic organization of the adrenal gland in the fetus is identical to that of an adult.
   c. The fetal adrenal gland does not express 3β-hydroxysteroid dehydrogenase and is therefore dependent on the placenta in order to synthesize cortisol.
   d. The cells of the adrenal cortex are derived from neuroectodermal precursors.

3. Which of the following genes (enzymes) is not expressed in the adrenal gland?
   a. CYP19 (aromatase)
   b. CYP21 (21-hydroxylase)
   c. CYP11B1 (11β-hydroxylase)
   d. CYP11B2 (11β-hydroxylase)
   e. All of the above enzymes are expressed and active in the adrenal gland

4. A patient is born with ambiguous genitalia and found to have a genetic defect leading to loss of function of CYP11A1 (cholesterol side-chain cleavage enzyme). Which of the following is likely true about the patient's karyotype?
   a. The karyotype is most likely XX, and the patient is overvirilized because of excess ACTH production.
   b. The karyotype is most likely XY, and the patient is undervirilized because of elevated 5α-reductase activity.
   c. The karyotype is mostly likely XX, and the patient is overvirilized because of decreased aromatase activity.
   d. The karyotype is most likely XY, and the patient is undervirilized because of insufficient substrate for androgen hormone biosynthesis.

5. You are alerted that one of your patients admitted for transient tachypnea of the newborn had an abnormal newborn screen for CAH. The patient is now a 5-day-old infant, born 40 weeks gestational age(WGA) via scheduled cesarean delivery, and has normal appearing male genitalia. Patient is clinically improving with decreasing fraction of inspired oxygen(FIO_2) requirement, normal blood pressure, and is tolerating feeds. The newborn screen specimen was drawn at 36 hours of age, and electrolytes drawn on DOL 1 showed normal sodium and potassium. What is the most appropriate next step?
   a. Immediately start hydrocortisone only at a dose of 15 mg/m^2/day.
   b. Immediately start hydrocortisone at a dose of 15 mg/m^2/day and fludrocortisone at a dose of 0.1 mg/day.
   c. Obtain a venous blood sample for measurement of 17-hydroxyprogesterone.
   d. Obtain a venous blood sample for measurement of 17-hydroxyprogesterone and electrolytes.

6. You are caring for a 1-week-old former 27 WGA infant with birth weight of 1000 grams transferred to your neonatal intensive care unit(NICU) from a community hospital on DOL 1. Patient is phenotypically male, intubated, and has required multiple fluid boluses, inotrope, and vasopressor support to maintain adequate perfusion. You receive a copy of the newborn screen report sent from the community hospital reporting a 17-hydroxyprogesterone value of 15,000 ng/dL. What is the appropriate next step?
   a. Do nothing; abnormal newborn screen result is likely the result of prematurity.
   b. Obtain a venous blood sample for measurement of 17-hydroxyprogesterone; wait until results are back to start hydrocortisone.
   c. Obtain a venous blood sample for measurement of 17-hydroxyprogesterone, and start hydrocortisone 100 mg/m^2/day.
   d. Obtain a venous blood sample for measurement of 17-hydroxyprogesterone, and start hydrocortisone 15 mg/m^2/day.

7. A newborn is found to have ambiguous genitalia including partial fusion of the labioscrotal folds and clitoromegaly. No testes are palpable on exam. Which of the following scenarios is NOT likely to be responsible for the clinical presentation in this case?
   a. 21-hydroxylase deficiency with karyotype XX
   b. 3-beta-hydroxysteroid dehydrogenase with karyotype XX
   c. 17-hydroxylase deficiency with karyotype XX
   d. 11-beta-hydroxylase deficiency with karyotype XX

8. An 11-month-old infant male in your unit is found to be hypertensive. Review of his medical records shows that blood pressures have been gradually increasing over the past several weeks to months. Which of the following is true regarding hypertension in congenital adrenal hyperplasia?
   a. Hypertension in 21-hydroxylase deficiency CAH is a sign that the Florinef dose needs to be increased.
   b. Serum aldosterone levels are typically low.
   c. The patient cannot have 17-hydroxlase deficiency because he has normal appearing genitalia.
   d. The majority of patients who will develop hypertension due to 11-beta-hydroxylase deficiency are identified on the CAH newborn screen.

9. Which of the following assessments is NOT standardly used to assess adequacy of medical treatment in a patient with classic 21-hydroxylase CAH?
   a. Linear growth
   b. Radiograph of left hand for bone age
   c. Androstenedione
   d. ACTH
   e. Plasma renin activity

10. You are asked to provide prenatal counseling to a mother who previously gave birth to a virilized female with 21-hydroxylase CAH. Which of the following statements should you provide to the mother?
   a. The incidence of CAH is the same in males and females.
   b. She has a one in four chance of having another virilized female with CAH.
   c. There is a decreased incidence of virilization in female infants with CAH born to mothers who take maintenance doses of hydrocortisone during pregnancy.
   d. Fetal sexual differentiation does not occur until the third trimester so she would only have to take dexamethasone for the last few weeks of her pregnancy to reduce the risk of virilization for an affected female.

31 Thyroid Disorders

DAVID R. WEBER

Thyroid Embryology and Physiology

BASIC INFORMATION

- Embryology: the thyroid gland is derived from two distinct embryologic tissues
  - Thyroid hormone producing cells (follicular cells): derived from endodermal cells lining floor of primitive pharynx (thyroid anlage)
    - Primordial thyroid identifiable at 4 weeks
    - Migrates downward through tongue to final location in anterior neck
    - Connected to tongue via thyroglossal duct
    - Thyroglossal duct can persist as thyroglossal duct cyst
  - Calcitonin producing cells (C-cells): derived from neural crest cells in the fourth and fifth pharyngeal pouches (ultimobranchial bodies)
    - Fuse with thyroid anlage to form the definitive thyroid gland by 8–10 weeks
- Physiology:
  - Thyroid hormone production in the follicular cell
    - Regulated by thyroid stimulating hormone (TSH) secreted from pituitary
    - Iodide transported into cell via sodium iodide symporter
    - Iodide is oxidized by thyroidal peroxidase and bound to tyrosine residues in thyroglobulin, forming monoiodotyrosine (MIT) and diiodotyrosine (DIT)
    - MIT and DIT molecules combine to form the thyroid hormones thyroxine (T_4) and triiodothyronine (T_3)
    - T_4 and T_3 are freed from thyroglobulin by enzymes and secreted in ~5:1 ratio
    - Majority of T_4 and T_3 circulates bound to thyroid binding globulin (TBG)
  - Peripheral metabolism and regulation of thyroid hormones
    - T_3 has three- to four-fold greater potency than T_4
    - T_3 generated from T_4 peripherally via type I and II deiodinase (D1, D2)
    - T_3 and T_4 are inactivated into reverse T_3 by type III deiodinase (D3)
  - Cellular action of thyroid hormones
    - Thyroid hormones enter peripheral cells via thyroid hormone transporters
    - Signal via the thyroid hormone receptor (THR)
      - Expressed in nearly all tissues
      - Critical regulator of growth and metabolism **(**Fig. 31.1**)**
- Fetal thyroid physiology
  - Maternal T_4 crosses placenta and essential for development until fetal thyroid hormone production begins
    - Fetal thyroid hormone synthesis begins by 12–14 weeks
    - Hypothalamic-pituitary-thyroid control in place by 18–20 weeks
  - T_3 and TSH do not cross placenta
  - TSH receptor stimulating and blocking antibodies can cross the placenta
- Thyroid physiology at transition
  - TSH surge at birth in response to exposure to colder ex utero environment
    - TSH peaks within 24 hours, then falls rapidly; risk of false-positive TSH screen drawn in first 24 hours
    - T_4 peaks on day of life (DOL) 2
  - TSH and T_4 peaks are lower in premature infants, though still present

Congenital Hypothyroidism

BASIC INFORMATION

- Epidemiology: incidence of congenital hypothyroidism is 1:2500 to 1:4000 live births
- Etiology
  - Thyroid dysgenesis: defect in thyroid development; ~80–90% of cases
    - Ectopic thyroid (failure of thyroid gland to descend completely)
    - Hypoplasia (incomplete development of gland)
    - Athyreosis (complete absence of gland)
    - Genes implicated include *TTF1, TSHR, PAX8,* and others
  - Thyroid dyshormonogenesis: defect in thyroid hormone synthesis; 10%–20% of cases
    - Genetic defects in *NIS, TPO, TG, NIS, THOX-2*, and others
  - Central hypothyroidism: defect in hypothalamic/pituitary thyroid control; rare
    - Genetic defects in *THRH, PROP, PIT-1*, and others
    - May be associated with other pituitary hormone defects
  - Peripheral forms of hypothyroidism: rare
    - Defective thyroid hormone transport: MCT8 deficiency, others
    - Consumptive hypothyroidism
      - Thyroid hormone deactivation because of D3 overexpression, most commonly in infantile hepatic hemangiomas

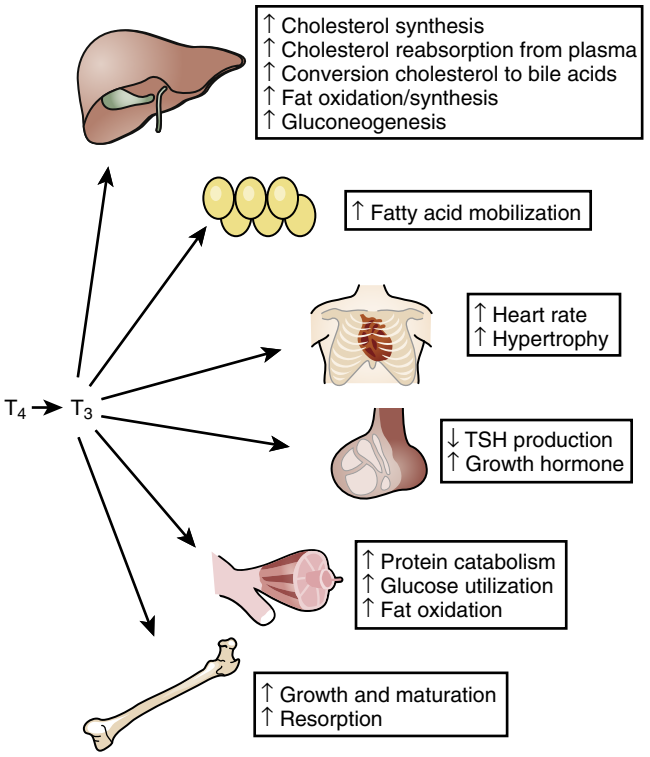

Fig. 31.1 Thyroid hormone action. Thyroid hormone acts in nearly all body tissues to promote growth and regulate metabolism. (From Wondisford FE. *Endocrinology: Adult and Pediatric*. 7th ed. Philadelphia: Elsevier; 2016:1336–1349.)

- Transient hypothyroidism
  - Exposure to maternal antithyroid medications in utero
  - Placental passage of maternal TSH receptor-blocking antibodies
  - Endemic iodide deficiency
  - Prenatal or postnatal iodide exposure
    - Inhibits iodide organification (Wolff-Chaikoff effect)
  - Transient hypothyroxinemia of prematurity (THOP)
    - Most common in premature infants less than 30 weeks gestational age (WGA)
    - May be associated with adverse neurodevelopmental outcomes. Insufficient evidence to determine if this relationship is cause or effect

CLINICAL PRESENTATION

- Signs/symptoms usually not present at birth, but if untreated the following may develop:
  - Jaundice
  - Lethargy/hypotonia
  - Poor feeding
  - Constipation
  - Hypothermia
  - Macroglossia
  - Large/persistent anterior fontanelle
  - Intrauterine growth restriction (IUGR)/failure to thrive
  - Progressive developmental delay

DIAGNOSIS AND EVALUATION

- Newborn screening from capillary blood spot
  - Primary TSH screen with back-up T_4 for elevated TSH
    - Cutoff selected to detect elevated TSH
    - False-positive result if drawn in first 24–48 hours (TSH surge)
    - False-negative result in newborns with central hypothyroidism
  - Primary T_4 screen with back-up TSH for low T_4
    - Cutoff set locally to detect low T_4
    - False-positive result in newborns with TBG deficiency
      - Most commonly because of X-linked mutation in *SERPINA7*
- Abnormal newborn screen
  - Confirm with venous TSH, T_4 (or free T_4), DOL 2 or later
    - Choice of T_4 versus free T_4 depends upon local lab
    - Free T_4 should be checked if TBG deficiency suspected, as patient is euthyroid with normal free T_4 and TSH, but low T_4
    - Elevated TSH with low T_4 (or free T_4) consistent with (c/w) primary hypothyroidism
      - Thyroid ultrasound or thyroid scan can be performed, but not required
    - Low/normal TSH with low T_4
      - Central hypothyroidism
        - Testing of other pituitary hormones should be done
        - Consider brain imaging
    - THOP (see earlier)
- Labs and clinical features in conditions of abnormal thyroid physiology are shown in Table 31.1

TREATMENT

- Goal is to attain normal thyroid hormone levels as soon as possible
  - Treatment should not be delayed if confirmatory labs not readily available
  - Normalize T_4 within 2 weeks
  - Normalize TSH within 4 weeks
  - Follow labs every 1–3 months for the first 12 months
- Levothyroxine (T_4) initiated at 10–15 micrograms/kg/day
  - Crushed tablets given with 1–2 mL of water/breast milk/formula are preferred
  - Liquid preparations exist, questions remain about variable absorption and stability
  - Intravenous dose of levothyroxine is one-half the oral dose in patients who cannot take enteral medications
- Monitoring
  - Labs: maintain T_4 (or free T_4) in the upper one-half of the normal range and TSH in the normal range for the 1st year of life
  - Growth: length should be checked regularly; growth rate should be normal
  - Cognitive development: assessed per routine developmental screening guidelines
    - Infants with adequately treated hypothyroidism should meet milestones
- Follow-up
  - At 3 years of age, consider trial off therapy to determine if hypothyroidism
    - Initial TSH value >50 mIU/L suggests permanent hypothyroidism
    - A rise in TSH or fall in T_4 (or free T_4) 30–45 days after stopping therapy indicates need for continued therapy
- Transient hypothyroidism

Table 31.1 Laboratory Findings and Clinical Findings in Conditions of Abnormal Thyroid Hormone Physiology Affecting Neonates

Condition	TSH	T_4	Free T_4	T_3	Free T_3	Reverse T_3	Notable Clinical Features
Congenital Hypothyroidism - Primary	↑	↓	↓	↓	↓	↓/nml	- AGA/LGA - Jaundice - Lethargy - Hypotonia
Congenital Hypothyroidism - Secondary	↓/nml/↑	↓	↓	↓	↓	↓/nml	
Consumptive Hypothyroidism	↑	↓	↓	↓	↓	↑	- Hemangioma
Neonatal Hyperthyroidism	↓	↑	↑	↑	↑	↑/nml	- Tachycardia - Hypertension - IUGR - FTT - Exophthalmos
Transient Hypothyroxinemia of Prematurity	nml	↓	↓	↓	↓	↓/nml	- <30 WGA - No abnormal clinical phenotype
TBG/other thyroid hormone carrier deficiency	nml	↓	nml	↓	nml	nml	- No abnormal clinical phenotype
MCT8/other thyroid hormone transport deficiency	nml/↑	nml/↓	nml/↓	↑	↑	↓	- Hypotonia - Cognitive impairment - Neurologic abnormalities

AGA, appropriate for gestational age; FTT, failure to thrive; IUGR, intrauterine growth restriction; LGA, large for gestational age; MCT8, monocarboxylate transporter 8; nml, normal; TBG, thyroid binding globulin; *TSH*, thyroid stimulating hormone; *T_3*, triiodothyronine; *T_4*, thyroxine; *WGA*, weeks gestational age.

- Neonatal hypothyroidism because of maternal antithyroid treatment or blocking antibodies requires short-term levothyroxine therapy as above
- Transient hypothyroidism as a result of iodine deficiency is treated with levothyroxine and iodine supplementation (90 micrograms/day in term infants)
- Current evidence does not support routine treatment of THOP

Neonatal Hyperthyroidism

BASIC INFORMATION

- Epidemiology: neonatal hyperthyroidism is rare and usually due to passage of TSH receptor stimulating antibodies (TRAb) in setting of maternal Graves disease
  - Antibodies can persist in maternal circulation for years after definitive treatment with thyroidectomy or radioactive ablation
  - 1%–10% of neonates born to mothers with Graves will develop thyrotoxicosis
  - Rarely, maternal Hashimoto thyroiditis can cause passage of TRAb
  - Rare genetic diseases that cause neonatal hyperthyroidism include McCune-Albright syndrome (activating mutation in *GNAS*) or activating mutations in the TSH receptor

CLINICAL PRESENTATION

- Neonatal Graves typically presents within the 1st week, but may be delayed up to 6–8 weeks
  - Presentation is delayed in mothers treated with antithyroid med during pregnancy
- Fetal tachycardia or goiter may be detected in utero in some, but not all cases
  - Increased risk of IUGR and premature delivery with fetal thyrotoxicosis
  - Microcephaly, craniosynostosis, exophthalmos may be present at birth
- Signs/symptoms of neonatal thyrotoxicosis
  - Tachycardia/hypertension
  - Jitters/poor sleep
  - Spitting up/vomiting
  - Failure to gain weight/weight loss

DIAGNOSIS AND EVALUATION

- All infants born to women with history of Graves should be monitored closely
  - Maternal TRAb levels should be checked in second and third trimesters
  - Higher risk of neonatal Graves in mothers with TRAb greater three- to five-fold the upper limit
- TSH, T_4 (or free T_4), T_3. TRAb should be assessed from cord blood or venous sample in high-risk infants (+ maternal TRAb; history of neonatal Graves with previous pregnancy) at birth
  - Suppressed TSH and elevated T_4 consistent with neonatal Graves
  - Initial lab values may be normal in mothers treated with antithyroid meds
- Low-risk infants (low maternal TRAb) or normal TRAb at birth can be followed clinically

TREATMENT

- Beta blocker to control symptoms of hyperthyroidism
  - Propranolol 1–2 mg/kg/day divided every 8 hours

- Antithyroid medication to reduce thyroid hormone production
  - Methimazole 0.25–1 mg/kg/day divided every 12 hours
  - Iodine (Lugol solution 126 mg/mL) can be added at 1 drop (8 mg)/day for 1–2 weeks
- Glucocorticoids can be considered in severely symptomatic infants
  - Decrease thyroid hormone production; decrease conversion of T_4 to T_3
- Labs monitored every 1–2 weeks; goal is normal TSH, T_4 (or free T_4), T_3 levels
- Self-limited, typically resolves within 3–6 weeks; may persist 6 months or longer
- Neonatal thyrotoxicosis in the absence of maternal Graves disease or that does not resolve within 6 months should be further evaluated for genetic etiology

Suggested Readings

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Zimmerman D. Fetal and neonatal hyperthyroidism. *Thyroid*. 1999;9(7):727–733.

Questions

1. Which of the following statements is true regarding the potential effects of maternal Graves disease on the fetus/neonate?
   a. Maternal T_3 is inactivated by the placenta, and therefore there is no risk of fetal hyperthyroidism.
   b. The fetus/neonate will be at increased risk of hypothyroidism.
   c. There is no risk to the fetus/neonate in mothers who had definitive therapy for Graves with thyroidectomy prior to conception.
   d. Maternal antithyroid therapy with methimazole or propylthiouracil (PTU) should be discontinued during pregnancy because of the risk of birth defects.

2. A full-term, newborn male is found to have an abnormal thyroid screen with elevated TSH of 500 mIU/mL and low T_4 of 2 micrograms/dL. Which of the following is not a possible cause of this child's hypothyroidism?
   a. Activating mutation in the TSH receptor
   b. Overexpression of deiodinase 3
   c. Inactivating mutation in the *NIS* gene
   d. Presence of a lingual thyroid gland

3. A 36 WGA infant born to a 16-year-old first-time mother has a hypoglycemic seizure on DOL 4. Brain imaging reveals absence of corpus callosum and hypoplasia of optic nerves. Which pattern of thyroid hormone tests is most likely to be present?
   a. Elevated TSH, low T_4, low free T_4
   b. Normal TSH, low T_4, normal free T_4
   c. Normal TSH, low T_4, low free T_4
   d. Low TSH, elevated T_4, elevated free T_4

4. All of the following statements are true regarding fetal goiter except:
   a. A finding of fetal goiter on prenatal ultrasound is pathognomonic for the presence of thyroid dyshormonogenesis in the fetus.
   b. It is associated with increased risk of fetal upper airway obstruction at delivery.
   c. There is increased incidence of fetal goiter in areas where iodine deficiency is endemic.
   d. Fetal thyroid testing can be performed via percutaneous umbilical vein sampling after 20 weeks if fetal thyroid status is uncertain.

5. You are notified that an otherwise healthy term infant had an elevated TSH and low T_4 on the newborn screen. All of the following statements are true regarding the management of congenital hypothyroidism in this infant except:
   a. The starting dose of levothyroxine will be 15 micrograms/kg/day.
   b. The infant should be discharged on an oral liquid preparation of levothyroxine because it is easier to administer.
   c. Serum T_4 levels should be maintained in the upper one-half of the normal range for the first year of life.
   d. Feeding intolerance with poor weight gain at the first follow-up visit may be a sign of overtreatment.

6. An otherwise healthy appropriate for gestational age (AGA) 34 WGA male is found to have an abnormal thyroid newborn screen on a blood spot obtained on DOL 2. You live in a state with a primary T_4 screening strategy. Follow up venous blood sample on DOL 4 showed a normal TSH for age, low T_3, low T_4, normal free T_4, normal free T_3. Which of the following statements is true about the most common form of his condition?
   a. He will be at risk for cognitive impairment if not started on levothyroxine immediately.
   b. His lab abnormalities are due to the fact that he was born prematurely.
   c. Evaluation of maternal serum would reveal elevated TRAb.
   d. He will be able to pass on his condition to a daughter, but not to a son.

7. An infant with which of the following conditions would be most likely to have elevated reverse T_3 levels?
   a. Congenital hypothyroidism due to athyreosis
   b. Consumptive hypothyroidism
   c. TBG deficiency due to *SERPIN7A* mutation
   d. Transient hypothyroxinemia of prematurity

8. Which of the following statements is true regarding the treatment of neonatal Graves disease?
   a. All infants born to mothers with Graves disease should be started on prophylactic antithyroid therapy with methimazole at birth.
   b. Prednisone dosed at 1 mg/kg/day is the first-line therapy for neonatal thyrotoxicosis.
   c. Infants with suppressed TSH and elevated T_4 levels at birth will require lifelong therapy.
   d. Treatment with Lugol solution is limited to 1–2 weeks because of "escape" from the Wolff-Chaikoff effect.

9. A term infant male with neonatal seizures is found to have abnormal thyroid studies, including elevated T_3 and free T_3 but low-normal T_4 and free T_4 levels. Which of the following statements is true regarding this condition?
   a. High-dose levothyroxine (T_4) treatment should be instituted.
   b. High-dose Cytomel (T_3) treatment should be instituted.
   c. The clinical manifestations of this condition result from low intracellular concentrations of T_3 in neurons.
   d. It is inherited in an autosomal recessive manner.

32 Glucose Metabolism

DAVID R. WEBER

Physiology of Energy Metabolism

BASIC INFORMATION

- Adenosine triphosphate (ATP) provides the energy for cellular metabolism
- Three major fuel sources of ATP: carbohydrates, fat, protein
- Sufficient ATP availability for cellular function is achieved through a complex web of hormonal, neural, and enzymatic regulation termed intermediary metabolism
- Carbohydrate metabolism
  - ATP generated from glucose via glycolysis
  - Plasma glucose maintained in tight range (70–100 mg/dL)
    - Hepatic glucose production (fasting/basal state)
      - Glycogenolysis (breakdown of glycogen to form glucose)
      - Gluconeogenesis (synthesis of glucose from substrates including lactate, glycerol, gluconeogenic amino acids); occurs mostly in liver, also in kidneys, brain, muscle, gut
    - Gastrointestinal absorption (fed state)
      - Regulated by rate of gastric emptying and controlled by incretins (GLP-1, CCK, others), vagal tone
      - Glucose absorbed via sodium-dependent SGLT-1 in small intestine
    - Glucose disposal
      - Transported into cells via GLUT transporters
        - GLUT-1 (red blood cell [RBC], blood-brain barrier) is glucose dependent
        - GLUT-2 (pancreas, liver, kidney, gut) is the glucose sensor
        - GLUT-3 (neurons, placenta)
        - GLUT-4 (liver, fat) is insulin dependent
      - Insulin released from pancreatic β-cells
        - Promote glucose uptake
        - Promote glycogenesis and block glycogenolysis
        - Promote lipogenesis and block lipolysis
- Fat metabolism
  - Adipose tissue is largest energy storage depot in the body
    - Lipolysis: catabolism of triglycerides into glycerol and free fatty acids
      - Glycerol used by liver for gluconeogenesis
      - Free fatty acids (FFA) generate ATP via β-oxidation and TCA cycle
        - Can also be converted into ketone bodies by the liver
        - Ketones used by brain, peripheral tissue as alternate fuel source for TCA cycle and ATP generation
- Protein metabolism
  - Catabolism of muscle during fasting releases amino acids into the circulation
    - Gluconeogenic amino acids (alanine, others) used for gluconeogenesis
    - Ketogenic amino acids (leucine, lysine, others) converted into ketone bodies
- Counterregulatory hormones
  - Secreted in response to falling blood sugar
    - Glucagon (pancreas): plasma glucose <65–70 mg/dL
      - ↑ Glycogenolysis and gluconeogenesis (liver)
    - Epinephrine (adrenal medulla): plasma glucose <65–70 mg/dL
      - ↑ Glycogenolysis and gluconeogenesis (liver), antagonize insulin
    - Cortisol/growth hormone (adrenal/pituitary): plasma glucose <65 mg/dL
      - Antagonize insulin, mobilize fatty acids, mobilize amino acids
- Fetal energy metabolism
  - Placental glucose accounts for majority (~65%) of fetal energy source
    - Glucose provides substrate for glycogen and adipose synthesis and deposition
    - Fetus is capable of glycogenolysis, gluconeogenesis, and lipolysis
    - Protective mechanism in setting maternal starvation
  - Lactate and ketone bodies also cross the placenta and provide an alternate fuel source
- Energy metabolism during transition to postnatal life
  - Acute loss in placental glucose transfer results in transient decline in plasma glucose
    - Stimulate hormonal response to raise and stabilize glucose
      - Increased secretion of counterregulatory hormones
      - Decreased secretion of insulin
    - Glycogen stores depleted in hours, infant becomes dependent on gluconeogenesis from amino acids, lactate, fatty acids; and oxidation of ketones from ketogenesis
  - Plasma glucose levels rise to normal child/adult levels (70–100 mg/dL) by 48 hours

Hypoglycemia

BASIC INFORMATION

- Hypoglycemia: glucose level at which brain function begins to be impaired

- By convention, glucose concentration reported as plasma glucose; whole blood glucose concentration is 10%–20% lower than plasma glucose
- Controversy exists regarding numerical cut-off to define hypoglycemia in neonates
- Level varies by age, availability of alternate fuel availability (ketones, lactate)
  - Brain glucose utilization impaired when plasma glucose <55–65 mg/dL
  - Conditions limiting availability of ketones/lactate increase risk of CNS damage and require maintenance of higher plasma glucose levels
- Generally, <48 hours of life hypoglycemia defined as plasma glucose <50–60 mg/dL
- Generally, ≥48 hours of life, hypoglycemia defined as plasma glucose <60–70 mg/dL
  - Above targets individualized based on risk factors
  - Glucose levels between 50–60 mg/dL may be tolerated beyond 48 hours in premature infants
  - Presence of metabolic disease: glucose levels must be maintained >70 mg/dL in hyperinsulinism where ketogenesis is impaired

CLINICAL PRESENTATION

- Signs/symptoms
  - Often asymptomatic
  - Jitteriness, irritability, lethargy, seizures

intrauterine growth restriction (IUGR), preterm, large for gestational age (LGA), and infant of diabetic mother (IDM) are associated with increased hypoglycemia risk

DIAGNOSIS AND EVALUATION

- Confirm low plasma glucose on glucometer with venous sample
- Full diagnostic work-up typically delayed until >48 hours
- Critical sample ± glucagon stimulation test to establish diagnosis (Tables 32.1 and 32.2)
  - Follow-up testing may be required based upon results
- Transient forms of hypoglycemia
  - Infant of diabetic mother: hyperinsulinism
  - IUGR/SGA/prematurity: limited glycogen stores
  - LGA infants: etiology unclear
  - Drug-induced
    - Surreptitious insulin, oral hypoglycemic agents
    - Ethanol, β-blocker, terbutaline
    - Suppressed C peptide with detectable insulin suggests exogenous exposure
  - Perinatal stress induced hyperinsulinism
    - May be severe, can last up to 12 months before resolving
  - Late dumping
    - Relatively common in infants with G-tubes and Nissen fundoplication
    - Characterized by hypoglycemia 1–2 hours post-feed
- Congenital disorders of hypoglycemia
  - Hypopituitarism (growth hormone [GH] and/or cortisol deficiency)
    - Low GH/cortisol on critical sample must be confirmed with provocative test

Table 32.1 Clinical Evaluation of Neonatal Hypoglycemia

1. Critical Sample (obtained with plasma glucose < 50 mg/dL)
- Basic metabolic panel
- Insulin
- C peptide
- β-hydroxybutyrate
- Free fatty acids
- IGF-BP1
- Growth hormone[a]
- Cortisol[a]
- Ammonia
- Lactate
- Acylcarnitine profile
- Free and total carnitine

2. Glucagon Stimulation Test
- Performed when blood glucose < 50 mg/dL
- Administer 1 mg glucagon IM/IV[b]
- Check blood glucose q10 minutes for 40 minutes
- An increase of blood glucose > 30 mg/dL is consistent with hyperinsulinism
- Test can be aborted if blood glucose has not risen by 20 mg/dL at 20 minutes
- Provide dextrose bolus (D10 at 2 cc/kg or similar) to restore normoglycemia

[a]Low cortisol and/or growth hormone is NOT DIAGNOSTIC of pituitary hormone deficiency. Appropriate follow-up provocative testing is required to make diagnosis.
[b]0.5 mg can be considered for premature or low birthweight infants.

  - Congenital hyperinsulinism (HI)
    - + Response to glucagon stimulation test
  - Beckwith-Wiedemann syndrome (BWS)
    - Hyperinsulinism
    - Often with macrosomia, hemihypertrophy
  - Glycogen storage disease (GSD)
    - Hepatomegaly (except GSD 0)
  - Disorders of fatty acid oxidation
    - Will have associated abnormalities on acylcarnitine profile
  - Congenital disorder of glycosylation

TREATMENT

- All hypoglycemia: enteral/parenteral dextrose to maintain plasma glucose above target
  - Age <48 hours, typical target plasma glucose >50 mg/dL
  - Age ≥48 hours, typical target plasma glucose >60 mg/dL
  - Target glucose >70 mg/dL for all patients with suspected hypoglycemia disorder
    - Suppressed ketogenesis and lipolysis limits availability of alternate fuels
- Hyperinsulinism
  - Glucose infusion rates (GIR) for congenital hyperinsulinism often exceed 20–30 mg/kg/min (normal ~4–6 mg/kg/min); dextrose fluid concentrations >12.5% require central line
  - Medical management
    - Glucagon infused IV at 1 mg/24 hours (independent of weight)
      - Can also be given PRN as subcutaneous (SC)/intramuscular (IM) injection
    - Diazoxide
      - Inhibits insulin secretion by opening the K_{ATP} channel
      - Effective in stress-induced HI, some forms of congenital HI

Table 32.2 Laboratory Findings on Critical Sample in Various Types of Neonatal Hypoglycemia

LABORATORY FINDINGS OBTAINED FROM CRITICAL SAMPLE (PLASMA GLUCOSE < 50 MG/DL)			
No Acidosis ↓ BOHB, ↓ FFA	**No Acidosis ↓ BOHB, ↑ FFA**	**+ Acidosis ↑ Lactate**	**+ Acidosis ↑ BOHB**
■ Congenital HI[a] ■ Stress HI[a] ■ Beckwith-Wiedemann ■ GH/cortisol deficiency[b] ■ Congenital disorder of glycosylation ■ Drug induced[c]	■ Disorder of fatty acid oxidation	■ GSD (type 0,1) ■ Fructose-1,6-bisphosphotase deficiency ■ Pyruvate carboxylase deficiency	■ GSD (types 3, 6, 9, 10) ■ Ketotic hypoglycemia ■ GH/cortisol[b] deficiency ■ Delayed transition in prematurity

BOHB, beta-hydroxybutyrate; FFA, free fatty acids; GH, growth hormone; *GSD*, glycogen-storage disease; *HI,* hyperinsulinism.
[a]Diagnosis of hyperinsulinism confirmed with glucagon stimulation test, consider genetic testing if suspicion for congenital HI.
[b]Low GH or cortisol on critical sample not sufficient for diagnosis, provocative testing required.
[c]Insulin, oral hypoglycemics, β-blockers, ethanol, terbutaline.

- Effective dose ranges from 5–20 mg/kg/day divided bid
- Potential side effects: edema/pulmonary HTN, cytopenia, hypertrichosis
  - Consider concomitant diuretics
  - Follow CBC every 3–6 months
- Octreotide
  - Somatostatin analog, inhibits insulin secretion
  - Given via intermittent SC injection or continuous IV (2–20 micrograms/kg/day)
    - Tachyphylaxis is common
  - May be associated with risk of necrotizing enterocolitis in young infants
- Surgical management: patients with congenital HI who fail medical management are surgical candidates
  - Transfer to specialized center is imperative
  - Genetics and imaging (PET/CT) to determine focal versus diffuse HI
    - Focal resection versus near-total (95%–98%) pancreatectomy

- Glycogen storage diseases
  - Continuous glucose delivery with frequent daytime feeds, continuous feeds overnight
  - Older children transitioned to uncooked cornstarch administered multiple times/night
- Disorders of fatty acid oxidation
  - Continuous glucose delivery, dietary medication/supplementation targeted to defect
- Late dumping
  - Continuous feeds; slowing of bolus rate including tapering of rate
  - Acarbose 12.5–75 mg/dose given with each bolus feed

Hyperglycemia

BASIC INFORMATION

- Persistent hyperglycemia is uncommon in neonates
- Controversy exists regarding numerical cut-off to define hyperglycemia in neonates
  - Plasma glucose >180 mg/dL is often used

CLINICAL PRESENTATION

- Often asymptomatic initially
- Polyuria, polydipsia, polyphagia
- Failure to thrive or weight loss
- IUGR/VLBW (very low birth weight)/premature infants at increased risk

DIAGNOSIS AND EVALUATION

- Confirm elevated plasma glucose on glucometer with venous sample
- Transient forms of hyperglycemia
  - Infection
  - Exposure to high dose enteral/parenteral glucocorticoids
  - Delayed maturation of physiologic mechanisms for glucose disposal
    - Exacerbated with exposure to high glucose infusion rate (GIR) in TPN
  - Transient neonatal diabetes
    - Onset in first week of life, median duration is 12 weeks
    - Most cases are a result of chromosome 6q24 mutations
- Permanent forms of hyperglycemia
  - Permanent neonatal diabetes
    - Median onset ~5 weeks, range is birth–6 months
    - Most cases caused by mutations resulting in β-cell under secretion of insulin
    - caused by β cell channelopathy
  - Type 1 diabetes
    - Exceedingly uncommon before 6 months of age
    - Autoimmune mediated destruction of β-cell
  - Congenital syndromes of insulin resistance
    - Insulin receptor mutations (Donohue and Rabson-Mendenhall syndromes)

TREATMENT

- Generally, goal to maintain plasma glucose between 80–180 mg/dL
- Initial response

- Reduce GIR
- Hydration, especially if evidence of osmotic diuresis

- Persistent hyperglycemia requires treatment with insulin
  - Initially, IV insulin infusion ranging from 0.03–0.1 units/kg/hour to stabilize glucose
  - Transitioned to SQ insulin when clinically stable, doses range from 0.2–2 units/kg/day

Suggested Readings

Palladino AA, Bennett MJ, Stanley CA. Hyperinsulinism in infancy and childhood: when an insulin level is not always enough. *Clin Chem*. 2008;54(2):256–263.

Thornton PS, Stanley CA, De Leon DD, et al. Recommendations from the pediatric endocrine society for evaluation and management of persistent hypoglycemia in neonates, infants, and children. *J Pediatr*. 2015;167:238–245.

Questions

1. A term infant is readmitted to the neonatal intensive care unit (NICU) at 3 weeks of age in shock with cardiorespiratory failure and oliguric renal failure. Labs at presentation showed plasma glucose of 25 mg/dL, metabolic acidosis with elevated lactate. Hepatomegaly is noted on physical exam. Parents state that the infant had not been feeding well for the past 3 days and slept through the night last night without waking to feed. What is the most likely diagnosis?
   a. Congenital hyperinsulinism due to K_{ATP} channel mutation
   b. Glycogen synthase deficiency
   c. Glucose 6-phosphatase deficiency
   d. Disorder of fatty acid oxidation

2. Laboratory results of a critical sample show venous glucose of 45 mg/dL, cortisol 2 μ/dL (normal stressed value >18 micrograms/dL), growth hormone 12 ng/mL, free fatty acids 0.1 mmol/L (normal <1 mmol/L), β-hydroxybutyrate 0.2 mmol/L (normal <1.5 mmol/L). Plasma glucose increased to 80 mg/dL 30 minutes after administration of 1 mg glucagon Which of the following is an appropriate next step?
   a. Start hydrocortisone 15 mg/m^2/BSA per day
   b. Perform an arginine/clonidine growth hormone stimulation test
   c. Resume intravenous dextrose infusion to maintain plasma glucose >60 mg/dL
   d. Trial diazoxide at dose of 15 mg/kg/day

3. A full term, LGA infant female has required GIR of 25 mg/kg/min throughout the first week of life to prevent plasma glucoses levels from falling to below 30 mg/dL. Treatment should target what plasma glucose level in this female?
   a. >50 mg/dL
   b. >60 mg/dL
   c. >70 mg/dL
   d. >80 mg/dL

4. Which of the following is true regarding the use of diazoxide in neonates?
   a. All infants with congenital hyperinsulinism will respond to diazoxide.
   b. Diazoxide should be used with caution in patients with congenital heart disease.
   c. Diazoxide causes hair loss.
   d. Neonates on diazoxide need to have regular monitoring of CBCs for development of polycythemia.

5. Which of the following conditions of neonatal glucose disturbance is not associated with increased risk of diabetes as an adult?
   a. Transient neonatal diabetes due to chromosome 6q24 mutation
   b. Permanent neonatal diabetes due to activating mutation in K_{ATP} channel
   c. Diffuse hyperinsulinism due to inactivating mutation in K_{ATP} channel
   d. Neonatal panhypopituitarism

6. Which of the following statements is not true regarding energy utilization by the brain?
   a. Glucose is the main source of ATP used by the brain.
   b. Glucose is transported into brain cells via GLUT 3.
   c. Fatty acids cross the blood-brain barrier and can be utilized as a source of ATP.
   d. Ketone bodies cross the blood-brain barrier and can be utilized as a source of ATP.

7. A 3-week-old AGA term male has persistent pre-fed plasma glucose levels between 45–60 mg/dL. Other notable clinical findings include partial cleft lip and palate and absent corpus callosum. Critical sample shows plasma glucose 47 mg/dL, cortisol of < 1 mcg/dL, growth hormone < 1 ng/dL, β-hydroxybutyrate < 0.1 mmol/L, free-fatty acids < 0.1 mmol/L. Which of the following statements is not consistent with these laboratory findings?
   a. The patient will likely need lifelong hydrocortisone replacement.
   b. Thyroid function with total or free T4 should be checked ASAP.
   c. Growth hormone therapy should be started immediately once diagnosis is confirmed.
   d. Uncooked cornstarch can be used to help manage his hypoglycemia.

8. A 10-month-old former 24 weeks gestational age (WGA) male infant has recently developed intermittent episodes of hypoglycemia with plasma glucose levels as low as 30 mg/dL. He was receiving continuous feeds via a G-tube; recently you have been working to condense his feeds, and he is now receiving daytime bolus feeds every 4 hours. Which of the following is true about his condition?
   a. Critical sample is likely to show inappropriately normal insulin and suppressed β-hydroxybutyrate.
   b. This condition is characterized by fasting hypoglycemia.
   c. The patient will have lifelong hypoglycemia.
   d. Hepatomegaly is an associated clinical finding.

9. Which of the following hormones is not involved in intermediary metabolism?
   a. Glucagon
   b. Insulin
   c. Thyroid hormone
   d. Growth hormone

10. Which of the following tests is most helpful in determining if source of hyperinsulinism is endogenous (i.e., congenital hyperinsulinism) or exogenous (i.e., surreptitious in Munchausen by proxy)?
    a. Insulin level
    b. β-hydroxybutyrate level
    c. Glucose response to glucagon administration
    d. C peptide level

33 Calcium, Phosphorus, and Magnesium Metabolism

DAVID R. WEBER

Overview of Bone Mineral Metabolism

BASIC INFORMATION

- Skeletal composition
  - Cellular components: osteoblasts, osteoclasts, osteocytes, and organic matrix
    - Osteoblasts build bone, secrete matrix; derived from mesenchymal stem cells
    - Osteoclasts reabsorb bone; derived from hematopoietic stem cells
    - Osteocytes are osteoblasts that become trapped in the matrix; they form a mechanosensation network and secrete hormones
    - Organic matrix composed of collagen, proteoglycans, stromal cells
      - Provides flexibility to skeleton; also a scaffold for mineral deposition
  - Bone mineral is primarily composed of hydroxyapatite ($Ca_{10}[PO_4]_6[OH]_2$)
    - Provides strength to skeleton, also a reservoir of calcium (Ca) and phosphorus (P)
    - Bone mineralization requires alkaline phosphatase (ALP)
      - ALP hydrolyzes pyrophosphate (inhibitor of mineralization), thereby allowing hydroxyapatite crystals to form
- Skeletal development occurs via endochondral or intramembranous ossification
  - Endochondral ossification (majority of skeleton)
    - Cartilaginous model of skeleton deposited by chondrocytes
      - Complete cartilage model by 9 weeks
    - Replacement of cartilage with bone through activity of osteoblasts
      - Ossification begins at 7 weeks
    - Initiated at ossification centers
      - Primary ossification centers in diaphyses (center of bone)
      - Secondary ossification centers in epiphyses (growth plate)
  - Intramembranous ossification (flat bones such as skull, jaw, clavicle)
    - No cartilage intermediary
    - Osteoblasts differentiation directly from local mesenchymal stem cells
    - Begins in the second trimester
  - Bone modeling
    - Process by which the skeleton grows and takes on mature shape
    - Begins in utero and continues until skeletal maturation after puberty
  - Bone remodeling
    - Lifelong process of skeletal maintenance where old bone is replaced
- Skeletal mineralization in utero
  - Majority of prenatal mineralization occurs in the third trimester
    - Calcium accretion of 120–150 mg/kg/day
  - Fetal blood Ca levels > postnatal/maternal levels to promote mineralization
  - Maternal skeleton is an important source of mineral for fetal skeletal development
  - Parathyroid hormone (PTH)
    - Secreted by fetal parathyroid glands
    - Maintain high blood fetal calcium levels
    - Promote osteoblast-mediated bone formation
  - Parathyroid hormone-related protein (PTHrP)
    - Secreted mostly by placenta
    - Regulate calcium transport across placenta
    - Maintain high blood fetal calcium levels
    - Regulation of ossification centers
- Physiologic changes at birth (Fig. 33.1)
  - Rapid decline in blood calcium
    - Loss of placental calcium supply, PTHrP
    - Calcitonin surge (decrease bone resorption)
    - Neonatal calcium accretion into bone ongoing at ~150 mg/kg/day
  - Compensatory increase in PTH secretion
    - ↑ Ca resorption (bone), reabsorption (kidney), absorption (GI tract)
  - Normocalcemia restored
- Pathophysiology: regulation of bone-mineral homeostasis postnatally
  - Calcium, phosphorus, magnesium: sites of regulation
    - Gastrointestinal tract
      - Active/passive absorption versus excretion in stool
      - Predominantly small intestine
    - Renal tubules
      - Active/passive reabsorption versus excretion in urine
    - Bone
      - Deposition versus resorption
  - Calcium and phosphorus: hormonal regulators
    - PTH

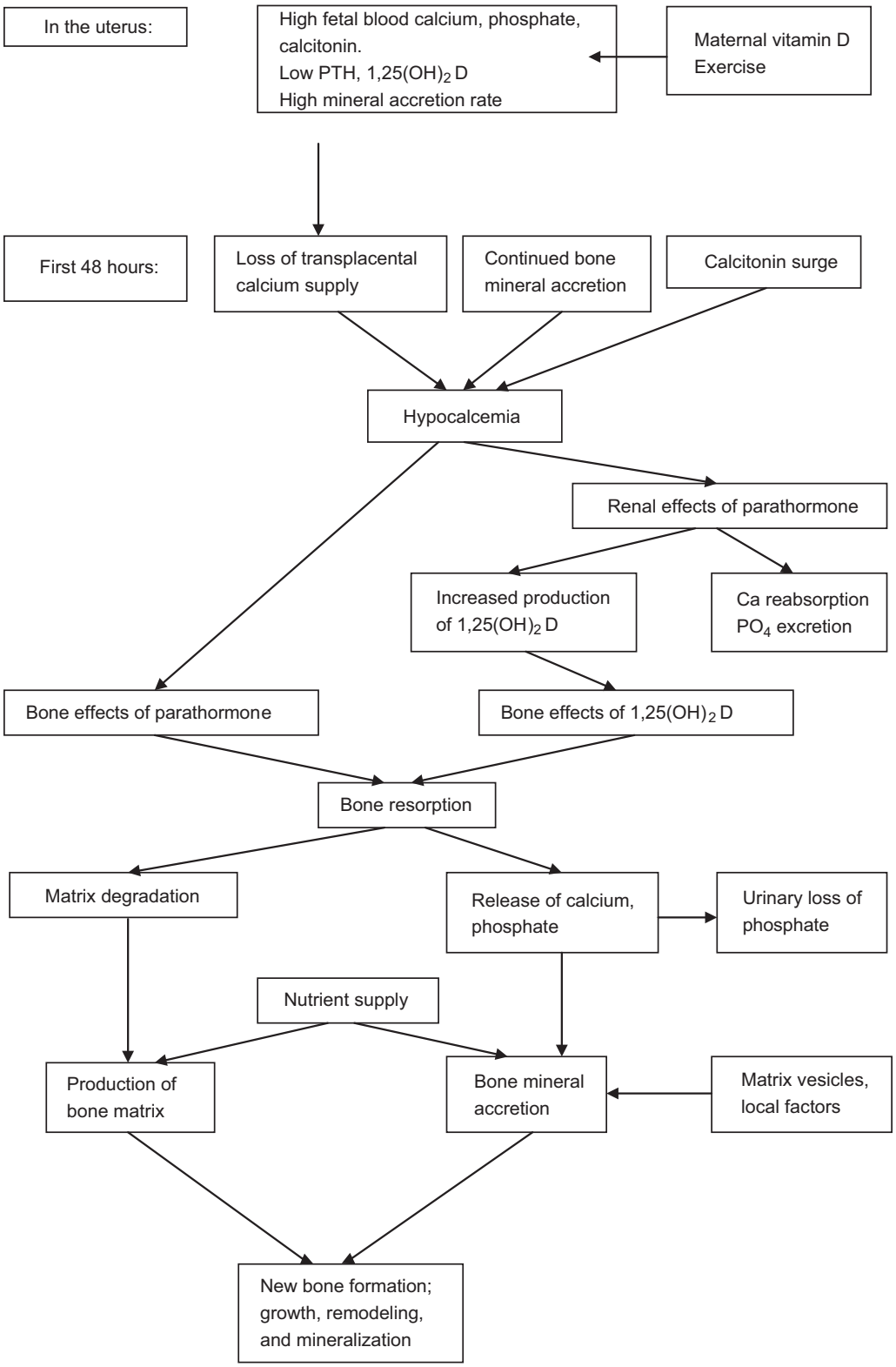

Fig. 33.1 Changes in calcium homeostasis at birth. Events influencing skeletal homeostasis around the time of birth in term infants. (From Bishop N, Fewtrell M, Harvey C. *Pediatric Bone*. 2nd ed. Philadelphia: Elsevier; 2012: 655–677.)

- All actions raise blood calcium levels
- PTH secretion requires normal magnesium
- Secreted from parathyroid glands in response to falling calcium; regulated by calcium sensing receptor (CaSR)
- Renal tubules
  - ↑ Calcium reabsorption
  - ↓ Phosphorus reabsorption
- Bone

- ↑ Calcium and phosphorus resorption (via osteoclast activity)
- GI tract
- ↑ calcium and phosphorus absorption (indirect, via activation of vitamin D)
- Vitamin D
- Hydroxylated from vitamin D_2 or D_3 into 25-OHD in liver via 25-hydroxylase (CYP2R1)
- Activated to 1,25-OHD by 1-alpha-hydroxylase (CYP27B1) in kidney
- ↑ Gastrointestinal absorption calcium and phosphorus (primary impact)
- ↑ Bone resorption and ↑ renal reabsorption of calcium (lesser impacts)
- Inactivated by 24-hydroxylase (CYP24A1)
- Fibroblast growth factor 23 (FGF-23)
- Secreted from osteocytes
- ↓ Decrease phosphorus reabsorption
- ↓ Activation of 1,25-OHD (inhibit CYP27B1)
- Calcitonin
- Secreted from C-cells in thyroid
- ↓ Blood calcium due to decreased osteoclast activity

Neonatal Hypercalcemia

BASIC INFORMATION/ETIOLOGY

- Maternal factors (present shortly after birth)
- Maternal hypoparathyroidism/hypocalcemia (hypertrophy of fetal parathyroid)
- Subcutaneous fat necrosis
- Birth trauma
- Local CYP27B1 activity increases 1,25OH vitamin D production
- Neonatal hyperparathyroidism
- Neonatal severe hyperparathyroidism (NSHPT)/familial hypocalciuric hypercalcemia (FHH)
- CaSR mutation (inactivating)
- Idiopathic infantile hypercalcemia
- CYP24A1 (vitamin D 24-hydroxylase) mutation results in hypervitaminosis D
- Williams syndrome (deletion on chromosome 7, unclear mechanism)
- Hypophosphatasia
- Low calcium deposition in bone due to ALP mutation
- Nutritional factors
- Excess calcium in total parenteral nutrition (TPN)/enteral feeds
- Low phosphorus in TPN/enteral feeds
- Hypervitaminosis D or A due to excess vitamin D or A supplementation
- Congenital lactase deficiency
- Presents with diarrhea in infancy
- Malignancy
- PTH- or PTHrP-secreting sarcomas

CLINICAL PRESENTATION

- Lethargy, irritability
- Failure to thrive
- Polyuria/dehydration

DIAGNOSIS AND EVALUATION

- Biochemical assessment
- Total calcium and/or ionized calcium
- Calcium circulates bound to protein
- Corrected Ca = total Ca + 0.8 × (4-albumin)
- Binding altered by pH
- Acidosis increases ionized calcium
- Source of lab error in improperly processed samples
- Phosphorus
- ALP
- Intact PTH
- 25-OH vitamin D (1,25-OHD if disorder of vitamin D metabolism suspected)
- Urine calcium (UCa), creatinine (UCr), phosphorus
- Normal UCa/UCr in term infant 1–1.2
- Altered by diuretics
- Screen parents for total calcium, UCa/UCr if NSHPT/FHH suspected
- Genetics: Fluorescence in situ hybridization (FISH)/array for chromosome 7, gene sequencing as indicated
- Imaging
- Renal US (nephrocalcinosis)

TREATMENT

- Targeted at etiology
- Acute therapy to decrease serum calcium
- Hydration with normal saline at 1.5- to 2-times maintenance (natriuresis promotes calciuresis)
- Lasix/loop diuretics should generally be avoided
- Minimally effective beyond fluids
- Worsen dehydration, exacerbate renal tubular damage
- Calcitonin (4–16 units/kg/day in 2–3 doses)
- May be effective in PTH, vitamin D–mediated etiologies (reduce bone resorption)
- Limited long-term efficacy due to tachyphylaxis
- May cause GI symptoms in infants
- Bisphosphonates (doses vary based upon agent)
- May be effective in PTH, vitamin D–mediated etiologies (reduce bone resorption)
- Contraindicated if renal insufficiency
- May cause hypocalcemia, hypophosphatemia, fever, GI symptoms with first dose
- Cinacalcet (dosing variable, 0.4–10 mg/kg per day reported)
- Calcimimetic, lowers PTH secretion in NSHPT
- Corticosteroids (dose varies based upon agent)
- May be effective in reducing inflammation in subcutaneous fat necrosis
- Nutritional calcium restriction
- Use of low calcium formulas
- Dialysis
- Parathyroidectomy
- If medical management of NSHPT fails

Neonatal Hypocalcemia

BASIC INFORMATION

- Early neonatal hypocalcemia (onset prior to DOL 4)
- Prematurity
- Decreased skeletal stores

- Inadequate intake (malabsorption, limitations of TPN)
- Immature/inadequate PTH response to hypocalcemia
- Renal resistance to PTH
- Maternal factors
  - Diabetes
  - Hyperparathyroidism (suppress fetal PTH)
  - Excessive calcium antacid use (suppress fetal PTH)
  - Vitamin D deficiency
  - Anticonvulsant use
    - Cytochrome P450 inducers altering vitamin D metabolism
- Late neonatal hypocalcemia (onset after DOL 4)
  - High phosphorus load in cow's milk formulas
    - Renal immaturity results in decreased phosphorus excretion
  - Malabsorption affecting calcium, magnesium, vitamin D absorption
  - Transient or permanent hypoparathyroidism
    - Hypo- or hypermagnesemia
    - DiGeorge (22q.11.2 deletion) syndrome
    - Autosomal dominant hypoparathyroidism
      - Activating mutation in CaSR
      - Loss of function mutation in PTH
    - Other rare X-linked and recessive genetic diseases
  - PTH resistance
    - GNAS mutations resulting in pseudohypoparathyroidism
      - May be associated with Albright hereditary osteodystrophy (brachydactyly, heterotopic ossification)
  - Osteopetrosis (decreased bone resorption)

CLINICAL PRESENTATION

- Irritability, weakness
- Tetany (muscle spasm), myoclonic jerks
- Chvostek sign (facial twitch with tapping of facial nerve)
- Seizure
- Apnea/laryngospasm
- Heart failure

DIAGNOSIS AND EVALUATION

- Biochemical assessment for suspected hypocalcemia
  - Total calcium and/or ionized calcium
  - Magnesium
  - Phosphorus
  - ALP
  - Intact PTH
  - 25-OH vitamin D (1,25-OHD if disorder of vitamin D metabolism suspected)
  - Urine Ca, Cr, P
- Electrocardiogram
  - Prolonged Q-Tc interval
- Imaging (consider)
  - Chest x-ray (CXR) (absent thymic shadow in DiGeorge)
  - Anterior-posterior (AR) wrist (metaphyseal abnormalities in rickets)
- Genetics (consider)
  - FISH/array for 22q11.2 deletion, gene sequencing as indicated

TREATMENT

- Symptomatic hypocalcemia
  - Rapid correction of hypocalcemia with IV calcium gluconate
    - 100–200 mg/kg calcium gluconate over 5–10 min
    - Repeat PRN in 5–10 minutes
    - ECG monitoring
    - Soft tissue necrosis with extravasation
  - Sustained IV calcium repletion may be necessary
    - Continuous infusion is superior than intermittent dosing
    - Doses vary, 25–100 mg/kg per day elemental calcium
  - Correct underlying contributors
    - Magnesium repletion
    - Vitamin D repletion
    - Acid/base status
  - Calcitriol can be added at 0.05 micrograms/kg per day divided into 1–2 doses if refractory
- Asymptomatic hypocalcemia
  - Enteral replacement 25–100 mg/kg/day of elemental calcium divided 3–4 times/day
  - Dose and duration of therapy will vary based upon underlying etiology

Rickets

BASIC INFORMATION

- Genetic and acquired disorders that result in impaired bone mineralization (Table 33.1)
  - Calcipenic rickets
    - Primary defect is diminished calcium availability
  - Phosphopenic rickets
    - Primary defect is diminished phosphorus availability
      - Gastrointestinal malabsorption: increased incidence with elemental formulas
      - Excess urinary wasting
  - Other defect in bone mineralization
    - Hypophosphatasia
    - Osteopenia of prematurity (metabolic bone disease of prematurity)

CLINICAL PRESENTATION

- Physical/clinical findings: variable, depend on etiology, severity, duration
  - Bowing of long bones, craniotabes (soft skull)
  - Failure to thrive
  - Fracture
  - Signs/symptoms of hypocalcemia (including seizure)
- Radiographic findings
  - Global undermineralization
  - Frayed/cupped/widened metaphases of long bones
  - Widened costochondral junctions of ribs "rachitic rosary"
- Laboratory abnormalities
  - Variable based upon etiology (see Table 33.1)

Table 33.1 Biochemical Characteristics of Inherited and Acquired Forms of Rickets Affecting Neonates

Rickets Form	Ca	PO_4	25OHD	1,25-OHD	PTH	ALP	UCa	UPO_4	Other
Calcipenic Rickets									
Vitamin D deficiency	nml/↓	↓	↓	nml /↑	↑	↑	↓	↑	
1α-hydroxylase rickets[a]	↓	↓	nml	↓	↑	↑	↓	↑	
Vitamin D receptor rickets[b]	↓	↓	nml	↑	↑	↑	↓	↑	Alopecia
25-hydroxylase rickets	nml/↓	nml/↓	↓	nml	↑	↑	↓	↑	
Phosphopenic Rickets									
Nutritional PO_4 deficiency	Nml	↓	Nml	↑	Nml/↓	↑	Nml	↓	
X-linked hypophosphatemic rickets	Nml	↓	Nml	↓	Nml/↑	↑	Nml	↓	↑ FGF23
Hereditary hypophosphatemic rickets with hypercalciuria	Nml	↓	Nml	↓	Nml/↓	↑	↑	↓	
Other Mineralization Defects									
Hypophosphatasia	↑	↑	Nml	Nml	↓	↓	↑	Nml/↑	Seizure
Osteopenia of prematurity	Nml/↓	Nml/↓	Nml/↓	Nml/↑	↑	↑	↑	Nml/↓	

[a]Vitamin D-dependent rickets type 1.
[b]Vitamin D-dependent rickets type 2.
ALP, Alkaline phosphatase; *PTH,* parathyroid hormone; *Ca,* calcium; *P04,* phosphorus; *25OHD,* 25-hydroxy vitamin D; *1,25OHD,* 1,25-hydroxy vitamin D; *nml,* normal; *Uca,* urine calcium; *UPO4,* urine phosphorus.

- All patients on elemental formulas should have phosphorus and ALP levels checked regularly due to increased risk of malabsorptive hypophosphatemia

TREATMENT/MONITORING

- Vitamin D deficiency rickets
  - Ergocalciferol (D_2) or cholecalciferol (D_3) can be used for prevention/treatment
  - Prevention
    - Vitamin D 400 IU daily (term), increase to 600 IU daily after 1 year of age
  - Vitamin D 200–400 IU daily (preterm)
  - Treatment
    - Vitamin D 2000 IU daily for at least three months
    - Elemental calcium 25–50 mg/kg/day
    - Vitamin D replacement in absence of calcium can cause hypocalcemia
    - Calcitriol (0.05 micrograms/kg/day) can be added for severe hypocalcemia
    - Continue treatment until normalization of labs and radiographic resolution
- Hypophosphatemic rickets
  - Elemental phosphorus 20–40 mg/kg/day in 3–4 divided doses
  - Calcitriol 0.02–0.05 micrograms/kg/day to prevent secondary hyperparathyroidism
  - Therapeutic goals are normal ALP, PTH, and urine Ca/Cr
  - Repletion of phosphorus in malabsorptive hypophosphatemia can cause hypocalcemia

Osteopenia of Prematurity (Metabolic Bone Disease of Prematurity)

BASIC INFORMATION

- Form of rickets due to prematurity
  - Insufficient prenatal skeletal mineralization
  - Inadequate postnatal skeletal mineralization
    - Limitations of enteral/parenteral calcium and phosphorus provision

CLINICAL PRESENTATION

- Risk factors:
  - Birth weight <1500 g
  - Gestational age <28 weeks
  - TPN requirement >4 weeks
  - Delay in attaining full enteral feeds
- Bone active medications
  - Loop diuretics
  - Corticosteroids
  - Anticonvulsants
- Often asymptomatic initially
- Need for routine biochemical screening
- At risk for fragility fractures
  - Often incidental finding on x-ray
  - Ribs, long bones typically affected

DIAGNOSIS AND EVALUATION

- Routine biochemical screening of at risk infants proposed, nonstandardized
- Calcium, phosphorus, ALP at 4–6 weeks' postgestational age
  - Abnormality in above triggers further testing with PTH, 25-OHD, radiographs
  - Screening repeated every 2–4 weeks in at-risk patients

TREATMENT

- Maximize calcium, phosphorus, vitamin D through enteral/parenteral nutrition
  - Calcium 150–200 mg/kg/day elemental
  - Phosphorus 75–140 mg/kg/day elemental
  - Vitamin D 200–400 IU/d
- For TPN, target calcium: phosphorus ratio of 1.7:1 (by weight)
- Consider supplementation with calcium, phosphorus, vitamin D if nutritional targets not met
- Consider calcitriol 0.05 micrograms/kg/day–0.2 micrograms/kg/day for persistently elevated PTH
  - Suppresses PTH mediated bone resorption, urinary phosphorus wasting
  - Can be given IV for patients on TPN
- Fractures
  - Splinting
  - Follow-up radiographs in 4–6 weeks to assess healing
- Consider PT/passive exercise
  - Mechanosensation promotes bone formation

Hypo/Hypermagnesemia

BASIC INFORMATION

- Causes of hypomagnesemia
  - Insufficient stores
    - Placental insufficiency, IUGR
  - Intestinal malabsorption
    - Short gut, congenital or resection
  - Increased losses
    - Chronic diarrhea
    - Decrease renal reabsorption
      - Renal tubulopathies such as Bartter syndrome
- Causes of hypermagnesemia
  - Maternal treatment with magnesium sulfate
  - Excess enteral/TPN supplementation
  - Magnesium-containing antacids/enemas

CLINICAL PRESENTATION

- Hypomagnesemia
  - Signs/symptoms of hypocalcemia
  - Respiratory insufficiency/failure
  - Seizure
- Hypermagnesemia
  - Signs/symptoms of hypocalcemia
  - Respiratory depression, hypotonia, GI hypomotility

DIAGNOSIS/TREATMENT

- Biochemical assessment
  - Serum total and ionized magnesium
    - Magnesium circulates bound to protein, correct for albumin using same equation as for calcium
  - Urinalysis to look for other signs of tubulopathy
- Treatment
  - Hypomagnesemia
    - Magnesium repletion
      - Acute symptomatic: IV/IM $MgSO_4$ 2–5 mg/kg elemental magnesium, repeated PRN
      - Chronic: enteral magnesium supplementation (dose/duration vary)
        - Dose limited by diarrhea
    - Hypermagnesemia
      - Supportive
      - If severe/symptomatic, consider
        - Fluids, loop diuretics to promote excretion
        - IV calcium gluconate, occupy magnesium receptors
        - Dialysis

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Questions

1. Which statement is true regarding skeletal development?
   a. The femurs are formed via intramembranous ossification.
   b. A genetic defect resulting in impaired chondrocyte maturation would be expected to cause early onset arthritis but would not negatively affect the skeleton.
   c. A genetic defect resulting in reduced alkaline phosphatase activity would negatively affect bone mineral density during infancy.
   d. PTHrP is the primary regulator of osteoblast-mediated bone formation in neonates.

2. Neonatal magnesium status affects calcium metabolism in which way?
   a. Hypermagnesemia results in hypercalcemia due to excessive secretion of PTH
   b. Hypermagnesemia results in hypocalcemia by binding calcium in the GI tract and thereby decreasing calcium availability for GI absorption
   c. Hypomagnesemia results in hypocalcemia via decreased PTH secretion
   d. Hypomagnesemia leads to hypercalcemia because magnesium is required for renal calcium excretion

3. What is the mechanism of hypocalcemia in DiGeorge (22q11.2 deletion) syndrome?
   a. Inactivating mutation in CYP27B1
   b. Hypoplasia/aplasia of parathyroid glands
   c. Renal resistance to parathyroid hormone
   d. Activating mutation in PHEX with associated hyperphosphatemia

4. All of the following are signs/symptoms of hypocalcemia EXCEPT
   a. Shortened QTc interval
   b. Laryngospasm
   c. Involuntary muscle contraction
   d. Seizure

5. A 5.1 kg, 39 Weeks gestational age (WGA) infant suffers a hypocalcemic seizure on DOL 2. What is the most likely etiology?
   a. Hyperparathyroidism due to inactivation mutation in CaSR
   b. Transient hypoparathyroidism due to hypomagnesemia
   c. Familial hypocalciuric hypercalcemia
   d. Permanent hypoparathyroidism due to 22q11.2 deletion

6. A 32 WGA infant develops respiratory failure shortly after birth. Radiographs show marked undermineralization of bones and multiple rib fractures. Labs are notable for a serum calcium of 12.5 mg/dL, serum phosphorus of 8.5 mg/dL, urine calcium to creatinine ratio of 2.5. Which of the following tests will be most helpful in confirming the diagnosis?
   a. Urine phosphorus
   b. 25-OH vitamin D
   c. Alkaline phosphatase
   d. Intact PTH

7. Which of the following is not a risk factor for osteopenia of prematurity?
   a. Postnatal furosemide exposure for CHD
   b. Large for gestational age due to maternal diabetes
   c. History of necrotizing enterocolitis
   d. Birth weight of 1250 grams

8. Which of the following is true regarding the clinical management of osteopenia of prematurity?
   a. Duration of TPN should be extended because this provides more phosphorus for bone mineralization compared to enteral feeds.
   b. DXA scans should be obtained every 4 weeks to screen for osteopenia in infants born <26 WGA.
   c. The goal calcium intake from enteral feeds in infants at risk of osteopenia of prematurity should be 150–200 mg/kg/day.
   d. All infants with birth weights <1500 grams should be supplemented with 1000 IU of vitamin D daily.

9. A 2-week-old, term male infant is re-admitted to the NICU with weight loss and dehydration. Labs are notable for serum calcium of 13.5, undetectable PTH, 25-OH vitamin D of 32 ng/mL, 1,25-OH vitamin D 175 pg/mL (normal range 31–87). He has been breastfed and is receiving 400 IU of vitamin D3 daily. Which of the following statements about the patient's underlying condition is false?
   a. He will be at increased risk of kidney stones in young adulthood.
   b. Initial therapy should include administration of normal saline at 1.5- to 2-times maintenance.
   c. His condition is iatrogenic due to excess vitamin D supplementation.
   d. A low calcium formula may be needed to manage his condition during infancy.

10. A 12-month-old, former 26 WGA female infant with short gut maintained on elemental formula for the past 6 months is found on AM rounds to have acute onset swelling and decreased movement of left femur. Radiograph confirms a mid-shaft femur fracture and cupping and fraying of the distal femoral and proximal tibia metaphysis. Which of the following is true regarding the patient's underlying diagnosis?
    a. Urine labs will show elevated phosphorus
    b. Hypocalcemia is a potential side effect of the treatment for her condition
    c. Her condition is expected to be lifelong
    d. Alkaline phosphatase will be low

34 Thermoregulation

ALISON FALCK and DAVID R. WEBER

Basic Information

- Neutral thermal environment: range of environmental temperature where infant can maintain normal core temperature and minimize oxygen and energy consumption
  - Normal core temperature range for infant: 97.7°F–99.5°F (36.5°C–37.5°C)
  - Mild hypothermia, 36°C–36.5°C; moderate hypothermia, 32°C–36°C; severe hypothermia, <32°C (metabolic processes begin to fail)
- Newborns at risk of heat loss and hypothermia
  - High body surface area relative to body weight (up to 3× that of adult)
  - Thin epidermis with increased evaporative losses, decreased subcutaneous fat
  - Immature response to cold stress, dependent on nonshivering thermogenesis as primary mechanism for heat production
  - All three factors more pronounced with decreasing gestational age
- Estimated heat loss after delivery
  - 0.18°F (0.1°C)/minute of core body temperature
  - Cumulative loss of ~3.6°F–5.4°F (2°C–3°C)
- Conductive heat loss: heat loss due to direct contact with a cooler object
- Convective heat loss: heat loss from warm skin to cooler air currents

Evaporation: heat loss to evaporation of moisture from skin and respiratory tract, most common at delivery; markedly increased in preterm (up to 15×) due to immature skin

- Radiant heat loss: heat loss from heat radiating toward a cooler surface (e.g., cold window, wall, incubator wall); in late preterm or term, most common type of heat loss
- Physiologic response to cold stress
  - Norepinephrine is key mediator of the following:
    - Peripheral vasoconstriction reduces conductive and convective heat loss
    - Thermogenesis via brown adipose tissue (nonshivering thermogenesis)
      - Norepinephrine stimulates release of thyroid hormone, thyroxine (T_4) → triiodothyronine (T_3).
      - T_3 upregulates expression of uncoupling protein 1 (UCP-1) in the mitochondria and uncouples oxidation from phosphorylation.
      - Adenosine triphosphate (ATP) synthesis is decreased; oxidation of free fatty acids → heat production.
  - In preterm, brown adipose is present by 25 weeks but inefficient; levels of UCP-1 and enzyme that convert T_4 to T_3 are low, but increase by 32 weeks' gestation.

Hypothermia

CLINICAL PRESENTATION, DIAGNOSIS, AND EVALUATION

- Hypothermia is defined as core temperature below normal range (<36.5°C); occurs when body losses exceed body heat generation
  - Temperature can be assessed via axillary, rectal, and skin probes
  - Untreated consequences include metabolic acidosis, hypoxemia, hypoglycemia, and free water loss.
- Risk factors for development of hypothermia include:
  - Prematurity, birth weight < 1500 g
  - Small for gestational age (SGA); intrauterine growth retardation (IUGR)
  - Hypoxia
  - Acute illness
  - Abdominal wall or neural tube defects

Treatment

- Infants should be dried immediately, removed from wet linens, exposed to heat source
- Term or late preterm: adequate room temperature; preheat radiant warmer, warm blankets
- Preterm "golden hour": delivery room temperature, 77°F–79°F (25°C–26°C); radiant warmer turned on prior to delivery; prewarmed blankets and hat; <29 weeks' gestation, use polyethylene bag and chemical mattress; transport in prewarmed incubator
- Heat sources
  - Mother (skin-to-skin contact): optimal in stable term or near-term newborn
  - Radiant warmer: temporary for infants needing resuscitation
  - Incubator: for premature or other at-risk newborns requiring ongoing management
    - Autonomous incubators that provide a controlled heat, humidity, and oxygen environment to support at-risk infants
    - Automatic (servo) and manual control
  - Use of warmed humidified air for infants requiring oxygen and ventilatory support

- Thermoregulatory support gradually weaned as infant matures and begins to maintain appropriate core temperatures

Hyperthermia

CLINICAL PRESENTATION, DIAGNOSIS, AND EVALUATION

- Hyperthermia defined as core temperature above normal range (>37.5°C); it occurs when body heat generation and absorption exceed dissipation.
- Untreated consequences include increased metabolic demand, increased water and electrolyte losses, cardiac stress, CNS injury, and seizures.
- It may be iatrogenic due to excessive clothing, inappropriate incubator settings, or failure of automatic control of autonomous incubators.
- Persistent hyperthermia following correction of the thermal environment may be a sign of underlying infection or other metabolic derangement and should prompt a clinical evaluation.

Treatment

- Treatment is directed at identifying and resolving any environmental or infectious causes.
- Acetaminophen and nonsteroidal antiinflammatory drugs (NSAIDs) pharmacologically reduce body temperature through the inhibition of hypothalamic temperature control and blocking of pyrogenic cytokines, respectively.
  - Both should be used with caution because there are no standard dosing recommendations in neonates due to lack of data and concerns over potential toxicities.

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Questions

1. Which of the following hormones is the primary driver of the acute physiologic response to cold stress?
   a. Cortisol
   b. Thyroid hormone
   c. Norepinephrine
   d. Growth hormone

2. Which of the following statements is true regarding brown adipose tissue?
   a. Fatty acids are the substrates for thermogenesis.
   b. Thermogenesis occurs in the nucleus of brown adipose tissue.
   c. Results in heat generation as a result of shivering.
   d. Infants have less brown adipose tissue, in proportion to body size, compared to adults.

3. Which of the following is not a mechanism of heat loss in premature infants?
   a. Convective heat loss due to cooler air environment in delivery room compared to womb
   b. Evaporative heat loss due to thin epidermis
   c. Excessive nonshivering thermogenesis
   d. Conductive heat loss to resuscitation bed because of decreased subcutaneous fat

4. Which of the following exposures is not a potential source of heat loss to a neonate?
   a. Mother's skin
   b. Inspired air via nasal cannula
   c. North-facing window in the neonatal intensive care unit (NICU)
   d. Blanket

SECTION 9

Immunology

KRISTIN SCHEIBLE

35 Development of the Immune System

KRISTIN SCHEIBLE

Development of Solid Organs of the Immune System

THYMUS

- This is a mediastinal structure that originates from the bilateral third and fourth pharyngeal pouches during the seventh week of gestation.
- Thymic tissue remnants can be found along the migratory tract in conditions with absent thymic development.
- This is the location of T lymphocyte maturation from a common lymphoid progenitor to a naïve T cell.
- T cell precursors ($CD4^-$, $CD8^-$) populate the thymus by week 8.
- Fully mature naïve T cells present in the thymus by week 12 (CD4, CD8, γδ T cells, T regulatory cells) and egress to the circulation by 12 weeks.
- Antigen-presenting cells in the thymus express autoimmune regulator (AIRE) transcription factor, which allows the transcription and presentation of self-antigens to test for (and eliminate) self-reactive T cell clones.
- Immune cells in the thymus do not communicate directly with circulating antigens or cytokines, enabling tight control over positive and negative selection and the prevention of autoimmunity.

SPLEEN

- Buds from dorsal mesogastrium by 5 weeks, hilar vessels from 8 weeks
- Hematopoietic cells by 7–8 weeks, secrete lymphotoxin, which stimulates structural organization of the spleen (red pulp, white pulp, venous sinuses)
  - Red pulp contains phagocytic monocytes, which remove senescent red blood cells and opsonized (antibody coated) bacteria and cells; it develops at 13 weeks' gestation.
  - White pulp contains T cells and B cells poised to react against bloodborne pathogens; it develops late in the second trimester.
  - The marginal zone is the interface between the red and white pulp, where pathogens and other antigens are presented to T and B cells; it is not fully developed until 1–2 years postnatally.
    - Contains specialized B cells that react against bacterial cell wall components and macrophages that bind bacterial polysaccharides—important defense against *Streptococcus pneumoniae, Staphylococcus aureus,* and *Escherichia coli*

LYMPH NODES

- Serve as sites for antigen concentration and presentation carried by antigen-presenting cells through the local lymphatic network
- Bud off jugular and cardinal veins to form reticular networks at 8–13 weeks
- Specialized lymphoid tissue inducer (LTi) cells infiltrate and secrete lymphotoxin, which stimulates structural organization
- Influx of naïve T and B cells into lymph nodes between 12 and 14 weeks; then ready to be primed by infection
  - B cell follicles detectable by 17–22 weeks, but no germinal centers until stimulated by infection or other antigen, usually postnatally
  - T cell zones by 16 weeks
- Lymphadenopathy (palpable lymph nodes)—occurs in roughly one-third of healthy newborns, usually in the inguinal and cervical regions
  - Supraclavicular lymphadenopathy is atypical.
  - This can also indicate the presence of a congenital infection, such as cytomegalovirus.

PEYER PATCHES (GUT-ASSOCIATED LYMPHOID TISSUE)

- Interface between gut lumen and immune system; concentrated in the distal ileum
- Biased toward antiinflammatory response
- T cell and B cell clusters form at 11 weeks, visible structures by 22 weeks
- Follicular dendritic cells seen by 24 weeks, take up and present antigen to T cells
- Increase postnatally with commensal colonization

Development of the Cellular Immune System

HEMATOPOIESIS

- This is a process whereby immune and blood cells arise from stem cells (Fig. 35.1).

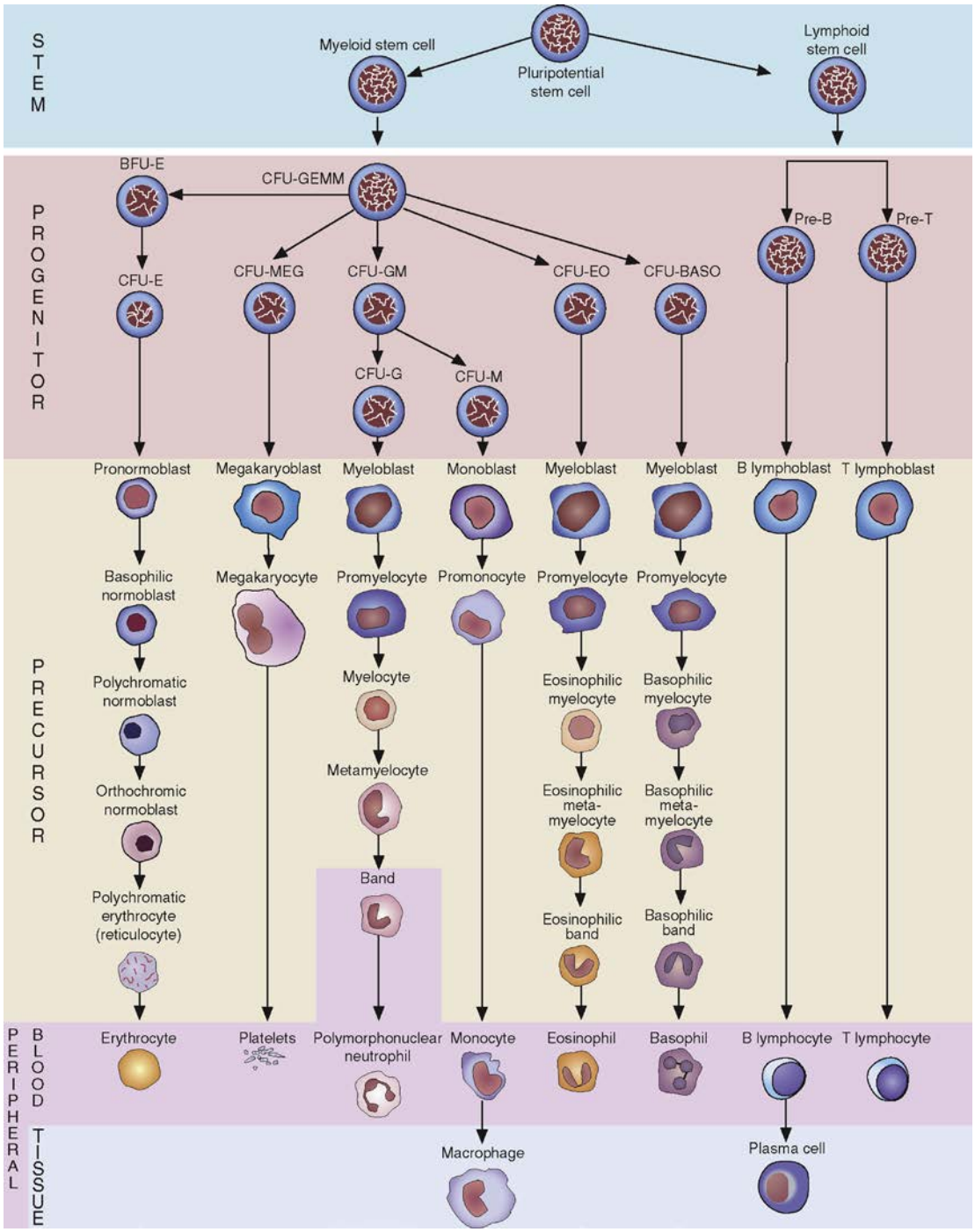

Fig. 35.1 Human hematopoiesis. (From Rodak BF, Jacqueline H, Carr JH. Hematopoiesis. In: *Clinical Hematology Atlas.* 5th ed. Philadelphia: Elsevier; 2009:11–16.)

- Hematopoietic stem cells (HSCs) originate in the yolk sac, then liver and bone marrow
  - Self-renewing pluripotent cell population that gives rise to multiple cell types, with increasing lineage commitment in response to specific environmental signals and internal cell-specific molecular programs
    - Common myeloid progenitors
      - Erythroid and myeloid lineages (granulocytes and monocytes)
    - Common lymphoid progenitors
      - Lymphoid lineages (T, B, ILC)
- The layered immune system hypothesis states that sequential events of embryonic hematopoiesis result in varying progenitor sources and functional potential of immune cells during early human development (Fig. 35.2).
- Innate immune system develops first; embryonic adaptive cells share some characteristics with innate cells (higher fractions of T and B cells with lower specificity compared to adults).
- Immune responses in premature newborns, and in some full-term infants, may be shaped by cells remaining from early fetal development.

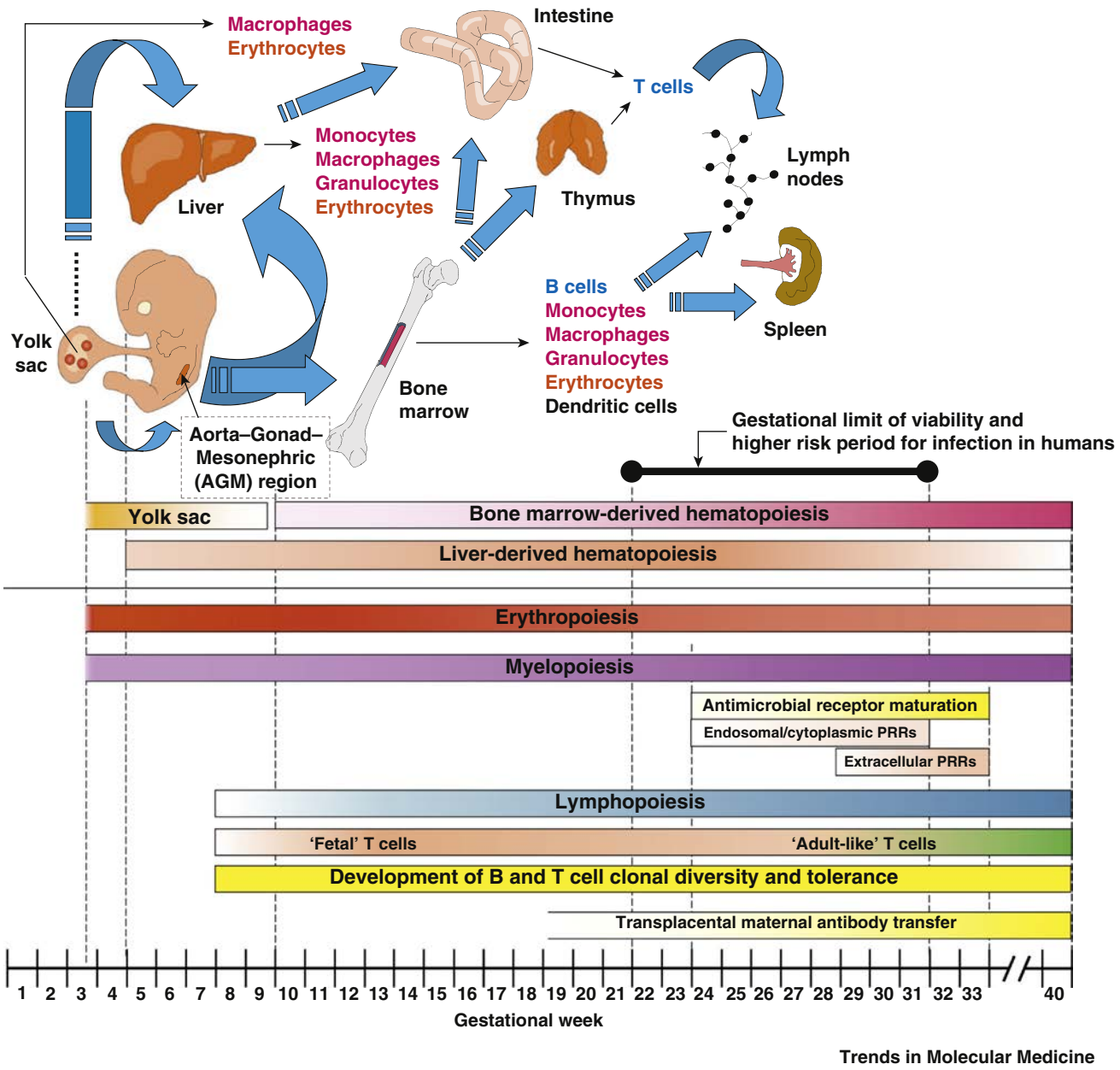

Fig. 35.2 Immune development during gestation. *PRR,* pattern recognition receptors. (From Kan B, Razzaghian HR, Lavoie PM. An immunological perspective on neonatal sepsis. *Trends Mol Med.* 2016;22(4):290–302.)

- Primitive hematopoiesis (2–6 weeks' gestation)—there are blood islands located in the yolk sac that produce only erythroid and myeloid progenitors.
  - Primitive monocytes are the only monocytes capable of differentiating into long-lived, self-renewing microglial cells.
- Definitive hematopoiesis (begins at 5 weeks' gestation) occurs in two overlapping stages based on the origin of the HSCs.
  - Aorta-gonad-mesonephros and liver (5–22 weeks) generates myeloid, erythroid, and some lymphoid (γδ T cells, natural killer (NK) cells, and $CD5^+$ B cells) progenitors.
    - Contribute to organ development, including specialized kidney and alveolar macrophages
  - Bone marrow (after 11 weeks) generates myeloid, lymphoid, and erythroid progenitors and contributes to the final mature circulating pool of myeloid and lymphoid cells.
- Individual components of the immune system are described in the next chapter.

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Question

1. An infant is successfully resuscitated following vaginal delivery at 23{0/7} weeks due to intrauterine infection. You are concerned that this patient could quickly develop overwhelming sepsis due to her extreme prematurity and exposure to infection. Which of the following immune-related factors does not contribute to this patient's increased susceptibility to infection?
   a. An underdeveloped stratum corneum increases permeability of skin to pathogens.
   b. Definitive hematopoiesis (bone marrow-derived) begins at 28 weeks' gestation, so extremely premature infants rely on primitive hematopoietic immune lineages for protection.
   c. There is impaired interferon-γ production by T cells and monocytes in neonates.
   d. Preterm infants and full-term neonates have decreased lectin-mediated complement activation.

36 Components of the Immune System

KRISTIN SCHEIBLE

Cellular Components of the Immune System

White blood cell levels vary by age and many clinical conditions. Normal levels and conditions affecting specific cell populations can be found in Table 36.1.

MYELOID LINEAGE IMMUNE CELLS

- Monocytes
  - Phagocytose, present antigen, produce cytokine and chemokines, participate in wound repair, tissue remodeling, and homeostasis
  - Development
    - Monocytes exist in circulation and then differentiate into macrophages, dendritic cells, histiocytes, or other tissue-specific resident cells when localized.
    - Granulocyte-macrophage colony-stimulating factor (GM-CSF) is secreted by macrophages, T cells, mast cells, natural killer cells, endothelial cells, and fibroblasts and functions as a cytokine, major growth factor.
    - Multiple subtypes of monocytes are categorized based on the source of the progenitor, resident location, and function.
      - Primitive monocytes originate in the yolk sac, are a minor transient population in circulation, and are able to differentiate into self-renewing microglia.
        - Prune synapses, scavenge and maintain neural tissue homeostasis
      - Definitive monocytes originate in the liver and then the bone marrow.
        - Liver-derived monocytes are able to differentiate into self-renewing resident macrophages in the lung (alveolar macrophages), skin (histiocytes), heart (cardiac macrophages), kidney (macrophages and dendritic cells), and liver (macrophages, Kupffer cells). They present antigen to T cells and participate in tissue homeostasis.
        - Bone marrow- and liver-derived monocytes contribute to the circulating pool of mature monocytes that differentiate into macrophages and serve immune functions, including phagocytosis, antigen presentation, and cytokine production.

Table 36.1 White Blood Cell Indices at Birth

Cell Type	Mean × 10^3/mL (range)	No. Present (%)	Postnatal Peak	Increase	Decrease
Total white blood cells	18.1 (9–30)		12 hours	Infection; leukemoid response to stress; steroids; congenital leukemia; transient myeloproliferative disease of the newborn	Preeclampsia; prematurity; infection
Neutrophil	11 (6–26)	61	12 hours	Infection; steroids; congenital leukemia; transient myeloproliferative disease of the newborn	Prematurity; preeclampsia; infection; rh hemolytic disease; bone marrow failure; syndromes organic acidemias; glycogen storage disease; copper deficiency; maternal anti–HNA-1b antibodies; drug-induced
Lymphocyte	5.5 (2–11)	31	6–12 months	Congenital syphilis; cytomegalovirus; *Bordetella pertussis;* phenytoin	Prematurity; infection; severe combined immunodeficiency; 22q11.2 deletion; steroids
Monocyte	1.1	6	12 hours	Prematurity; infection; candidal infection; congenital syphilis; steroids	Prematurity; infection
Eosinophil	0.4	2	2–4 weeks	Candidal infection; allergic sensitization; furosemide	Prematurity; infection

Adapted from The Johns Hopkins Hospital, Kahl L, Hughes HK. *The Harriet Lane Handbook*. 21st ed. Philadelphia: Elsevier; 2017.

- Three activation pathways
  - Innate: Toll-like receptor stimulation, increases nitric oxide synthase (NOS), reactive oxygen species (ROS)
  - Classic: interferon-γ (IFN-γ) and lipopolysaccharide (LPS) enhance antigen presentation, inflammatory cytokines, microbicidal activity
  - Alternate: interleukin-4 (IL-4) and IL-13 increase cell growth, tissue repair, parasite killing
- Granulocytes
  - Neutrophils represent the highest fraction of granulocytes and are present in the liver by 5 weeks' gestation.
    - Development
      - Mature in the liver and bone marrow (myeloblast → promyelocyte → myelocyte → metamyelocyte → banded neutrophil → segmented neutrophil)
      - Production stimulated by granulocyte-colony stimu-lating factor (G-CSF) >> IL-6 > IL-3
      - Increase in circulation during third trimester, peak at 12–24 hours of life from granulocyte-colony stimulating factor (G-CSF) surge, rise to adult levels by 4 weeks
    - Activation
      - Attach to endothelial tissue until activated, then migrate directionally to sites of inflammation in response to chemical signals (chemoattractants such as IL-8)
      - Function through phagocytosis and bactericidal activity of intracellular respiratory burst and secreted mediators
        - Phagocytosis activity preterm < term < adult due to lower CR3 and Fc receptor activity (poor recognition of opsonized pathogens)
        - Respiratory burst diminished in preterms, enhanced in full-term infants
        - Higher IL-6 and IL-10, and lower IL-1β levels, tumor necrosis factor-α (TNF-α) and IFN-γ compared to adults
        - Reduced neutrophil extracellular trap (NET) activity (extrusion of chromatin and antimicrobial material that mechanically and chemically neutralizes bacteria at mucosal surfaces; NET inactivated by deoxyribonuclease)
        - Reduced chemokine-directed localization to infected sites
  - Eosinophils
    - Present in liver at 5 weeks
    - Higher in neonates, but lower in preterm compared to full-term infants
    - Increase over first 1–2 months postnatally in response to Th2 cytokines (IL-4, IL-5, IL-13)
    - Located mainly at mucosal surfaces
    - Key cells in allergic and antiparasite responses
      - Activate in response to cytokines and cross-linking of surface-bound immunoglobulin E (IgE)
      - Release of allergy-related cytokines (IL-4, IL-5), toxic granules, collagenases, chemoattractants, leukotrienes, platelet-activating factor
  - Mast cells and basophils
    - Cord blood mast cells, basophils release higher amounts of histamine and IL-4 compared to adults when stimulated by IgE
    - Activated through cytokines and cross-linking of surface-bound IgE
    - Mast cells implicated in neonatal lung disease (hyperoxia-induced animal models and human lung tissue)
    - Mast cells—may participate in tissue remodeling, including early follicular development in the ovary

LYMPHOID LINEAGES

- T lymphocytes
  - Important for recognizing and clearing cells infected with intracellular pathogens (e.g., viruses, *Listeria monocytogenes*, *Chlamydia*, *Salmonella*).
  - Provide cytokine signals to stimulate B cells to mature and secrete appropriate antibody isoforms, orchestrate immune response
  - Development
    - Progenitors originate in liver, then bone marrow, during embryonic development, circulate as double-negative (CD4- and CD8-antigen negative) common lymphoid progenitors, localize to thymus and mature into double-positive and then released as single-positive naïve T cells
    - Undergo terminal deoxynucleotidyl transferase (TdT)–dependent somatic DNA rearrangement of VDJ segments during thymic maturation that enables production of random T cell receptor sequences; loop of DNA excised during rearrangement, is detectable in recent thymic emigrants as T cell excision circle (TREC)
    - TREC content measured by dried blood spot as part of newborn screening program to detect severe combined immune deficiency (SCID); TRECs increase with gestational age, preterm infants therefore have higher risk for false-positive SCID screening
    - Two checkpoints during T cell receptor development in the thymus prevent autoreactivity—positively selected (survive) when able to recognize self—major histocompatibility complex (MHC), negatively selected (deleted) when react too strongly to self-antigen presented in self-MHC
  - Activation
    - Each T cell recognizes a single peptide sequence when presented within an MHC molecule on another cell. Expansion of a pathogen-specific T cell clone after initial priming results in a higher number of antigen-specific memory cells able to respond more rapidly on secondary exposure.
    - Each CD4 T cell clone recognizes a unique short peptide sequence presented within the pocket of MHC II on infected antigen-presenting cells (monocytes, dendritic cells, macrophages, B cells) and polarizes toward unique functions:
      - Th1 (IFN-α, IFN-γ, TNF-α, IL-2) → antiviral, intracellular pathogen killing
      - Th2 (IL-4, IL-5, IL-13) → antiparasite, allergen, antibody production
      - Th17 (IL-17, IL-9, IL-23) → antibacterial, antifungal
      - T regulatory—IL-10, suppressive receptor activity, dampens inflammatory response
    - Each CD8 T cell clone recognizes specific peptide sequences presented within the MHC (expressed on most nucleated cells) and matures into cytotoxic cells.
      - Produces inflammatory cytokines, granzyme, perforin, executes Fas-mediated killing

- γδ T cells recognize patterns on antigen-presenting cells, behave in a more innate-like fashion, and localize primarily to mucosal sites.
- Neonatal T cells have several unique properties:
  - Require multiple reinforcing signals in addition to peptide-MHC binding to activate
  - Require multiple exposures to establish protective memory
  - Prone to differentiating into T regulatory cells and short-lived cytokine producers rather than long-lived memory T cells
  - Higher CD4/CD8 ratio, higher IL-8 and TNF-α cytokine production
  - IFN-γ production suppressed by promoter site hypermethylation

- B lymphocytes
  - Produce and secrete antibody, present antigen to T cells in the lymph node
  - Development
    - B cell receptor (BCR) undergoes a DNA rearrangement similar to T cells, as well as a second somatic hypermutation event during active infection that increases binding affinity of BCRs.
    - Secreted antibody is a soluble B cell receptor and heavy chain isotype; it switches from IgM, IgD → IgG, IgA, IgE (isotype functions listed in Table 36.2).
    - Progenitors (pro–B cells) and precursors (pre–B cells) detected in liver by 8 weeks' gestation, transition to bone marrow by 12 weeks
      - Naïve B cell matures in lymph node, becomes plasma cell (antibody-secreting) or memory B cell (more rapidly differentiates into plasma cells on secondary infection)
      - Two major subsets of B cells
        - B-1 ($CD5^+$) B cells are a minor population; present during fetal development, only secrete IgM spontaneously, do not fully differentiate into memory, recognize carbohydrate antigens, and are enriched in fetal omentum
        - B-2 B cells are major subclass, undergo class switching, affinity maturation, and differentiate into memory B cells
  - Activation: can be T-independent (against polysaccharides and haptens) or T-dependent (against protein or peptide antigens)
    - T-dependent activation occurs when B cells present peptide antigen to T cells, which then provide reinforcement signals to mature the B cell response.
    - Newborn B cells have diminished splenic marginal zone B cells, which recognize polysaccharide antigens and protect against T-independent (nonprotein) antigens.
    - *Haemophilus influenzae* type B (HiB) and pneumococcal vaccines include a polysaccharide capsular antigen linked to a peptide antigen. T cells recognize the peptide and provide cytokine signals that induce antibody class switching and affinity maturation.
- Innate lymphoid cells
  - Present in fetal liver at 6 weeks, recognize pathogen via patterned recognition receptors, function through cytokine production and receptor-mediated cytotoxic activity
  - Growing interest in this newly identified cell population that bridges innate and adaptive immune functions
  - Grouped by cytokine function and marker expression:
    - Group 1 produces IFN-γ and TNF-α and includes natural killer (NK) cells (dominant lymphoid cells in fetal lung and liver, diminished function in newborns);
    - Group 2 produces IL-4, IL-5, IL-9. and IL-13;
    - Group 3 produces IL-17 and IL-22.

Development of Humoral and Soluble Components of the Immune System

CYTOKINES

- These are small proteins secreted by cells to signal behavior to receptor-expressing cells in an autocrine, paracrine, or systemic fashion.
- They can be inflammatory, antiinflammatory, or both, depending on the receiving cell type and presence of other cytokines.
- IFN-γ is critical for protection against intracellular pathogens; its production and activity are blunted in newborns.
- Newborns produce higher levels of innate-type inflammatory cytokines (IL-1, IL-2, IL-6, IL-8, TNF-α) and regu-

Table 36.2 Antibody Isoforms

Isoform	Major Functions	Location	Placental Transfer	Age When Adult Levels Are Achieved
IgM	Complement activation	Circulation, mucosal sites	No	1 year
IgG1	Opsonization, neutralization, complement activation	Circulation, extravascular space	Yes; active transport during third trimester	Higher at birth than adult (in term gestation due to maternal antibody), nadir at 6–8 months, then comparable to adult by 3–4 years
IgG2	Neutralization	Circulation, extravascular space	Some	
IgG3	Complement activation, neutralization, opsonization	Circulation, extravascular space	Yes	
IgG4	Neutralization	Circulation, extravascular space	Some	
IgA	Neutralization	Mucosal sites, extravascular space	No	4–6 years
IgE	Mast cell activation	Circulation, extravascular space	No	Varies by genetic predisposition to atopy

latory (TGF-β, IL-10) compared to adults and lower levels of adaptive-type responses (IFN-γ, IL-4, IL-17).
- The balance of the cytokines instructs the immune system to respond appropriately to a given antigen (e.g., Th1, Th2, Th17; see above).

COMPLEMENT

- Collection of proteins that interact to augment, and sometimes inhibit, immunity through multiple pathways (Tables 36.3 and 36.4)
- Enhance antibody function, recruit leukocytes, prime and mature adaptive immune cells, lyse microbial membranes
- Activated through three overlapping pathways that have variable functions during fetal and neonatal development
- Produced in liver, except C7, which is secreted by neutrophils
- Measured by CH50 assay (measures lysis of sheep erythrocytes in serial dilutions of human sera)
- Most components diminished in newborns, with the exception of C7 and factor D; C9 (terminal element) is neurotoxic, low levels may protect newborns against hypoxia-induced brain injury

ANTIMICROBIAL PEPTIDES AND PROTEINS (APP)

- Soluble cationic molecules that neutralize infections, recruit and modulate immune cell activity at sites of infection, opsonize and enhance phagocytosis
- Produced by many cell types (e.g., epithelial, immune), concentrations usually increase during normal gestation and postnatally
- Can be constitutive or induced by inflammation
- Human breast milk is an important source of APP in neonates
- Common peptides and proteins listed in Table 36.5

Table 36.3 Complement Pathways During Fetal and Neonatal Development

Pathway	Mechanism of Activation	Components	Preterm vs. Full Term	Full Term vs. Adult
Classic	Antibody + antigen, CRP	C1	↓	↓
		C2	→	↓
		C3	↓	↓
		C4	↓	↓
Lectin	Lectin + pathogen, carbohydrate, IgA	C2	→	↓
		C3	↓	↓
		C4	↓	↓
		Mannose-binding lectin	↓	↓
		Ficolins	↓	↓
		MASP-2	↓	↓
Alternative	Spontaneous hydrolysis of C3, foreign surfaces	C3	↓	↓
		Factor B	→	↓
		Factor D	→	↑
		Properdin	→	↓

CRP, C-reactive protein.

Table 36.4 Terminal and Regulatory Complement Components and Neonatal Development

Role	Component	Preterm vs. Full Term	Full Term vs. Adult
Terminal	C5	↓	↓
	C6	↓	↓
	C7	→	→
	C8	↓	↓
	C9	↓	↓↓
Regulator or role	Factor I; cleaves C4b, C3b	→	↓
	C1 inhibitor or binds C1r/s protease, inactivates MASP-1, MASP-2	Unknown	↓
	Factor H binds C4b, C3b	→	↓

Table 36.5 Selected Antimicrobial Peptides and Proteins Found in Neonates

Peptide or Protein	Detected in Tissue	Function(s)	Preterm vs. Full Term	Full Term vs. Adult
C-reactive protein	Blood	Opsonization of bacteria and apoptotic cells	→	→
Defensins	Blood, breast milk, gut, trachea, vernix, amniotic fluid	Bactericidal; recruit innate and adaptive cells to sites of inflammation	↓	↓
Cathelicidins	Blood, breast milk, gut, trachea, skin, vernix	Bactericidal; recruit innate and adaptive cells to sites of inflammation	→	↑
Bactericidal, permeability-increasing protein	Blood, trachea	Opsonization of gram-negative bacteria	↓	↓
Lactoferrin	Breast milk, skin, vernix	Iron chelation; enhances immune cell adhesion and ROS production	→	↑
Lysozyme	Vernix, amniotic fluid	Bacterial lysis	↓	→
Collectins (mannose-binding protein surfactants A and D)	Gut, lung	Bind to nonhuman bacterial surface carbohydrates; opsonize bacteria and apoptotic cells	↓	→

ROS, Reactive oxygen species.

Suggested Readings

Battersby AJ, Khara J, Wright VJ, Levy O, Kampmann B. Antimicrobial proteins and peptides in early life: ontogeny and translational opportunities. *Front Immunol*. 2016;7:309.

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Mold JE, Venkatasubrahmanyam S, Burt TD, et al. Fetal and adult hematopoietic stem cells give rise to distinct T cell lineages in humans. *Science*. 2010;330(6011):1695–1699.

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Questions

1. In accordance with guidelines, a newborn screen was carried out prior to the first blood transfusion in an infant born at 23{0/7}weeks' gestational age. The screening test is positive for severe combined immunodeficiency (SCID), showing low, but not absent, T cell receptor excision circles (TRECs). The most appropriate next step for this patient is which of the following?
   a. Urgent hematology and oncology consult to assess for bone marrow transplantation candidacy
   b. Newborn screen repeated until patient reaches term-equivalent gestational age
   c. Antimicrobial prophylaxis started with sulfamethoxazole-trimethoprim (Bactrim)
   d. Blood specimen sent to laboratory for measurement of lymphocyte subsets by flow cytometry

2. Vaccines against *Haemophilus influenzae type b* and *Pneumococcus* infections are highly successful in reducing the incidence of invasive disease. The vaccine platform against these pathogens is well-tailored for the neonatal immune system in that:
   a. The polysaccharide antigen is T-independent, and the protein toxin enables T cell help in inducing B cell memory differentiation and antibody class switching.
   b. They contain monophosphoryl lipid A adjuvant, which boosts a newborn's naïve adaptive response.
   c. The antigens are recombinant proteins, which more specifically target antigen-specific naïve T cells and therefore generate more effective memory.
   d. The polysaccharide antigen is conjugated to a DNA fragment, which provides costimulation of antigen-specific T cells through Toll-like receptors.

3. A term newborn's antibody concentration at birth is which of the following?
   a. Higher in IgG compared to maternal circulation due to active transport across the placenta
   b. High in IgA due to mucosal immune responses
   c. High in maternal IgM in the setting of maternal infection with *Toxoplasmosis*
   d. Similar in IgE due to passive transport across the placenta

37 Abnormal Immune System Development

KRISTIN SCHEIBLE

Inflammation

- Broadly defined as innate and adaptive immune activation triggered by pathogen invasion or tissue damage
  - Molecular events vary based on initiating event, specific mediators activated, and location.
    - Consistent event: vasodilation, vascular permeability facilitates recruitment of proteins, fluids, leukocytes into damaged tissue
  - It involves collateral damage to the host (primary target is pathogen, but host tissue sustains secondary injury).
    - Often the inflammatory component causes more damage than the pathogen or injury.
      - Especially maladaptive if inflammation occurs in immunologically privileged sites (e.g., eye, brain, uterus, testicle, ovary)
    - Many canonical diseases in the preterm infant are thought to have an inflammatory component, including bronchopulmonary dysplasia, necrotizing enterocolitis, and periventricular leukomalacia,
- Characterized by four components: pain, swelling, heat, redness
- Can be infectious (viral, bacterial, fungal invasion), sterile (trauma, ischemia), or both (e.g., ventilator-induced lung injury, mucosal colonization)
- Three phases
  - Recognition and activation
    - Infection: there is immediate recognition of the invading organism by the innate system through pathogen-associated molecular patterns (PAMPs).
      - Bind to cell surface pattern recognition receptors (PRR) and Toll-like receptors (TLR)
    - Tissue injury: there is recognition of damaged tissue or noxious exposure through damage-associated molecular patterns (DAMPs).
      - Bind to TLRs and intracellular nod-like receptors (NLRs)
    - Many PAMPs and DAMPs signal transcription of inflammatory mediators through the NF-κB transcription factor pathway.
    - DAMP and PAMP pathways activate the complement system.
  - Isolation and clearance
    - Transcription and release of inflammatory mediators such as interleukin-1β (IL-1β), tumor necrosis factor-α (TNF-α) and IL-6, chemoattractants (IL-8), and upregulation of costimulatory molecules
    - Recruitment of effector cells (activated immune cells that kill and clear infected cells and pathogen)
      - Neutrophils, monocytes phagocytose infectious particles, release reactive oxygen and reactive nitrogen species (forms purulent fluid)
    - Production of proinflammatory eicosanoids (e.g., histamine, prostaglandins, thromboxane, leukotrienes)
    - Recruitment of adaptive system (delayed if novel infection)
      - Coordinates immune response by programming appropriately polarized cytokine bias
        - Th1 (interferon-α [IFN-α], IFN-γ, TNF-α, IL-2) → antiviral, intracellular pathogen killing
        - Th2 (IL-4, IL-5, IL-13) → antiparasite, allergen, antibody production
        - Th17 (IL-17, IL-9, IL-23) → antibacterial, antifungal
      - Establishes memory cells that can respond more rapidly on secondary challenge
    - Proinflammatory cytokine release: causes temperature instability in newborn (hyper- or hypothermia)
    - Increased metabolic rate: results in increased glucose consumption, somnolence, lactic acidosis, increased CO_2 production
  - Restoration of homeostasis
    - Critical step that prevents ongoing collateral injury, chronic inflammatory disease, and autoimmunity
    - Switch from proinflammatory eicosanoids to antiinflammatory lipoxins, resolvins, and protectins
      - Blocks further neutrophil influx, recruits monocytes for wound healing
    - Release of antiinflammatory hormones, including cortisol
    - Release of suppressive mediators
      - T regulatory cells: secrete suppressive IL-10 and transforming growth factor-β (TGF-β) cytokines, shut down inflammatory cells through receptor engagement
      - Innate cells: secrete adenosine, IL-10
    - Tissue repair
      - Recruitment of monocytes to clear damaged tissue, promote scar formation
      - Tissue resident macrophages: assist in wound healing, removal of apoptotic immune cells, other cellular debris remaining following acute inflammatory process

Newborn Susceptibility to Infection (Normal Immune System)

- Skin: physical barrier and rich source of specialized resident antigen-presenting cells, including histiocytes; stratum corneum (outer keratinized skin surface) incomplete until 34 weeks' gestation and is more easily penetrated by bacteria
- Mucosal epithelium: includes internal surfaces that interface with the external environment (gut, airway, genital tract)
  - Mucosal integrity varies by site, poor mechanical barrier function at earlier gestational ages
  - Diminished mucus production
  - Poor airway clearance
- Tears: high concentrations of antibody, but not fully mature until postnatal months 1–3
- Gastric pH higher in neonates, changing microbial environment
- Blood-brain barrier more permeable in newborns, allowing passage of pathogens and inflammatory mediators
- Medications commonly used in sick newborns to suppress the immune system (Table 37.1)

Table 37.1 Immunomodulating Medications

Medication	Interaction With Immune System
NSAIDs (Indomethacin, Ibuprofen)	Inhibit COX1/COX2 activity: diminished eicosanoid production and immune cell activation
G-CSF	Stimulates neutrophil survival, proliferation, and activity
GM-CSF	Stimulates granulocyte and monocyte survival, proliferation, and activity
Steroids	Demargination of bands and PMNs (increase in CBC), decreased monocytes, lymphopenia, reduced endothelial adhesion, downregulation of antigen-presenting molecules (MHC), suppression of eicosanoids, suppression of NF-κB
IVIG	Binds to and inhibits Fc-receptor, activation of antiinflammatory pathways through complement-binding, blocks phagocytosis of desired cells, inhibition of T cell cytotoxicity
Macrolides	Inhibit release of arachidonic acid and inflammatory eicosanoid production, inhibit NF-κB pathways, increase IL-10 and decrease TNF-α/IL-8/IL-1β production

CBC, Complete blood count; *G-CSF,* granulocyte-colony stimulating factor; *GM-CSF,* granulocyte-macrophage colony-stimulating factor; *IL-1β,* interleukin-1β; *IVIG,* intravenous immunoglobulin; *MHC,* major histocompatibility complex; *NSAIDs,* nonsteroidal antiinflammatory drugs; *PMN,* polymorphonuclear leukocyte; *TNF,* tumor necrosis factor.

Primary Immunodeficiencies

BASIC INFORMATION

- Can affect the solid organs, innate or adaptive immune system
- Differential can be directed by observing clinical stigmata (Table 37.2) or sentinel infections (Table 37.3)
- Often X-linked
- Concern for primary immune deficiency should be raised if:
  - Two or more serious bacterial infections
  - Two or more serious respiratory or soft tissue infections within 1 year
  - Unusual pathogens
  - Usual pathogens with severe illness or in unusual sites
- Failure to thrive—common presenting sign

Table 37.2 Stigmata of Primary Immunodeficiencies

Clinical Presentation	Syndrome
Petechiae	Wiskott-Aldrich
Telangiectasias	Ataxia-telangiectasia
Eczematoid rash	Wiskott-Aldrich, hyper IgE
Seborrhea behind ears	Chronic granulomatous disease
Generalized seborrhea	Langerhans histiocytosis, T cell deficiencies
Nose tip dermatitis	Chronic granulomatous disease
Poor scar formation, delayed cord separation	Leukocyte defects
Rachitic rosary, bone in bone	ADA (AR-SCID)

ADA, Adenosine deaminase deficiency; *AR-SCID,* autosomal recessive severe combined immunodeficiency.

ABNORMAL ORGAN DEVELOPMENT

- Asplenia and hyposplenia
  - Presentation
    - Can be isolated or associated with syndrome
      - Ivemark syndrome: bilateral right-sidedness, cardiac anomalies (transient global amnesia [TGA], Pulmonary stenosis or atresia, total anomalous pulmonary venous return [TAPVR]), intestinal malrotation
      - Smith-Fineman-Myers syndrome: mental retardation, short stature, cryptorchidism
      - Heterotaxy syndrome: left-sided (polysplenia) or right-sided (asplenia or hyposplenia) isomerism
      - Familial: autosomal dominant, isolated anomaly
    - Risk for severe infections with encapsulated bacteria (e.g., *Streptococcus pneumoniae, Haemophilus influenzae b* (Hib), *Neisseria meningitidis, Staphylococcus aureus, Salmonella*)

Table 37.3 Sentinel Infections Associated With Primary Immunodeficiencies

Infection	Syndrome
Nocardia, Aspergillus spp.	Chronic granulomatous disease
Burkholderia cepacia pneumonia	Chronic granulomatous disease
Recurrent *Neisseria* spp.	Terminal complement deficiency
Escherichia coli bacteremia	Galactosemia
Pneumocystis carinii	T lymphocyte deficiency
Recurrent *Streptococcus pneumonia* bacteremia	Asplenia, hemoglobinopathy, agammaglobulinemia, Kartagener
CMV, HSV	Hyper IgE, SCID, HIV
Gingivostomatitis	Neutrophil abnormalities

CMV, Cytomegalovirus; *HSV,* herpes simplex virus; *SCID,* severe combined immunodeficiency.

Table 37.4 Selected Syndromes With Severe Congenital Neutropenia

Syndrome	Gene Defect	Presentation (in Addition to Neutropenia)	Management
Autoimmune primitive neutropenia	(Autoantibody against FcRgIIIb)	Most frequent chronic neutropenia in children; late arrest of neutrophils; macrophagia of intramedullary PMNs	Conservative
Elastase mutation (severe congenital cyclic neutropenia)[a]	*ELANE* (AD)	Maturation arrest of neutrophils, no extrahematopoietic findings	G-CSF, sulfamethoxazole-trimethoprim (Bactrim)
Kostmann	*HAX1* (AR)	Arrest of neutrophils at promyelocytes; cognitive delay and epilepsy	G-CSF, Bactrim, bone marrow transplant (BMT)
Cartilage hair hypoplasia	*RMRP* (AR)	Short-limbed dwarfism, fine hair, lymphopenia	Bactrim
Wiskott-Aldrich	*WAS* (X-linked)	Eczema, thrombocytopenia	IVIG, Bactrim, BMT
Shwachman-Diamond	*SDBS* (AR)	Exocrine pancreas insufficiency, anemia, thrombocytopenia	G-CSF (cautious), Bactrim erythropoietin, growth hormone, supportive treatment for pancreatic insufficiency
Barth	*G4-5* (X-linked)	Cardiomyopathy and fibrosis, acidopathy	G-CSF, Bactrim
Chédiak-Higashi	*LYST* (AR)	Oculocutaneous albinism, bleeding	Bactrim, BMT

[a]Most frequent primary neutropenia.
AD, Autosomal dominant; *AR,* autosomal recessive; *G-CSF,* granulocyte-colony stimulating factor; *IVIG,* intravenous immunoglobulin; *PMN,* polymorphonuclear leukocyte.

- Neonates with asplenia at highest risk for *Klebsiella* and *Escherichia coli* infections
- Persistent thrombocytosis and Howell-Jolly bodies—remain in circulation
- Male predominance (60%)
- Evaluation
  - Genetic testing
  - Screening imaging to assess cardiac, abdominal anatomy
  - Complete blood count (CBC)
- Treatment and prophylaxis
  - PCV13 (pneumococcal polysaccharide), Hib conjugate, meningococcal (Menveo) vaccines indicated in infancy; household contacts encouraged to receive age-appropriate vaccines
  - Antibiotic prophylaxis with oral penicillin VK from birth until 5 years of age

- Athymia
  - Presentation
    - Compromised T cell maturation, can be complete or partial
      - Complete causes T-negative (T−), B-positive (B+), NK-positive (NK+) deficiency
    - Usually found as part of DiGeorge anomaly; criteria are two of the three following features:
      - Cellular immunodeficiency with absence of part or all of thymus
      - Parathyroid deficiency
      - Congenital heart disease
    - 55% have 22q11 deletion
      - Facial features: hypertelorism, hooded eyelids, short philtrum, micrognathia, low-set ears
    - Athymia also found in CHARGE association and FOXN1 deficiency
  - Evaluation
    - Serum ionized calcium levels
    - CBC; consider flow cytometry subset analysis
    - Testing for 22q11 deletion
    - Screening imaging for cardiac anomalies
  - Transplantation (of mature T cells or thymus) indicated for complete athymia

- Bone marrow failure, impaired hematopoiesis
  - Heterogeneous group of diseases with variable presentation
    - Short stature, severe diarrhea, physical anomalies
    - Due to defects in hematopoiesis; syndromes affect more than one blood cell subset
    - High risk for malignant transformation of myeloid lineages
      - Malignant transformation: may be associated with granulocyte-colony stimulating factor (G-CSF) treatment in these patients
  - Immunodeficiencies from bone marrow failure presenting in newborn period
    - Fanconi aplastic anemia (AR or X-linked)—poor growth, severe anemia, thrombocytopenia, neutropenia
    - Shwachman-Diamond syndrome (autosomal recessive)—predominant neutropenia, pancreatic insufficiency

INNATE SYSTEM

Neutrophils

- Primary neutropenias are rare; neutropenias usually secondary to viral infection or autoimmune disorders (Table 37.4)
- Defined as persistent neutropenia (<1500/mL); can also be cyclic
- Present with infections of skin, mucosa (especially ear-nose-throat [ENT], gingivostomatitis, lungs)
- Ethnic neutropenia G-CSF: mild, benign neutropenia common in individuals of African or Middle Eastern descent, most common chronic form
- Can occur as primary neutrophil defect or as minor feature of other hematopoietic deficiencies
- Many neutropenia syndromes respond to high-dose G-CSF
- Severe, chronic neutropenia is an indication for antimicrobial prophylaxis (e.g., sulfamethoxazole-trimethoprim [Bactrim]) and/or G-CSF

Table 37.5 Specific T and B Cell Deficiencies

Cell Type (All T− or T Low)	Gene Defect (Inheritance)	Cell Activity Impaired	Management
T CELL DEFICIENCIES (SCID)			
B+, NK+	*IL-7rα, IL-7rγ* (X-linked)	T cell maturation, survival, and differentiation	Isolation; avoid live vaccines; sulfamethoxazole-trimethoprim (Bactrim) IVIG; immune replacement therapy (transplantation), ideally prior to first infection
	CD3 complex defects (AR)	T cell signaling and T cell regulation	
	PTPRC (CD45) (AR)	T cell receptor-signaling regulation	
	CORO1A (variable)	T cell thymic egress and actin dynamics, calcium release	
B+, NK−	*IL-2RG* (X-linked)	IL-2cγr–mediated T and NK survival (shared receptor for IL-2, IL-4, IL-7, IL-9, IL-15 and IL-21), antibody maturation in B cells	
	JAK3 (AR)	IL-2cγr signal transduction (see above)	
B−, NK−	*ADA* (AR)	Purine salvage and clearance (purines are toxic to lymphocytes, induce apoptosis)	
	AK2 (reticular dysgenesis; AR)	Regulation of adenosine diphosphate, (accumulation causes apoptosis in myeloid and lymphoid precursors)	
B−, NK+	*RAG1* (Omenn) (AR)	V(D)J recombination	
	RAG2 (Omenn) (AR)	V(D)J recombination	
	DCLRE1C (Artemis)	V(D)J recombination, double-stranded DNA repair	
B CELL DEFICIENCIES			
Transient hypogammaglobulinemia of infancy		Exaggerated physiologic nadir beyond 6 months (excellent prognosis)	None (conservative)
X-linked agammaglobulinemia		*BTK* deficiency causes failure of B cell maturation—good prognosis	IVIG
X-linked hyper IgM		Absence of CD40L on T cells causes failure of antibody class switching—poor prognosis	Transplantation, IVIG
IgA deficiency (AD with variable penetrance)		Impaired class switching isolated to IgA isotype—most common PID, good prognosis	Symptomatic, avoid IVIG (host anti-IgA antibodies can react against donor IgA)
Hyper IgE (AD)		STAT3 signaling defect causes dysregulated cytokine production, with secondary preference for IgE class switching	Skin care, Bactrim, immunomodulators (IFN-γ, IVIG)

AD, Autosomal dominant; *AR,* autosomal recessive; *IFN-γ,* interferon-γ; *IVIG,* intravenous immunoglobulin; *PID,* primary immunodeficiency; *SCID,* severe combined immunodeficiency.

ADAPTIVE IMMUNE SYSTEM

- T cell deficiencies (severe combined immunodeficiency [SCID]; Table 37.5)
  - B and/or natural killer (NK) cell subsets can also be affected due to shared mechanisms of cell maturation
  - Presentation
    - Early detection is possible by newborn screening (NBS) programs and, when present, is considered a pediatric emergency.
      - NBS with low T cell receptor excision circle (TREC) can be false-positive.
        - 50% of false-positives for primary immunodeficiency are secondary to prematurity; 50% are due to secondary lymphopenias in full-term infants.
      - NBS with absent TRECs is highly specific for SCID.
    - If not detected by NBS, it can present with nystatin-resistant thrush, recurrent infections, absent lymph nodes or lymphadenopathy, rash, and/or atypical or severe infections.
    - There is a family history of immunodeficiency or early death in a maternal uncle.
  - Laboratory evaluation
    - CBC with differential
    - T cell proliferative response, lymphocyte subsets (by flow cytometry)
    - Genetic testing
    - Serum immunoglobulins (after 6 months)
      - Antibody affinity maturation and class switching dependent on T cell activity; B cell and immunoglobulins levels may be normal but may not be protective without T cell help.
    - Chest radiography
  - Diagnosed by genetic testing or
    - HIV-negative status plus one of two criteria:
    - Absent or low T cells, or low T cell proliferation with mitogen stimulation testing;
    - T cells of maternal origin (lack of fetal adaptive immune response enables maternal cell engraftment).
  - Management
    - Isolation
    - *Pneumocystis* prophylaxis and aggressive, prolonged treatment of infections
    - Intravenous immunoglobulin (IVIG)
    - Avoidance of live vaccines in patient and household contacts
    - Avoidance of ionizing radiation in T−, B−, NK+ subtype (impaired dsDNA repair)
    - Poor prognosis without bone marrow transplantation or if transplantation occurs after first serious infection
- Humoral deficiencies (B cell and antibody)
  - Presentation

Table 37.6 Functional Leukocyte Immunodeficiencies

Function	Syndrome, Inheritance	Presentation	Diagnosis	Management
Adhesion	Leukocyte adhesion deficiency (types I-III) (AR)	Neutrophilia, delayed cord separation, omphalitis, gingivitis, peritonitis, absence of abscess formation or pus accumulation	Low CD18 and CD11b	Oral hygiene, stem cell transplantation, fucose supplementation (LAD II)
Respiratory burst	Chronic granulomatous disease (x-linked)	Recurrent pneumonia, abscesses, *Aspergillus* infection	Abnormal nitroblue tetrazolium (NBT) test	Antimicrobial prophylaxis, BMT
	Myeloperoxidase deficiency (compound heterozygous)	May be asymptomatic, *Candida albicans* infection	Normal NBT, absent MPO staining	Treatment of infections
Antigen presentation	MHC II deficiency (AR)	Hypogammaglobulinemia, CD4 lymphopenia, severe, recurrent infections (SCID phenotype)	Absent MHC II on B cells	Avoid live vaccines, transplant
	MHC I deficiency (unknown)	Necrotizing granulomatous skin lesions, frequent respiratory infections, bronchiectasis	Absent MHC I on cells	Avoid live vaccines, transplantation

AR, autosomal recessive; *BMT,* bone marrow transplant; *MHC,* major histocompatibility complex; *SCID,* severe combined immunodeficiency.

- Severe respiratory tract infections with encapsulated bacteria (e.g., *S. pneumoniae, H. influenzae)*
- Poor growth, chronic diarrhea, recurrent fevers, chronic enteroviral infections

- Laboratory evaluation
  - Total serum immunoglobulin (after 6 months)
    - Antibody subclass levels
  - Antibody titers to vaccine or isohemagglutinins in incompletely vaccinated infants
  - Genetic testing
  - CBC with differential, lymphocyte subsets
- Management and prognosis—depend on specific deficiency

LEUKOCYTE FUNCTION DEFECTS

- Can affect function shared by more than one cell type
- Presentation and management—depend on cell and function affected (Table 37.6)

Suggested Readings

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Questions

1. You are asked to evaluate a term infant born 4 hours ago by scheduled cesarean section for persistent central cyanosis. The infant is male, appropriate weight for gestational age, and appears in no distress. Vital signs are within normal limits, with the exception of oxygen saturation, which measures 81% preductal and postductal. Your examination reveals a hyperdynamic precordium with a single S2 and a regurgitant murmur. You obtain an x-ray, which shows dextroposition of the heart and a midline liver and stomach. You determine that once stable, this infant may ultimately require antimicrobial prophylaxis with which of the following?
   a. Bactrim due to high risk for *Pneumocystis* pneumonia
   b. IVIG due to low antibody levels
   c. Amoxicillin due to high risk for infection with encapsulated bacteria
   d. FFP to restore complement levels

2. A term infant is admitted to the NICU for evaluation and management of her prenatally diagnosed pulmonary stenosis. On examination, she is found to have hypertelorism, hooded lids, a short philtrum, and micrognathia. Her oral examination reveals a bifid uvula. Her postnatal echocardiogram shows anatomy consistent with tetralogy of Fallot, and there is adequate flow through the outflow tract, without prostaglandins. Her vital signs remain stable on the monitors. Electrolytes remain within normal limits, with the exception of a low ionized calcium level detected on day of life 4. The tests most likely to reveal a contraindication to live vaccine administration in this patient include which of the following?
   a. Lymphocyte subsets by flow cytometry
   b. Complement levels
   c. Complete blood count with differential
   d. Immunoglobulin levels

3. A term infant presents to the special care nursery with a 24-hour total serum bilirubin of 13 (11.9 indirect, 1.1 direct). The mother's blood type is O, Rh+. The infant's blood type is B, Rh+, and her hematocrit and reticulocyte counts are 38 and 9.2%, respectively. In this setting, the likely mechanism of intravenous immunoglobulin's (IVIG) therapeutic effect is which of the following?
   a. IVIG inhibits NK cell activation.
   b. IVIG saturates B-antigen sites on the erythrocytes, thereby blocking maternal antibodies from attaching.
   c. IVIG binds to Fc portion of anti-B maternal antibodies, rendering bound erythrocytes "invisible" to the infant's immune system.
   d. IVIG saturates Fc receptor on infant's phagocytes, thereby blocking recognition and destruction of antibody-bound erythrocytes.

4. A healthy-appearing term infant presents with a newborn screen that is positive for severe combined immunodeficiency (SCID). The laboratory report details that the T cell receptor excision circle content is "absent." Lymphocyte subsets by flow cytometry reveal a T-negative, B-positive, NK-positive SCID phenotype. The most likely genetic defect explaining this patient's T cell deficiency is which of the following?
   a. Absent IL-7 α-receptor expression, leading to T cell maturation defects
   b. RAG1 deficiency (Omenn syndrome), causing defective T cell receptor production
   c. Low CD40L expression, causing T cell cycle arrest
   d. Low adenosine deaminase (ADA) expression, leading to accelerated apoptosis of T cells

5. A 26-week-old infant presents at birth in shock from *E. coli* sepsis and is found to have an absolute neutrophil count of 500/mL, which falls to 200/mL on a subsequent CBC. Which of the following is most accurate regarding medical therapy for sepsis-induced neutropenia?
   a. Dexamethasone increases the absolute neutrophil count by stimulating bone marrow production.
   b. IVIG improves sepsis outcomes by blocking complement-induced cytolysis and neutrophil consumption.
   c. Granulocyte-colony stimulating factor (G-CSF) increases bone marrow monocyte and neutrophil production.
   d. G-CSF will improve neutrophil count by stimulating bone marrow neutrophil production.

6. A term infant is admitted to the NICU for tachypnea and increased work of breathing after delivery complicated by preeclampsia. On physical examination, he is found to have a narrow chest, but otherwise appears normal. A chest radiograph reveals a narrow chest, increased vascular markings, and fluid in the minor fissure. Some long bones also have metaphyseal sclerosis. A CBC with differential shows an absolute neutrophil count of 500 cells/mL, absolute lymphocyte count of 700/mL, hemoglobin of 9.4 g/dL, and platelets of 110×10^3/mL. His blood cultures remain negative, the absolute neutrophil count (ANC) improves to >1500 cells/mL, his respiratory symptoms resolve, and he is discharged to home. He is seen repeatedly at the pediatrician for foul-smelling, oily stools, recurrent respiratory infections, and persistent growth failure. His CBC again shows anemia (hemoglobin, Hgb, 7.6 g/dL) and neutropenia (400/mL). This patient's most likely diagnosis is which of the following?
   a. Cystic fibrosis
   b. Asphyxiating thoracic dystrophy
   c. Shwachman-Diamond syndrome
   d. Hemophagocytic lymphohistiocytosis

SECTION 10

Infectious Diseases

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38 Infections of Organ Systems

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Sepsis

BASIC INFORMATION

- Definitions
  - Sepsis: a clinical syndrome characterized by systemic signs of infection, leading to morbidity and mortality
    - Sepsis is usually thought of as being caused by bacterial pathogens but may also result from infection with fungal or viral pathogens.
    - SIRS, the systemic inflammatory response syndrome, is the physiologic characterization of the sepsis syndrome; SIRS can be caused by sepsis itself or by proinflammatory cytokines resulting from inflammation.
  - Early- versus late-onset sepsis
    - Early-onset sepsis (EOS) traditionally is defined as having its onset at <7 days of life, although some experts use the definition of <3 days (72 hours) of life; most signs and symptoms of EOS develop in the first 3 days of life.
    - Late-onset sepsis (LOS) is then defined as sepsis occurring from 7–90 days of life.
    - Sepsis caused by group B streptococci (GBS) with onset >90 days of life has been termed *very late-onset sepsis*; with prolonged long hospital stays of extremely premature infants; some definitions of LOS sepsis simply include 7 days until discharge from the neonatal intensive care unit (NICU).
  - Proven versus probable sepsis—sepsis with positive bacterial, fungal, or viral diagnostic tests from clinically relevant body sites, considered proven sepsis
    - Many definitions of probable sepsis are found in the literature: signs of sepsis or SIRS with improvement after antibiotics, with serially elevated nonspecific markers of inflammation such as serum C-reactive protein (CRP) or procalcitonin assays, or by some clinical risk assessment system. When analyzing clinical studies of neonatal sepsis, careful attention must be paid as to how these definitions are construed.
- Epidemiology
  - EOS remains a major cause of global morbidity and mortality, especially in low- and middle-income countries but also in higher income countries.
    - Estimated EOS incidence is 50–150 cases/1000 live births annually in lower income countries; 0.5–5 cases/1000 live births annually in the United States and Western Europe.
  - Incidence rates are difficult to ascertain in LOS because LOS may depend on variable definitions, nosocomial outbreaks, and the distribution of birth weights in a particular nursery.
    - GBS LOS rates were lower than those of EOS GBS infection until recently; GBS EOS rates have decreased with peripartum antibiotic prophylaxis, but GBS LOS rates have not, so that now US GBS EOS rates approximate GBS LOS rates.
  - The leading causes of bacterial sepsis in US neonates have changed over time, for uncertain reasons.
    - Before the 1950s: *Staphylococcus aureus* and *Streptococcus pyogenes* were the most common.
    - Late 1950s–1960s: gram-negative enteric bacilli, especially *Escherichia coli*, increased.
    - Late 1960s to the present day: group B beta-hemolytic streptococci (GBS; *S. agalactiae*) emerged to be the most common.
    - With the advent of GBS peripartum antibiotic prophylaxis in the US, the incidence of GBS EOS has decreased, but GBS remains an important LOS pathogen. In LOS GBS, *E. coli*, coagulase-negative staphylococci (*S. epidermidis*), and group D enterococci are prominent.
    - Both EOS and LOS may also be caused by *Listeria monocytogenes* in certain areas, particularly in Western Europe, although its incidence seems to have decreased in most of the United States, likely from better agricultural infection control and possibly also from effects of peripartum antibiotic prophylaxis against GBS.
- Risk factors and routes of transmission
  - Maternal risk factors: maternal urinary tract infection; chorioamnionitis; colonization or past infection with GBS, *Neisseria gonorrhoeae*, herpes simplex virus; membrane rupture at >18 hours; preterm delivery; complications in delivery; site of delivery (community, hospital)
  - Infant risk factors: immaturity of immunologic mechanisms (e.g., neutrophil function, complement and immunoglobulin levels); congenital malformations (e.g., cardiac, neural tube, gastrointestinal disease); metabolic disease (galactosemia); indwelling medical devices (e.g., endotracheal tubes, umbilical arterial or venous catheters, central venous catheters, ventricular drainage systems)
  - Routes of transmission of infection:
    - EOS generally occurs from ascending bacteria entering the uterus following membrane rupture, from exposure to microbes during passage through the birth canal, from chorioamnionitis or, less commonly, from transplacental infection.
    - LOS more often occurs from environmental sources such as indwelling catheters, endotracheal tubes, hand contamination of hospital personnel and family members, contaminated formula, and equipment.

Notably, however, LOS GBS or *Candida* infection may result from colonization at birth or shortly thereafter, yet present only later, for reasons that remain to be determined.

- Causes (see Chapter 39)
  - Gram-positive bacteria: GBS, *S. aureus, L. monocytogenes, Enterococcus faecalis, S. epidermidis*; rarely, *S. pneumoniae*
  - Gram-negative bacteria*: E.coli, Klebsiella* spp., *Enterobacter* spp., *Pseudomonas aeruginosa*; rarely, *N. gonorrhoeae*, nontypeable *Haemophilus influenzae*
  - Fungi*: Candida albicans*, non-*albicans* candidal spp.
  - Viruses: enterovirus; herpes simplex virus (HSV) types 1 and 2

CLINICAL PRESENTATION

- Signs and symptoms: neonates with sepsis, particularly EOS, may show variable and nonspecific symptoms and signs:
  - These include fetal tachycardia, foul-smelling amniotic fluid, low Apgar scores, temperature instability (either hyper- or hypothermia), poor feeding, lethargy, irritability, apnea, tachypnea, tachycardia, hypotension, poor peripheral perfusion, emesis, diarrhea, abdominal distention, jaundice, and cyanosis.
  - Symptoms and signs of sepsis may mimic those of other neonatal conditions (e.g., congenital heart disease, respiratory distress syndrome, bowel malformations), and sepsis and other neonatal conditions may occur concordantly in the neonate as well, causing further diagnostic confusion.
  - EOS tends to be more systemic, whereas focal infections (e.g., cellulitis, meningitis, urinary tract infections [UTIs]) are more common with LOS, but not exclusively so. To some extent, the neonate with EOS may present more often with hypothermia than with fever, especially with very premature neonates, who do not seem to generate febrile responses as often.

DIAGNOSIS AND EVALUATION

- Risk-based empiric diagnoses: several approaches are commonly used to manage neonates with possible sepsis.
  - GBS EOS (CDC Guidelines, 2010): All pregnant women in the United States are to be screened for GBS vaginal-rectal colonization at 35–37 weeks' gestation, and initial intrapartum penicillin or ampicillin prophylaxis is given to those women who are colonized. Risk stratification decisions for neonates are made on the basis of the maternal colonization status, the administration of antibiotics for >4 hours before delivery, signs of sepsis in the neonate, gestational age ≥ 37 weeks, and membrane rupture of 18 hours (see Chapter 40).
  - All-cause EOS (Kaiser Sepsis studies): Recent validated scoring system using Bayesian analyses of precise estimates of the effects of maternal risk factors on neonatal sepsis, combined with current US EOS incidence rates in the GBS peripartum prophylaxis era, is available at https://neonatalsepsiscalculator.kaiserpermanente.org. The score is calculated using a baseline estimate of the incidence of EOS in the clinician's area, further adjusted by data inputs from the clinician of several simple maternal risk factors and the clinical appearance of the neonate. Management guidance of observation alone, enhanced observation, or admission to an intensive care unit with antibiotic therapy is determined by the magnitude of the calculated change in EOS incidence. Data have suggested that the score may accurately categorize the risk of EOS sufficiently to allow low-risk patients not to receive antibiotic therapy, even when antibiotics would be suggested by the more general CDC GBS guidelines.
- Blood cultures are the gold standard for the determination of the presence of bacterial or fungal (candidal) sepsis. Blood culture sensitivity is heavily dependent on the volume of blood cultured, which may be limiting in very-low-birth-weight neonates; specificity is heavily dependent on the fidelity of aseptic technique with which cultures are obtained.
  - Methods: modern automated continuously monitored blood culture machinery (e.g., Bactec, BacTAlert systems) is now standard in larger hospitals and allow better and faster organism recovery due to advances in culture media and growth detection.
    - Most relevant pathogens will have growth recognized in 36–48 hours, often by 24 hours; identification of antimicrobial susceptibility is often semiautomated and may take only another 24–36 hours. Some institutions use blood culture bottles containing resins to inactivate antimicrobials in the blood and improve recovery; it is uncertain whether any increase in pathogen recovery is outweighed by the extra expense of such techniques.
  - Volume: blood culture pathogen recovery is directly correlated with the volume of blood cultured, with studies in adults showing increased recovery at 40 mL of blood taken per culture set versus 10–20 mL/set. In young children, infants, and especially premature infants, such volumes clearly are untenable.
    - In full-term neonates, 1–2 mL of blood should be cultured per bottle, for a total of 2–4 mL per two-bottle (aerobic and anaerobic) set.
    - In smaller premature infants, 0.5–1 mL per bottle should be obtained (total blood 1–2 mL per two-bottle set).
    - In extremely premature infants who have very low total blood volumes, the minimum useful blood culture volume of 0.5 mL can be placed entirely in one aerobic bottle only.
    - Ideally, two sets of blood cultures from different anatomic sites are obtained; each set consists of an aerobic media bottle and anaerobic media bottle. This technique increases the sensitivity by increasing volume and allows some estimate of contamination to be made (see contamination, below).
  - Contamination: in general, true bacteremia occurs with recognized pathogens and is present throughout the body, so that both blood culture sets will be positive. If one set is positive but the other is not, growth in the one set may represent growth of a low inoculation with a skin flora contaminant. Obviously, if only one culture set at a time is obtained, this distinction cannot be made. Selected pathogens (e.g., *S. aureus, Candida*) are unlikely to be contaminants, even if growth is obtained in only one set.
- Lumbar puncture: examination of cerebrospinal fluid (CSF) is the gold standard for the diagnosis of meningitis.

- Indications: all ill newborns should be considered for lumbar puncture.
  - LOS: meningitis commonly associated with bacteremia and sepsis
  - EOS: meningitis less common in babies with EOS but does occur; in up to 30% of cases in very-low-birth-weight infants, positive CSF cultures found in the absence of detectable bacteremia
- Contraindications: lumbar puncture may need to be deferred in critically ill neonates who cannot be safely positioned for the procedure due to cardiorespiratory compromise or in those with severe bleeding diatheses.
- Interpretation: the interpretation of the Gram-stained smear and culture are the same as in older children, but the cell content and protein content of neonatal CSF differ from those of older children and adults. Nevertheless, generalizations may be made from reported data. The ratio of CSF to blood glucose in neonates is similar to that in older infants and children, although the absolute CSF glucose content may appear low because neonates may be hypoglycemic relative to older infants.
  - Mean CSF white blood cell (WBC) counts in healthy neonates of any postmenstrual age are <10 cells/μL (range, 1–44), with <10% polymorphonuclear leukocytes (PMNs) in the differential.
  - Mean CSF protein in healthy neonates—60–80 mg/dL full term; 150 mg/dL preterm (range, 54–360)
  - Mean CSF glucose–46-51 mg/dL full term; 64 mg/dL preterm (range, 33–217)
- Urine culture: in distinction to meningitis, it is very rare for neonates younger than 72 hours of age to have ascending urinary tract infection; thus urine cultures are not required at <72 hours of age. Urine should be obtained in neonates with possible sepsis who are 72 hours of age or older by either catheterization or suprapubic aspiration.
- Laboratory aids to diagnosis: many biomarkers, including components of the complete blood count (CBC), CRP, procalcitonin, various cytokines, acute-phase reactants, and neutrophil membrane markers; none has high enough sensitivity and specificity to predict neonatal sepsis accurately, although repeatedly high serial levels are concerning. A better use of many of these markers, especially CRP, is the exclusion of sepsis (allowing antibiotics to be discontinued after empiric therapy has begun) when serial measurements are normal over a 24- to 48-hour duration because of the high negative predictive value in this situation.
  - CBC components: after birth, PMNs and immature WBC forms are released from the bone marrow, producing a relative leukocytosis and left shift; however, it is variable enough that using high or low WBC counts, total neutrophil counts, or total band counts are not sensitive or specific enough for routine diagnostic assistance, except in the following cases:
    - WBC < 5000 cells/μL is somewhat more predictive of sepsis.
    - An immature-to-total neutrophil ratio ([band plus metamyelocyte plus myelocyte count]/[all immature forms + band + absolute neutrophil count]) > 0.2 is somewhat more predictive of sepsis, with ~75% sensitivity and ~75% specificity.
  - CRP: a CRP >10 mg/L has a modest predictive value for sepsis; however, serial levels of CRP < 10 mg/L at 8 and 24 hours of age may exclude sepsis, with a high (>99%) negative predictive value
  - Procalcitonin levels normally rise up to ~10 ng/mL in the first 36 hours of life; in several studies, it was found that procalcitonin > 2 ng/mL after 48 hours of life is more predictive of sepsis (or >10 ng/mL at any time after birth).

THERAPY

- Antimicrobial agents
  - Duration of therapy is generally 10 days for uncomplicated bacterial sepsis, 14–28 days with concurrent meningitis (pathogen-dependent length of therapy)
  - Antibacterials
    - EOS: the combination of ampicillin and an aminoglycoside (e.g., gentamicin) remains the cornerstone of EOS empiric therapy for potency against GBS, coliforms, enterococci, and *Listeria*. For definite or highly suspected meningitis, the combination of ampicillin and a third-generation cephalosporin (e.g., cefotaxime, or sometimes, the fourth-generation agent cefepime or a carbapenem) is preferred. Definitive therapy may be tailored after pathogen identification.
    - LOS: the combination of vancomycin and an aminoglycoside (gentamicin) is preferred to broaden activity against *S. aureus* and coagulase-negative staphylococci while maintaining potency against GBS and gram-negative rods. If meningitis is suspected, vancomycin plus a third-generation cephalosporin (or carbapenem) is preferred. Tailoring of definitive therapy may be done after pathogen identification.
  - Antifungals: duration often 21 days for *Candida* sepsis
    - Amphotericin B deoxycholate is preferred for empiric therapy of high-risk infants with severe illness and possible fungal sepsis.
    - Fluconazole is a less toxic alternative in less ill neonates but will not be potent against several non-*albicans* candidal yeasts. Fluconazole does have good central nervous system (CNS) and urinary tract penetrance, however, and may be used for susceptible yeasts.
    - Echinocandins (e.g., micafungin) have good antifungal activity against yeasts but do not penetrate the CNS or urinary tract well.
  - Antivirals
    - HSV infection requires therapy with high-dose systemic acyclovir, for 14–21 days at minimum, depending on the extent of disease.
    - Enteroviral sepsis of the newborn is treated with supportive therapy, but there are no current antienteroviral agents available. Anecdotal data have suggested that infusion of intravenous immunoglobulin might be effective.

Central Nervous System Infections

BASIC INFORMATION

- More often associated with LOS (>7 days of age) than EOS
- Causes

- GBS—serotypes of late-onset GBS meningitis often differ from EOS sepsis
- *E. coli*, other coliforms
- *L. monocytogenes*
- Rarely, *Candida albicans*, *S. aureus*, HSV

CLINICAL PRESENTATION

- Symptoms and signs may be subtle or masked by comorbid conditions (e.g., heart or lung disease, abdominal disease).
- They may overlap those of sepsis (see earlier); unlike the case in older infants, nuchal rigidity or meningeal signs are rarely seen in neonates.
- A bulging anterior fontanel may be present.
- Development of a brain abscess should be anticipated with selected unusual gram-negative pathogens (e.g., *Citrobacter* spp. and *Cronobacter* [formerly *Enterobacter*] *sakazakii*).

DIAGNOSIS AND EVALUATION

- Blood and CSF cultures as for sepsis (see above); lumbar puncture should be performed if at all possible in all critically ill neonates suspected of sepsis and/or meningitis.

THERAPY

- Empiric (<7 days of age)
  - Ampicillin and a third- or fourth-generation cephalosporin (e.g., cefotaxime or cefepime) or ampicillin and a carbapenem (e.g., meropenem)
  - Highly protein-bound third-generation cephalosporin ceftriaxone avoided in neonates < 30 days of age because of possible displacement of bilirubin from albumin, risking kernicterus, and because of possible interactions with intravenous calcium supplementation
- Empiric (>7 days of age)
  - Vancomycin and a third- or fourth-generation cephalosporin (e.g., cefotaxime or cefepime) or ampicillin and a carbapenem (e.g., meropenem)
- Definitive therapy (any age)
  - GBS: ampicillin, 14–21-day course
  - *E. coli,* other gram-negative rods—as per susceptibility testing; cefotaxime, cefepime, or meropenem, 21–28-day course
  - *L. monocytogenes:* ampicillin, 14–21 day course
- Additional evaluations after antibiotics—all neonates surviving meningitis need to have hearing evaluations and close attention in follow-up for attainment of developmental milestones.
- Rates of all neurodevelopmental sequelae (including deafness, blindness, hydrocephalus, functional abnormalities) after gram-negative meningitis are 15%–30% mild to moderate, 5%–10% major; those after GBS meningitis, 25% mild to moderate, 25% major

Cutaneous and Soft Tissue Infections

BASIC INFORMATION

- Neonatal rashes and skin abnormalities may reflect:
  - Cutaneous infections (e.g., impetigo, bullous impetigo)
  - Soft tissue infections (e.g., boils, abscesses)
  - Toxin-induced infectious disease (e.g., *S. aureus* scalded skin syndrome) or
  - Cutaneous manifestations of systemic infection (e.g., listeriosis, syphilis, neonatal invasive *Candida* infection, neonatal HSV infection)

CLINICAL PRESENTATION

- Impetigo, boils, cutaneous or soft tissue abscesses: present similarly to those in older infants, children, generally after 5–10 days of life, often in diaper area or skinfolds; bullae not as closely grouped as HSV vesicles
- *S. aureus* scalded skin syndrome: tender scarlatiniform erythema of skin, with superficial (stratum granulosum layer of epidermis) desquamation of sheets of skin on gentle pressure or traction in affected and other areas (Nikolsky sign); rarely bacteremic, but dehydration, superinfection may result
- *Listeria* infection: in severe early-onset listeriosis, granulomatosis infantisepticum uncommonly seen, with small pale papules scattered across the skin; on biopsy, histology shows granulomata
- Syphilis: congenital syphilis may present with a postdate dry peeling skin, moist nasal and mucous membrane lesions, or moist lesions on hands and feet (moist lesions can be very infectious); chancres not seen in neonates
- Neonatal candidiasis: rash may appear as simple oral or genital thrush or as part of a more invasive form of dermal candidiasis, with angry red plaque-like lesions over buttocks
- HSV: typical grouped or single dewdrop vesicles on an erythematous base may be seen in skin, eye, mouth form of neonatal HSV disease and in disseminated or CNS disease, especially at sites of iatrogenic breaks in the skin (e.g., scalp electrode monitor, circumcision)

DIAGNOSIS AND EVALUATION

- Impetigo, boils, abscesses: bacterial cultures of infected area
- Syphilis: nontreponemal and treponemal serologic assays (e.g., rapid plasma reagin [RPR] assay, enzyme immunoassay, *Treponema pallidum* particle agglutination [TPPA])
- *Listeria*: blood cultures
- HSV: viral polymerase chain reaction (PCR) assay of scrapings from lesion (or culture if PCR assay not available)

THERAPY

- Impetigo, boils, abscesses
  - For minor impetiginized skin, therapy for group A beta-hemolytic streptococci (*S. pyogenes*) and *S. aureus* with a first-generation cephalosporin (cephalexin, cefazolin) or amoxicillin-clavulanic acid may suffice.
  - For more extensive bullous or invasive lesions, or in more ill neonates, methicillin-resistant *S. aureus* (MRSA) also must be a consideration; thus clindamycin or vancomycin is indicated.
- *S. aureus* scalded skin syndrome: clindamycin or vancomycin (or cefazolin if MRSA excluded)
- *Listeria*: ampicillin, initially with gentamicin added

- *Candida*: for thrush, topical nystatin or an azole cream or ointment; for invasive candidiasis, fluconazole, micafungin, or amphotericin B deoxycholate
- HSV: acyclovir

Gastrointestinal Infections

BASIC INFORMATION

- Diarrheal illness (acute gastroenteritis) is a major source of morbidity and mortality in older infants in lesser income countries but generally not in the NICU.
- Globally, the most commonly identified causes of severe acute gastroenteritis are rotavirus, norovirus, *Shigella*, enterotoxigenic and enteroaggregative *E. coli*, and *Cryptosporidium*, but many other viruses and bacteria can cause acute gastroenteritis.
- Colitis or gastroenteritis in the neonate in a US (or other high-income country) NICU is more likely to be related to necrotizing enterocolitis (NEC), which may be caused by a combination of bacterial or viral infections, gut ischemia, and other unknown factors.
- In the neonate < 1000 g birth weight and younger than 10 days of age, spontaneous intestinal perforation may occur in the absence of NEC; often, coagulase-negative staphylococci and *Candida* are recovered from abdominal fluid cultures, but their role in causing the perforation is uncertain.

CLINICAL PRESENTATION

- Both NEC and spontaneous intestinal peroration may present with poor feeding, abdominal distention, abdominal discoloration, emesis, diarrhea, and/or sepsis.

DIAGNOSIS AND EVALUATION

- Abdominal radiographs may show distended loops of bowel, pneumatosis of the bowel, portal venous air, or free air in the peritoneum.

THERAPY

- For so-called medical NEC (i.e., signs of NEC without evidence of perforation)—an antibiotic with potency against bowel aerobic gram-positive and gram-negative bacteria and anaerobic bacteria, such as piperacillin-tazobactam (a single drug alternative to the combination of ampicillin + clindamycin + gentamicin), is used.
- If perforation or severe sepsis is present, exploratory surgery with bowel resection and possible creation of an ostomy may be performed.

Genitourinary Infections

BASIC INFORMATION

- An ascending UTI or pyelonephritis (as opposed to simply recovering the same organism in urine from a neonate with bacteremic sepsis) is rare in the first 3–7 days of life.
- Fungal UTI with *Candida* may occur in very premature infants, with development of fungal balls leading to obstructive uropathy.

CLINICAL PRESENTATION

- Generally similar to presentation of sepsis; uncommonly, foul-smelling urine identified

DIAGNOSIS AND EVALUATION

- Urinalysis, urine culture obtained by catheterization or suprapubic aspiration
- If *Candida* UTI present, renal and bladder ultrasonography

THERAPY

- Organism dependent; for fungal UTI, fluconazole has the best urinary penetration of available systemic antifungals; a prolonged course of therapy may be required, but rarely is urologic surgery needed to relieve obstruction.

Ocular Infections

BASIC INFORMATION

- Ophthalmia neonatorum is purulent conjunctivitis occurring within the first month of life. It is often thought of as conjunctivitis being caused by *N. gonorrhoeae* or *Chlamydia trachomatis.*
- However, early neonatal conjunctivitis may also be caused by skin, vaginal, and gastrointestinal pathogens, such as *S. aureus, S. pneumoniae, H. influenzae, Moraxella catarrhalis, S. pyogenes,* GBS, *E. coli, Klebsiella* spp., and *P. aeruginosa.*
- Chemical conjunctivitis may occur in the first day or two of life if silver nitrate is used for the prevention of ophthalmia neonatorum (Credé prophylaxis); in the United States, the vast majority of birth centers now use erythromycin ointment instead of silver nitrate.

CLINICAL PRESENTATION

- Gonococcal ophthalmia has an incubation period of 2–7 days and generally results in severe conjunctivitis, with purulent discharge.
- Chlamydial ophthalmia has an incubation period of 5–14 days and is less severe, with minimal watery discharge or crusting.
- Conjunctivitis caused by other microbes is of variable severity, often in the neonate older than 5–7 days of age.
  - Neonatal HSV may cause conjunctivitis as well, particularly in the skin, eye, and mouth form of HSV, generally at 6–14 days of life.
  - *P. aeruginosa* may cause conjunctivitis in older neonates with chronic sedation and mechanical ventilation.

DIAGNOSIS AND EVALUATION

- Maternal culture for gonococci, *Chlamydia*
- Cultures of conjunctival exudate (or PCR if HSV is suspected)

THERAPY

- Gonococcal ophthalmia or asymptomatic baby with exposure to maternal gonorrhea: ceftriaxone, one dose IM (if disseminated gonococcal infection suspected in neonate, cefotaxime 7 days by IV); may need to irrigate eyes with saline
- Chlamydial ophthalmia: oral azithromycin or erythromycin
- Conjunctivitis due to other infectious agents: topical antimicrobials, possibly with additional systemic antibiotics

Omphalitis

BASIC INFORMATION

- Infection of the umbilical structures, with or without cellulitis of the abdominal wall
- Common causative organisms: *S. aureus, S. pyogenes*, GBS, *E. coli* and other gram-negative coliforms, *P. aeruginosa*
  - Rarely, causative anaerobes include *Clostridium perfringens* and *Clostridium tetani*, especially in low-income countries where contaminated instruments or traditional medicines (some of which are contaminated with soil or dung) are applied to the umbilical stump.
  - Rarely, syphilis may cause funisitis alone.

CLINICAL PRESENTATION

- May progress through four stages
  - Stage 1 (least serious): funisitis (wet, possibly purulent inflammation of the umbilical cord only)
  - Stage 2: cellulitis of the insertion of the umbilical cord
  - Stage 3: abdominal wall cellulitis
  - Stage 4: necrotizing fasciitis of the abdominal wall
  - Neonatal tetanus may have few local signs at the umbilicus despite systemic paralytic toxemia

DIAGNOSIS AND EVALUATION

- Cultures of the umbilical cord and affected areas should be done.
- Consider syphilis antibodies for isolated funisitis.

THERAPY

- Empiric therapy
  - For mild to moderate umbilical cellulitis, an agent with gram-positive and gram-negative potency, such as cefazolin; clindamycin if MRSA suspected or common in the NICU, with gentamicin for gram-negative coverage
  - For more severe cellulitis, a broad-spectrum antibiotic combination such as piperacillin-tazobactam plus vancomycin for MRSA, or a carbapenem + vancomycin

Otitis Media

BASIC INFORMATION

- Neonatal otitis media is uncommon; caused by sinopulmonary pathogens as in older infants (e.g., *S. pneumoniae, H. influenzae*) but also gram-negative bacteria (e.g., *E. coli*)

CLINICAL PRESENTATION

- May have nonspecific symptoms, requiring otoscopy for diagnosis

DIAGNOSIS AND EVALUATION

- Otoscopy; tympanocentesis for culture of middle ear fluid traditionally thought to be more important in otitis media in the first 6 weeks of life

THERAPY

- Organism dependent; empiric therapy in hospitalized neonates could include a third- or fourth-generation cephalosporin.

Osteoarticular Infections

BASIC INFORMATION

- Generally occur in late-onset time frame
- GBS, *S. aureus,* and *Candida* each can cause primary bone or joint infections or can be associated with bone or joint relapse after previous bacteremia or fungemia.
- Syphilis osteitis may present as early-onset or later-onset failure to move a limb (pseudoparalysis of Parrot).

CLINICAL PRESENTATION

- Septic arthritis: warmth, redness, swelling, tenderness, and limitation of range of motion of joint; often fever
- Osteomyelitis: possible warmth, redness over infected site on bone; fever; point tenderness, failure to move the extremity if a long bone
- Pseudoparalysis of Parrot: may or may not have swelling over the affected bone, or fever; can mimic Erb palsy

DIAGNOSIS AND EVALUATION

- Inflammatory markers: CRP, erythrocyte sedimentation rate (ESR), complete blood count and differential
- Radiography; possibly MRI or technetium-99 bone scintigraphy
- Arthrocentesis or bone biopsy with Gram staining and culture of material obtained
- Blood cultures

THERAPY

- Empiric therapy
  - Targeted against GBS, *S. aureus*—first-generation cephalosporin (cefazolin) or antistaphylococcal penicillin (nafcillin); third-generation cephalosporin such as cefotaxime also may be considered, especially if prior sepsis with gram-negative bacteria
  - Fluconazole, micafungin, caspofungin, or amphotericin B deoxycholate if prior fungemia
- Definitive therapy: organism dependent
- Adjunctive surgical therapy may be necessary for both diagnosis and therapy, especially in septic arthritis or periosteal abscess

Pneumonia

BASIC INFORMATION

- This may be difficult to distinguish from neonatal sepsis, acute respiratory distress syndrome, aspiration, or bronchopulmonary dysplasia.
- Causative organisms and presentation are similar to neonatal sepsis (EOS or LOS).
- Occasionally, late-onset pneumonia may be caused by less common organisms acquired during birth (e.g., *C. trachomatis*) or from visitors or caretakers in the NICU (e.g., as respiratory syncytial virus, influenza virus, *Bordetella pertussis*).

CLINICAL PRESENTATION

- Respiratory distress, including apnea, tachypnea, cyanosis, grunting, retractions, rales, desaturation (some or all of these)

DIAGNOSIS AND EVALUATION

- Blood cultures
- Endotracheal tube aspirate, Gram staining, cultures difficult to interpret—endotracheal colonization with many types of potentially pathogenic bacteria is both common and nonspecific (not necessarily indicative of deeper respiratory tract infection)
- Chest radiograph

THERAPY

- Empiric: as for sepsis (either EOS or LOS, depending on the age of the neonate)
- Definitive: organism dependent

Suggested Readings

Benjamin DK Jr, Stoll BJ, Gantz MG, et al. Neonatal candidiasis: epidemiology, risk factors, and clinical judgment. *Pediatrics*. 2010;126. e865–e873.

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Nizet V, Klein JO. Bacterial sepsis and meningitis. In: Wilson CB, Nizet V, Maldonado YA, Remington JS, Klein JO, eds. *Infectious Diseases of the Fetus and Newborn Infant*. 8th ed. Philadelphia: Elsevier Saunders; 2016:1132–1146.

Shane AL, Sánchez PJ, Stoll BJ. Neonatal sepsis. *Lancet*. 2017;390:1770–1780.

Stoll BJ, Hansen NI, Sánchez PJ, et al. Early onset neonatal sepsis: the burden of group B Streptococcal and E. coli disease continues. *Pediatrics*. 2011;127:817–826.

Willson DF, Conaway M, Kelly R, Hendley JO. The lack of specificity of tracheal aspirates in the diagnosis of pulmonary infection in intubated children. *Pediatr Crit Care Med*. 2014;15:299–305.

Questions:

1. What are the major causes of neonatal early-onset sepsis?
   a. Group B beta-hemolytic streptococci, Escherichia coli, & Listeria monocytogenes
   b. Candida albicans, coagulase-negative staphylococci & Staphylococcus aureus
   c. Enteroviruses and herpes simplex viruses
2. What are the major causes of neonatal late-onset sepsis?
   a. Group B beta-hemolytic streptococci
   b. Escherichia coli, & Listeria monocytogenes
   c. coagulase-negative staphylococci & group D enterococci
   d. all of the above

39 Causative Agents of Infections

GEOFFREY A. WEINBERG

BACTERIA

Group B Streptococci (GBS; *Streptococcus agalactiae*)

BASIC INFORMATION

- Major cause of perinatal infections in mothers and neonates, including early-onset and late-onset sepsis (EOS and LOS)
- Gram-positive aerobic cocci in pairs or short chains
- GBS commonly colonize gastrointestinal and genitourinary tracts, rarely the pharynx; colonization during pregnancy, constant or intermittent, ranges from 15%–35% of pregnant women
- GBS transmitted from mother to neonate shortly before birth, during delivery, or after delivery; if after delivery, uncommonly transmitted from others (e.g., family members, caregivers, health care professionals)
- Routine screening for GBS and chemoprophylaxis of colonized pregnant women at labor and delivery—has significantly reduced incidence of GBS EOS infection; for unknown reasons, incidence of LOS unaffected by chemoprophylaxis (see Chapter 40)

CLINICAL PRESENTATION

See also Chapter 38.

- Maternal infections: urinary tract infections, bacteremia, endometritis, chorioamnionitis
- Neonatal infections caused by GBS: EOS (<7 days of age), LOS (7–90 days of life), focal infections
  - EOS: respiratory distress, apnea, hypotension, pneumonia, sometimes neutropenia; meningitis in ~5%–10%; typically presents in first 24 hours of life
  - LOS: bacteremia, hypotension, meningitis (~30%); presents around 3–4 weeks of age
  - Focal infections: cellulitis, pneumonia, adenitis, bone or joint infections
- Late late-onset or very late-onset GBS infection—presents beyond 90 days of life, often as focal infection
- High morbidity of GBS meningitis—≈45% overall morbidity, with 25% mild to moderate sequelae and 20% major sequelae (e.g., blindness, bilateral sensorineural hearing loss, cerebral palsy, profound developmental delay).
- Recurrence of GBS infection—may be seen in 1%–3% of infants despite appropriate treatment of first episode

DIAGNOSIS

- Gram stain and by recovery of organisms in culture of blood, cerebrospinal fluid, urine, or infected tissue

THERAPY

For prevention, see Chapter 40.

- GBS best treated by beta lactams (ampicillin or penicillin G); some synergy thought to be afforded by aminoglycosides (e.g., gentamicin)
  - Presumptive treatment of EOS: intravenous (IV) ampicillin + gentamicin
  - Presumptive treatment of LOS: IV ampicillin + gentamicin or ampicillin + cefotaxime
- Definitive therapy once GBS identified: IV ampicillin or penicillin G
  - For GBS meningitis, high-dose ampicillin or penicillin G (plus an initial 3 days of aminoglycoside) administered for 14–21 days; if significant ventriculitis or delayed sterilization of the CSF occurs, some experts would treat for 28 days.
  - For GBS bacteremia or cellulitis without meningitis, 10 days of ampicillin or penicillin G may suffice.
  - Treatment of septic arthritis or osteomyelitis may require 3–4 weeks.

Staphylococcus aureus

BASIC INFORMATION

- *Staphylococcus aureus* cause of a number of localized and invasive suppurative infections, as well as three toxin-mediated syndromes (e.g., scalded skin syndrome, and in older children, toxic shock syndrome and food poisoning)
- Gram-positive cocci in pairs or grapelike clusters; coagulase-positive, in contrast to coagulase-negative staphylococci such as *Staphylococcus epidermidis*
- Ubiquitous human flora, colonizes skin and mucous membranes of 30%–50% of healthy children and adults (especially anterior nares, throat, axilla, perineum, rectum)
- Second to coagulase-negative staphylococci as cause of health care–associated infection
- Transmitted by direct contact
- Unique clones of *S. aureus* have acquired beta-lactam resistance genes, rendering them resistant to antistaphylococcal penicillins such as methicillin, as well as most

cephalosporins—called methicillin-resistant *S. aureus* (MRSA) as opposed to methicillin-susceptible *S. aureus* (MSSA)

CLINICAL PRESENTATION

- Localized infections include cellulitis, skin and soft tissue abscesses, pustulosis, impetigo (bullous and nonbullous), mastitis, furuncles, carbuncles, omphalitis, and wound infections.
- Staphylococcal scalded skin syndrome (SSSS) is a toxin-mediated infection in neonates and young children who are thought to have less immunity to the toxins that cause cleavage of the skin at the superficial stratum granulosum layer of the epidermis.
  - Presents with red, painful skin, which peels in sheets on gentle pressure or traction (Nikolsky sign)
  - Oral or intravenous antibiotics—may be used to clear the causative organisms, nearly always an MSSA isolate
- Invasive infections include bacteremia (especially associated with foreign bodies such as intravascular catheters or cerebrospinal fluid shunts), septicemia, osteomyelitis or septic arthritis, endocarditis, pneumonia with or without pleural empyema, and visceral abscesses; septic thrombophlebitis of intravenous catheter sites may also be seen.

DIAGNOSIS

- Gram stain and recovery of organisms in culture of blood, infected tissue, or infected sites

THERAPY

- For localized infections, an antistaphylococcal penicillin such as nafcillin or methicillin, a first-generation cephalosporin such as cefazolin, or clindamycin is given intravenously for neonates with MSSA infections; if the isolate is already known to be MRSA (or the child is known to be previously colonized or infected with MRSA), vancomycin is used instead.
- For more serious skin and soft tissue wound infections, or any invasive infections, IV therapy is used for both MSSA and MRSA.
  - One should empirically use agents active against both MSSA and MRSA, such as IV vancomycin.
  - Definitive therapy is tailored according to antimicrobial susceptibility test results; for most MSSA infections, nafcillin or cefazolin is more potent than vancomycin.

Coagulase-Negative Staphylococci

BASIC INFORMATION

- Coagulase-negative staphylococci (CoNS)—most common cause of health care–associated infections, which most commonly appears as bacteremia associated with intravascular catheters
- Gram-positive cocci in pairs or grapelike clusters; coagulase-negative, in contrast to *S. aureus*
- Ubiquitous human and environmental flora; commonly colonize skin and mucous membranes
- Many species of CoNS exist; not all hospital laboratories independently speciate them, but *S. epidermidis, S. haemolyticus, S. schleiferi, S. lugdunensis,* and *S. saprophyticus* most often associated with infection in humans
- CoNS can generate biofilm—allows them to adhere to both native and prosthetic surfaces; leads to difficulty in clearing infection, despite their relatively low virulence
- May be transmitted by direct contact, but most infection likely from one's own flora
- Most strains of CoNS resistant to antistaphylococcal penicillins and cephalosporins and often other antibiotics such as clindamycin—but susceptible to vancomycin

CLINICAL PRESENTATION

- Most common—late-onset bacteremia or sepsis in extremely low and very-low-birth-weight infants
- Also common in neonates with intravascular catheters or indwelling foreign bodies (e.g., cardiac grafts, shunts, valves; ventriculoperitoneal shunts)
- Recovery of CoNS can be indicative of infection, but likely more often a clinical contaminant, representing contamination of a culture with skin flora; can make it difficult to interpret culture results

DIAGNOSIS

- Gram stain and recovery of organisms in culture of blood, infected tissue, or infected sites

THERAPY

- For CoNS isolates thought to be causing true infection, the therapy of choice is vancomycin.

Listeria monocytogenes

BASIC INFORMATION

- *Listeria monocytogenes* uncommon cause of infection in pregnant women and neonates
- Gram-positive, nonsporulating rod can be variable in shape (and misidentified as "diphtheroids"); intracellular pathogen that can also grow extracellularly at colder temperatures
- Predominantly a foodborne-transmitted illness in adults; neonates acquire it vertically
  - Common food sources contaminated with *L. monocytogenes* include deli-style ready to eat meats, poultry, unpasteurized milk, soft cheeses
  - In past 20 years, incidence of listeriosis in the United States has decreased, largely due to more rigorous agricultural screening and food-processing regulations

CLINICAL PRESENTATION

- Pregnancy-associated infections may cause spontaneous abortion, fetal death, chorioamnionitis, and preterm delivery.

- Rarely, a serious congenital infection characterized by an erythematous, small papular rash (granulomatous papules under histologic examination) called *granulomatosis infantisepticum* is seen.

DIAGNOSIS

- Recovery of organisms in culture of blood or cerebrospinal fluid (CSF)
- Gram stains of CSF in neonates with *Listeria* meningitis—may be negative, in contrast to the usual positive CSF examination in neonatal meningitis; organisms are intracellular, tend to adhere to the meninges, or may be inappropriately considered to represent diphtheroid contaminants

THERAPY

- IV ampicillin plus an aminoglycoside (e.g., gentamicin)
- Cephalosporins not active against *L. monocytogenes*
- For bacteremia, 14-day treatment course is used; for meningitis, 21 days or longer (e.g., if brain abscess is present)

Escherichia coli and Other Gram-Negative Bacilli

BASIC INFORMATION

- *Escherichia coli, Klebsiella* spp., *Enterobacter* spp., *Proteus* spp., *Pseudomonas aeruginosa, Serratia* spp., *Citrobacter* spp., and *Acinetobacter* spp. can all cause neonatal bacteremia, sepsis, and (particularly for *E. coli*) meningitis.
- Gram-negative rods may have the ability to ferment lactose (e.g., *E. coli*) or not (e.g., *Pseudomonas*).
- Neonatal infections caused by *E. coli*, especially meningitis, are often members of clones of K1 capsular serotypes, which are distinctly different from uropathogenic or diarrheagenic *E. coli.*

CLINICAL PRESENTATION

- Early signs of sepsis and/or meningitis can be subtle and similar to signs observed in GBS EOS or LOS.
- Gram-negative sepsis may also be associated with necrotizing enterocolitis, with or without intestinal perforation.

DIAGNOSIS

- Gram-stain and recovery of organisms in culture of blood or CSF is carried out.
- Antimicrobial susceptibility testing important—many gram-negative bacteria have acquired multidrug resistance elements (e.g., extended spectrum beta-lactamases and carbapenemases).

THERAPY

- Ampicillin plus an aminoglycoside (e.g., gentamicin) is the traditional empiric therapy for sepsis possibly caused by gram-negative bacteria.
- For gram-negative rod meningitis, many authorities now favor combination therapy with ampicillin plus an advanced generation cephalosporin, such as cefotaxime, (or ampicillin plus a carbapenem) over ampicillin plus gentamicin, to take advantage of the improved pharmacokinetics and pharmacodynamics in the CSF.
- Suspected *Pseudomonas, Acinetobacter*, and other non–lactose-fermenting gram-negative bacteria require empiric therapy with an antipseudomonal penicillin such as piperacillin-tazobactam or a carbapenem such as meropenem; antimicrobial susceptibility testing should guide definitive therapy.

Syphilis (*Treponema pallidum*)

BASIC INFORMATION

- Intrauterine infection with *T. pallidum* may cause congenital syphilis, which can cause stillbirth, hydrops fetalis, or premature birth, resulting in symptomatic or asymptomatic infants.
- Untreated congenital syphilis may cause significant, crippling morbidity throughout childhood and adulthood, but late manifestations are prevented by adequate treatment of early infant infection.
- Thin motile spirochetes are unable to be cultured in clinical laboratories and are difficult to identify under a microscope without darkfield optics; thus the diagnosis is made by serologic tests.
- Intrauterine transmission may occur throughout pregnancy but is most common between 16 and 28 weeks' gestation; the earlier transmission occurs during pregnancy, the more likely a stillbirth or premature symptomatic infant will result. Transmission during the third trimester very often results in an infected but asymptomatic or mildly symptomatic infant.
- The stage of maternal syphilis also affects transmission risk; mothers with early syphilis are more likely to transmit the infection than those with late latent or tertiary infection.

CLINICAL PRESENTATION

- It is asymptomatic in 50%–60% of infected infants at birth, but illness may appear in the ensuing first few weeks of life.
- Symptoms of congenital syphilis include radiographic bone changes (osteochondritis and periostitis), hepatomegaly with or without splenomegaly, a desquamative generalized rash, sometimes with blistering or moist skin over the palms and soles, and also the mucocutaneous junctions, jaundice, lymphadenopathy, disuse of a limb mimicking Erb palsy (pseudoparalysis of Parrot), or persistent rhinitis ("snuffles").

DIAGNOSIS

- All pregnant women should be screened serologically for syphilis early in pregnancy and preferably again near delivery.

- There are two serologic testing algorithms, along with two serologic assay types.
  - Traditional Screening Algorithm: Uses initial nontreponemal screening tests (detects nonspecific IgG antibody to cardiolipin, reported as titers) (Figure 39.1)
    - Rapid plasma reagin (RPR) assay
    - Venereal Disease Research Laboratory (VDRL) test (older)
    - These antibodies decrease over time, and should revert to negative with successful treatment
  - Due to high false-positive rate, if maternal screen positive, confirm with treponemal-antibody specific test such as *T. pallidum* particle agglutination (TPPA) or fluorescent treponemal antibody absorption (FTA-ABS); these antibodies, once reactive, are reactive for life, even after successful treatment
  - Newer reverse sequence screening algorithm (Fig. 39.1)—a treponemal enzyme immunoassay (EIA) is used first; if positive, followed by RPR and confirmatory second test (TPPA or FTA-ABS).
- Other tests that are frequently used in the evaluation for congenital syphilis include chest x-ray, long bone radiography, lumbar puncture, complete blood count and differential, and hepatic transaminases (Fig. 39.1).

THERAPY

- Penicillin is the therapy of choice for congenital syphilis; the route and extent of the therapy depend on the certainty of the diagnosis and the presence of symptoms of infection (see Fig. 39.1).
- Therapy of pregnant women with syphilis is also best achieved with penicillin. If therapy is completed more than 4 weeks before delivery, it is considered adequate to prevent congenital syphilis. However, therapy within 4 weeks of delivery; undocumented therapy; therapy associated with failure of response (≥four-fold increase in maternal RPR) even if given more than 4 weeks before delivery; or therapy comprised of an antimicrobial other than penicillin, is considered not adequate to prevent congenital syphilis (see Fig. 39.1).

Tuberculosis

BASIC INFORMATION

- Although tuberculosis likely infects 2 billion people globally, congenital tuberculosis is very rare (although perhaps underdiagnosed, especially in developing countries).
- Vertical transmission of tuberculosis may occur from the hematogenous spread from an infected placenta or by aspiration or ingestion of infected amniotic fluid or genital secretions; genital tuberculosis in women frequently causes sterility, which might in turn result in the rarity of congenital infection.

CLINICAL PRESENTATION

- Mimics sepsis or other congenital infections; often causes prematurity, respiratory distress, hepatomegaly with or without splenomegaly, and irritability

DIAGNOSIS

- This is best made by the recovery of organisms in blood culture, endotracheal aspirates (or gastric aspirates), cerebrospinal fluid (CSF), or maternal placenta, or genital specimens.
- Chest x-ray and tuberculin skin test may be useful as well, although the tuberculin skin test may not be reactive for 6 weeks or more even in infected infants.

THERAPY

- Multidrug therapy for an extended duration is the standard of care, although clinical trials in neonates have not been performed; an infectious disease or tuberculosis expert should be consulted.

Chlamydia trachomatis

BASIC INFORMATION

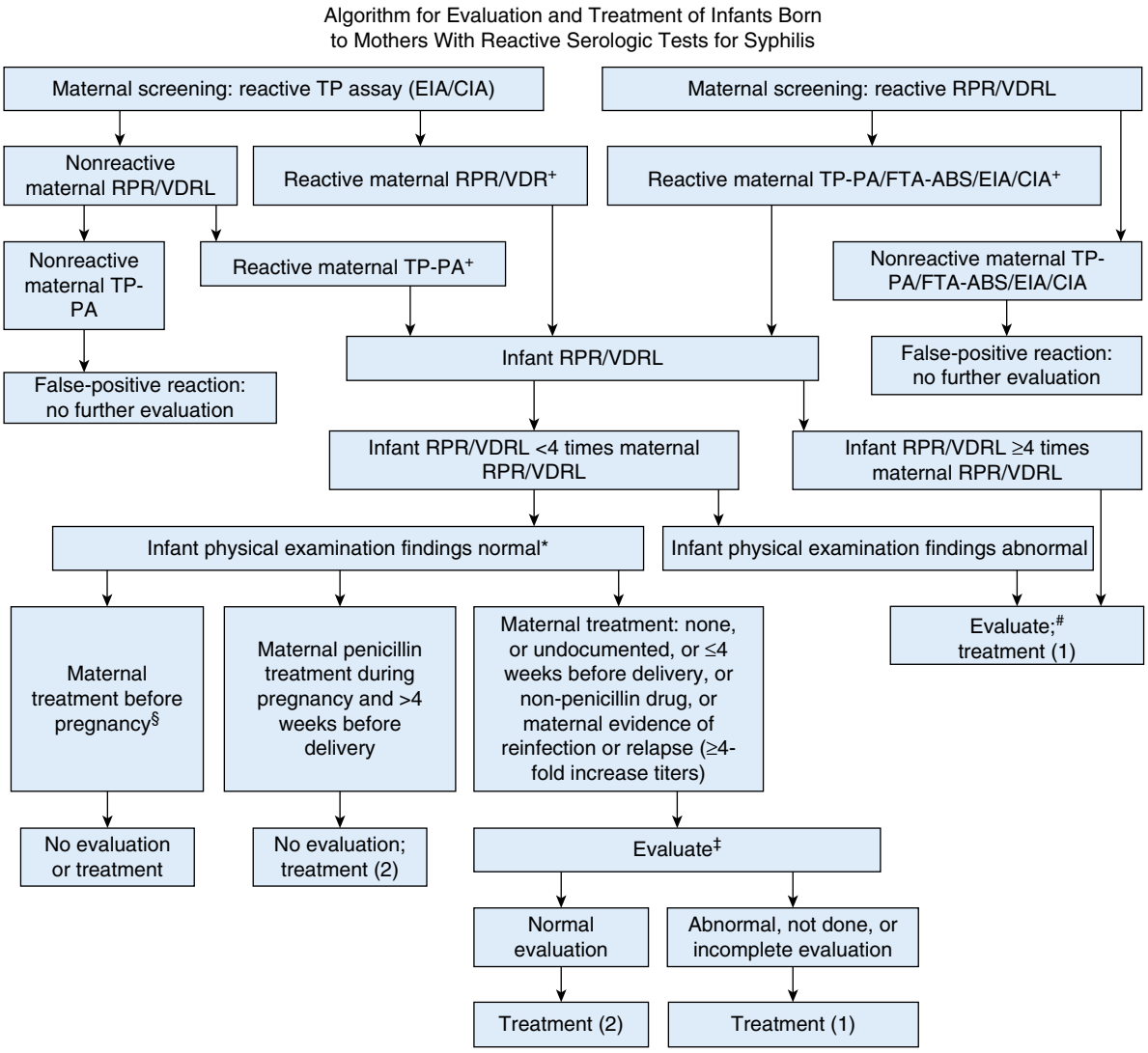
- *Chlamydia trachomatis* is a very common cause of symptomatic and asymptomatic urogenital infections in men and women and can be transmitted from pregnant women to their neonates, causing neonatal conjunctivitis **or** pneumonia,
- Transmission from infected mothers is ~50% in vaginal births, less after cesarean section; infants may remain infected for much of the first year of life.
- Topical ophthalmia neonatorum prophylaxis given at birth is targeted at the prevention of gonococcal infection, but it does not fully prevent chlamydial conjunctivitis and is ineffective against preventing chlamydial pneumonia.

CLINICAL PRESENTATION

- Neonatal conjunctivitis (nongonococcal ophthalmia neonatorum)
  - Ocular congestion, edema of the eyelids, and conjunctival discharge developing in days to a few weeks (usually 5–14 days) after birth
  - May last for 1–2 weeks if untreated
- Neonatal pneumonia:
  - Presents insidiously, typically with afebrile, staccato cough, tachypnea, and rales, at a few weeks to 5–6 months of life (typically around 4–6 weeks of age)
- Chest radiograph may show hyperinflation and infiltrates
- Sometimes accompanied by peripheral blood eosinophilia

DIAGNOSIS

- Nucleic acid amplification tests (NAATs) are superior to culture techniques for the diagnosis of *C. trachomatis* in urogenital infection at all ages, but are not yet approved for use in the United States for the diagnosis



\+ Test for HIV antibody. Infants of HIV-infected mothers do not require different evaluation or treatment.

* If the infant's RPR/VDRL is nonreactive AND the mother has had no treatment, undocumented treatment, treatment ≤4 weeks before delivery, or no evidence of reinfection or relapse (≥4-fold increase in titers), THEN treat infant with a single IM injection of benzathine penicillin (50,000 U/kg). No additional evaluation is needed.

§ Women who maintain a VDRL titer ≤1 : 2 (RPR ≤1 : 4) beyond 1 year following successful treatment are considered serofast.

\# Evaluation consists of CBC, platelet count; CSF examination for cell count, protein, and quantitative VDRL. Other tests as clinically indicated: long-bone X-rays, neuroimaging, auditory brainstem response, eye examination, chest X-ray, liver function tests.

‡ CBC, platelet count; CSF examination for cell count, protein, and quantitative VDRL; long-bone X-rays.

TREATMENT:

(1) Aqueous penicillin G 50,000 U/kg IV every 12h (≤1 week of age), q8 hr (>1 week) or procaine penicillin G 50,000 U/kg IM single daily dose, x 10 days

(2) Benzathine penicillin G 50,000 U/kg IM x 1 dose

Fig. 39.1 Algorithm for evaluation and treatment of infants born to mothers with reactive serologic test results for syphilis. *CBC*, Complete blood cell; *CIA,* chemiluminescence immunoassay; *CSF,* cerebrospinal fluid; *EIA,* enzyme immunoassay; *FTA-ABS,* fluorescent treponemal antibody absorption; *HIV,* human immunodeficiency virus; *IM,* intramuscular/intramuscularly; *IV,* intravenously; *RPR,* rapid plasma reagin; *TP*, Treponema pallidum; *TP-PA, Treponema pallidum particle agglutination; VDRL,* Venereal Disease Research Laboratory. (Modified from Michaels MG, Sanchez P, and Lin L. Congenital Toxoplasmosis, Syphilis, Malaria, and Tuberculosis. In: Gleason CA, Juul SE, eds. *Avery's Diseases of the Newborn*, 10th Ed. Philadelphia: Elsevier, 2018.)

of neonatal conjunctivitis or pneumonia (eye or nasopharyngeal specimens).
- Recovery of organisms by culture of conjunctival or nasopharyngeal samples is less sensitive than an NAAT but may be done; if not easily available, a clinical diagnosis of neonatal chlamydial infection may be made in the appropriate clinical scenario,

THERAPY

- A macrolide, such as erythromycin (14-day course) or azithromycin (3-day course), is used for neonatal conjunctivitis or pneumonia.
  - Azithromycin is preferred because of the association of erythromycin and infantile hypertrophic pyloric stenosis.
  - Mothers of infected infants, and the mother's sexual partners, should receive therapy for *C. trachomatis* as well.
- Systemic therapy rather than topical therapy is used for neonatal chlamydial conjunctivitis to prevent subsequent pneumonia.
- Routine preventive therapy generally is not suggested for infants of mothers known to have untreated chlamydial infection at birth, but may be done if adequate clinical follow-up cannot be ensured.

Genital Mycoplasmas and Ureaplasmas

BASIC INFORMATION

- *Mycoplasma genitalium, M. hominis, Ureaplasma urealyticum,* and *U. parvum*—small, pleomorphic bacteria lacking cell walls, identified best by polymerase chain reaction (PCR) assays or less so by culture
- Thought to cause nongonococcal, nonchlamydial urethritis in men and women and endometritis in women; associated in some studies, but not in others, with pregnancy loss, preterm birth, and development of bronchopulmonary dysplasia
- *Ureaplasma* spp.—have been isolated from blood and CSF of neonates but their contribution to clinical outcome is uncertain

Anaerobic Bacteria

BASIC INFORMATION

- Anaerobic bacteria such as *Bacteroides* spp. and *Clostridium* spp. are uncommonly recovered from the bloodstream of infants with bacteremia or sepsis—most often in neonates with necrotizing enterocolitis, postoperative abdominal infections, or fasciitis or after maternal chorioamnionitis.
- They are best treated with an anaerobe-active beta-lactam such as piperacillin-tazobactam, or meropenem or an agent such as clindamycin or metronidazole.
- *Clostridium difficile* is a very common colonizer of neonatal and infant gastrointestinal tracts but is thought not to cause pseudomembranous colitis in infants younger than 1–2 years; in general, studies for *C. difficile* should not be carried out in an infant younger than 1–2 years.

Fungi *Candida albicans* and Non–*albicans* Spp.

BASIC INFORMATION

- Invasive fungal infection with *Candida* spp. occurs in up to ~2% of all US neonatal intensive care unit (NICU) admissions.
  - The risk of infection rises dramatically with decreasing gestational age and birth weight.
  - *Candida* spp. are ubiquitous, colonizing the skin, mouth, gastrointestinal tract, and genitourinary tract but is an uncommon cause of infection in pregnant women and neonates; it is acquired in utero (rare), during birth, or postnatally,
    - Budding yeast, some species of which form long buds or chains of buds—called pseudohyphae
- *C. albicans* causes about 50% of neonatal yeast infections.

CLINICAL PRESENTATION

- Local infections
  - Congenital candidiasis: very rare form of dermal infection seen in the first day of life; deeply erythematous skin, which soon desquamates
  - Diaper dermatitis (thrush): common, erythematous dermatitis in perianal area or groin, with papular or pustular satellite lesions
- Invasive (disseminated) infections
  - Candiduria, UTI: renal candidiasis may be a local infection, but often associated with upper tract disease and possible systemic infection
    - Characterized by presence of yeast in catheterized urine sample, often with cortical abscesses or collections of fungal material in the collecting system demonstrable on renal ultrasound; may lead to urinary obstruction
  - Peritonitis, as a consequence of bowel perforation—either from spontaneous intestinal perforation in the first week of life in neonates <1000 g or later from necrotizing enterocolitis
  - Candidemia associated with central venous catheters
  - Candidemia associated with disseminated candidiasis—for example, with pneumonia, septic arthritis, hepatosplenic lesions, or meningitis

DIAGNOSIS

- Made by recovery of organisms in culture of urine, blood, CSF, or peritoneal fluid
- Retinitis present in ~5% of cases of disseminated candidiasis; ophthalmologic examination may assist in looking for sites of disease in addition to renal ultrasound, lumbar puncture

THERAPY

- Amphotericin B remains the most potent agent, with the longest clinical experience.
  - Amphotericin B deoxycholate is well tolerated by neonates and is significantly less expensive than liposomal amphotericin B used in older children and adults.
- Fluconazole, which has excellent penetration into the CSF and urinary tract, may be used if the yeast is identified as *C. albicans* or a fluconazole-susceptible, non-albicans *Candida*
- Echinocandins such as micafungin or caspofungin are active against *Candida* spp. and may be used especially for azole-resistant isolates (e.g., *C. krusei*).
- For catheter-associated fungemia, a 14-day treatment course is most often recommended; for disseminated disease or meningitis, 21 days or longer is recommended.
- For prevention of candidiasis with prophylactic fluconazole, see Chapter 40.

Malassezia furfur and Other Fungal Infections

BASIC INFORMATION

- Uncommonly, infection is seen with the cutaneous lipophilic yeast *Malassezia furfur*; *Malassezia* spp. causes tinea versicolor in older children and adults but may invade the bloodstream of infants with central venous catheters who are receiving total parenteral nutrition, especially parenteral lipid alimentation.
  - Removal of the catheter, with interruption of the total parenteral nutrition for a few days, may suffice for therapy, but some experts recommend additional therapy with amphotericin B for 7–10 days.
- Noncandidal fungal infections (e.g., other yeasts such as cryptococcosis or mold infections such as aspergillosis or fusariosis, or endemic mycoses such as histoplasmosis, blastomycosis, or coccidioidomycosis) are very rare in the NICU.

VIRUSES

- General comments on viral infection
  - Viral infections in the neonate are likely more common than is currently recognized or able to be diagnosed with current diagnostic tests.
  - Transmission can occur prenatally (in utero), in the peripartum or intrapartum period, or in the immediate postpartum period.
    - Important prenatal (in utero) viral infections: cytomegalovirus (CMV), rubella virus, parvovirus B19, HIV, lymphocytic choriomeningitis virus (LCMV) varicella zoster virus (VZV)
    - Important peripartum viral infections: hepatitis B virus (HBV), HIV, HSV, enterovirus, VZV
    - Important postpartum viral infections: respiratory syncytial virus, influenza virus, VZV, CMV
  - Some general clinical findings suggest a specific diagnosis (Table 39.1).

Cytomegalovirus

BASIC INFORMATION

- CMV infection is present at birth in 0.5% to 1% of all live-born infants; it is the most common congenital viral infection in the United States.
  - In utero fetal infection can occur in women with no preexisting CMV immunity (maternal primary infection), or in women with preexisting antibody to CMV (maternal non-primary infection), either from reactivation of an existing maternal infection or infection with a new viral strain.
  - Congenital infection and associated sequelae can occur irrespective of the trimester of pregnancy when the mother is infected.
  - Primary maternal infection, although less common, is associated more with severe neonatal sequelae, especially if maternal infection is acquired during the first half of gestation.
- Congenital CMV infection is the leading nongenetic cause of sensorineural hearing loss (SNHL) in US children; ~ 20% of all hearing loss at birth and 25% of all hearing loss at 4 years of age is attributable to congenital CMV infection.

Table 39.1 Clinical Findings Suggesting a Specific Congenital Viral Infection

Congenital Infection	Findings
Rubella	Congenital cataracts, pigmented retina; petechiae with blueberry muffin rash; bone defects with longitudinal bands of demineralization ("celery stalking"); cardiovascular malformations (patent ductus arteriosus, pulmonary artery stenosis); sensorineural hearing loss; fetal hydrops
Cytomegalovirus	Microcephaly with periventricular calcifications; chorioretinitis; petechiae with thrombocytopenia; jaundice; sensorineural hearing loss
Herpes simplex virus	Skin vesicles, keratoconjunctivitis, acute central nervous system findings (seizures), hepatitis, pneumonitis, sepsis-like picture
Parvovirus B19	Fetal hydrops, ascites, hepatomegaly, ventriculomegaly, hypertrophic myocardiopathy, anemia
Varicella zoster virus	Limb hypoplasia, dermatomal scarring in cicatricial pattern
Lymphocytic choriomeningitis virus	Hydrocephalus, chorioretinitis, intracranial calcifications; negative studies for CMV, toxoplasmosis

Modified from Schleiss MR, Patterson JC. Viral infections of the fetus and newborn and HIV infection during pregnancy. In: Gleason CA, Devaskar SU, eds. *Avery's Diseases of the Newborn.* 9th ed. Philadelphia: Elsevier Saunders; 2012.

- CMV is a member of the herpesvirus family; it is found only in humans, is ubiquitous across the globe, and exhibits extensive genetic diversity, allowing nonprimary reinfection.

CLINICAL PRESENTATION

- Congenital CMV infection has a wide spectrum of clinical manifestations, from asymptomatic to life-threatening disease. Symptoms and signs at birth include intrauterine growth retardation, microcephaly, periventricular intracranial calcifications, jaundice, hepatosplenomegaly, retinitis, and dermal hematopoiesis ("blueberry muffin" rash). Sequelae are mostly neurologic. (Fig. 39.2)

DIAGNOSIS

- Neonates with congenital CMV shed CMV in saliva and urine; either fluid may be subjected to PCR amplification or rapid shell vial culture for timely diagnosis.
- A positive CMV PCR or culture result in the first month of life is diagnostic for congenital CMV infection; after 4–6 weeks of age, positive results could represent postnatal infection (from breast milk, transfusions, or other contact)

THERAPY

- Controlled clinical trials have shown that neonates with symptomatic congenital CMV disease have improved audiologic and neurodevelopmental outcomes at 2 years of age when treated with oral valganciclovir (an orally bioavailable prodrug of ganciclovir).

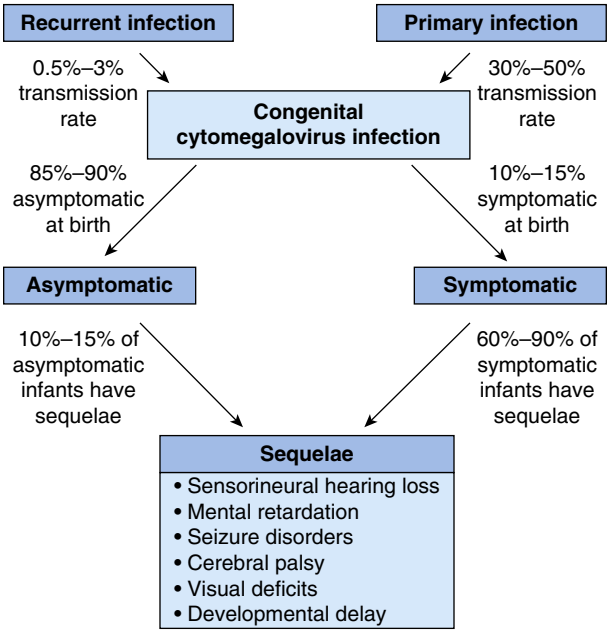


Fig. 39.2 Profiles of congenital cytomegalovirus (CMV) epidemiology, infection, and outcome. (Modified from Schleiss MR, Marsh KJ. Viral infections of the fetus and newborn infant. In: Gleason CA, Juul SE, eds. *Avery's Diseases of the Newborn*, 10th Ed. Philadelphia: Elsevier, 2018.)

- Valganciclovir is administered orally or by gastrostomy tube for 6 months.
- For infants unable to tolerate enteral feeding, intravenous ganciclovir provides similar systemic ganciclovir exposure.
- Significant neutropenia occurs in ~20% of infants treated with oral valganciclovir and in ~67% of infants treated with parenteral ganciclovir; absolute neutrophil counts should be performed frequently (along with monthly serum aminotransferase concentrations to exclude uncommon hepatitis).
- In contrast, infants with asymptomatic congenital CMV infection should not receive antiviral treatment, because currently the drug risks appear to outweigh theoretic benefits.

Herpes Simplex Virus

BASIC INFORMATION

- Herpes simplex virus-1 (HSV-1) and HSV-2 are members of the herpesvirus family that may cause recurrent mucocutaneous disease and, in neonates (and older immunocompromised hosts), more severe invasive disease,
- HSV-1 and HSV-2 persist for life in latent form after causing the primary infection,
- Neonatal HSV is acquired vertically, usually during birth through an infected maternal genital tract and uncommonly from an ascending infection through ruptured amniotic membranes.
  - Rarely, postnatal transmission from a parent or other caregiver, usually from a nongenital infection (e.g., herpetic whitlow or herpes labialis lesion)
- Both HSV-2 and HSV-1 may cause neonatal HSV infection.
- The overall incidence of neonatal HSV infection in the United States is ~1 in 3000 to 10,000.
- Most cases of neonatal HSV occur in women who have had a recent primary infection, although most maternal infections are asymptomatic or subtle enough to escape diagnosis; thus the history of past maternal HSV lesions is not clinically useful in the diagnosis of neonatal HSV.
  - The transmission rate of HSV among women who already have recurrent HSV in the first half of pregnancy is ~2% and that of primary HSV acquired late in pregnancy is ~33% to 50%.

CLINICAL PRESENTATION

- Neonatal HSV presents in three forms, which may overlap to some extent.
  - Disseminated disease: a sepsis-like condition involving multiple organs, most prominently liver and lungs, but also the central nervous system (CNS); represents about 25% of all neonatal HSV infections
  - CNS disease, with or without skin involvement: about 30% of neonatal HSV infections

- Skin, eye, and/or mouth disease (SEM disease), which is localized to the skin, eyes, and/or mouth: about 45% of neonatal HSV infections
- The onset of disease is generally around 2 weeks of age—during the first or second week of life for disseminated or SEM disease and between the second and third weeks for CNS disease.
- More than 80% of neonates with SEM disease and ~67% of those with CNS disease or disseminated HSV infection will have skin vesicles at some point in the illness—but these lesions may not be present at the time of onset of symptoms in CNS disease or disseminated forms.
- Disseminated and CNS diseases often are severe, with attendant high mortality and morbidity rates, even when antiviral therapy is administered.
  - Disseminated disease—30% mortality, 20% of survivors with sequelae
  - CNS disease—10% mortality, 70% of survivors with sequelae

DIAGNOSIS

- Neonatal HSV should be considered in neonates with culture-negative sepsis, severe liver dysfunction, or consumptive coagulopathy.
- For the diagnosis of neonatal HSV infection, the following specimens should be obtained—(1) swab specimens from the mouth, nasopharynx, conjunctivae, and anus ("surface cultures") for HSV culture or if available, for HSV PCR assay; (2) specimens of skin vesicles for HSV culture and, if desired, for PCR assay; (3) CSF sample for HSV PCR assay; (4) whole-blood sample for HSV PCR assay; and (5) whole-blood sample for measuring alanine aminotransferase (ALT).

THERAPY

See Chapter 40 for preventive therapy after exposure.

- Parenteral acyclovir should be administered to all neonates with HSV disease, regardless of manifestations and clinical findings for 14 days in SEM disease and for a minimum of 21 days in CNS or disseminated disease.
- All infants with neonatal HSV disease, regardless of disease classification, should have an ophthalmologic examination and neuroimaging studies.
- All infants with CNS involvement should have a repeat lumbar puncture performed near the end of therapy to document that the CSF is negative for HSV DNA by a PCR assay.
- In the unlikely event that the PCR result remains positive near the end of a 21-day treatment course, acyclovir therapy should be extended, with a repeat CSF PCR assay performed near the end of the extended treatment period.
- Oral acyclovir suppressive therapy for the 6 months following treatment of acute neonatal HSV disease improves neurodevelopmental outcomes and prevents skin recurrences, and should be administered.

Varicella Zoster Virus

BASIC INFORMATION

- VZV is another member of the herpesvirus family; it causes chickenpox and herpes zoster (shingles) in older children and adults and, rarely, infection in neonates.
  - Neonatal varicella may occur if a nonimmune pregnant women has varicella near the time of delivery.
  - In contrast, congenital varicella syndrome is a very rare complication of maternal varicella earlier in the first 20 weeks of gestation (only ~100 cases reported).

CLINICAL PRESENTATION

- Congenital varicella syndrome results in an embryopathy with cicatricial limb rashes and asymmetric muscular atrophy, limb hypoplasia, and other CNS, eye, and gastrointestinal tract anomalies; these infants have a significant infant mortality rate and also may develop early herpes zoster in infancy.
- Maternal varicella in the last month of pregnancy or immediately postpartum may lead to neonatal varicella (chickenpox).
  - If the mother's varicella develops during the period from 5 days before delivery to 2 days after delivery, the neonate may have severe disease, with high morbidity and mortality, developing at 5 to 10 days of life, similar to varicella in an immunosuppressed host—fever, hemorrhagic rash, and visceral dissemination.
  - Conversely, maternal varicella with onset of rash >5 days before delivery, is less consequential for the infant, with mild disease developing, presumably because transplacental antibody has had time to begin to protect the fetus (assuming that it is >28 weeks' gestational age).
- Neonates born to women who have never had varicella or varicella immunization, or those born at <28 weeks' gestation in whom transplacental antibody may not have begun to cross into the fetal circulation, are susceptible to airborne varicella infection from other babies, visitors, or health care workers who have chickenpox or adults with herpes zoster.

DIAGNOSIS

- VZV infection is best diagnosed from lesions by PCR assay.

THERAPY

See Chapter 40 for preventive therapy after exposure.

- Parenteral acyclovir should be administered to all neonates with VZV disease, whose mothers had onset of their varicella between 5 days prepartum and 2 days postpartum.
- Neonates with milder infection from maternal varicella >5 days prepartum or those infected when >2 days old may be given oral or intravenous acyclovir.

Human Parvovirus B19

BASIC INFORMATION

- Human parvovirus B19 is a small DNA virus that causes erythema infectiosum—fifth disease—in older immunocompetent children and fetal hydrops (hydrops fetalis) if a pregnant woman is first infected before 20 weeks' gestation.
  - ~50% of US women of childbearing age are susceptible to parvovirus B19 infection; transmission in the household is generally <50%, with even lower transmission to the fetus.
  - Thus only a minority of neonates are affected by parvovirus, with an annual seroconversion rate of susceptible women estimated at 1.5%; however, in documented seroconversion before 20 weeks' gestation, the rates of fetal hydrops or death are ~5%.

CLINICAL PRESENTATION

- Fetal demise is very rare in the absence of fetal hydrops, and no birth defects among surviving neonates have been confirmed.

DIAGNOSIS

- Parvovirus B19 may be detected by PCR amplification in blood, as well as by IgG and IgM assays.

THERAPY

- No specific antiviral therapy
- Intrauterine fetal transfusions for hydrops fetalis and neonatal anemia of parvovirus infections

Enterovirus

BASIC INFORMATION

- Enteroviruses include the small RNA viruses, polioviruses, coxsackieviruses, and echoviruses.
- Non–polio enteroviruses can cause a neonatal sepsis syndrome, particularly after late in utero or intrapartum transmission, when the neonate may become ill in the first week of life.

CLINICAL PRESENTATION

- Uncommonly, presents as culture-negative sepsis in the neonate <7 days of age born to a mother with a febrile respiratory or nonspecific illness
- Commonly, nonspecific febrile illness in an older neonate or infant

DIAGNOSIS

- Enteroviruses may be detected by PCR amplification or, less often, viral culture, in nasopharyngeal, blood, CSF, or stool samples; stool is least preferred because excretion may last for several weeks

THERAPY

- Supportive therapy alone

Rubella Virus

BASIC INFORMATION

- An RNA virus infecting humans only
- Causes rubella (also formerly known as German measles), a mild illness with low-grade fever and exanthema
- Congenital rubella syndrome (CRS), a serious embryopathy, occurs if maternal rubella occurs <17 weeks' gestation; completely preventable by maternal immunization against rubella virus before child-bearing

CLINICAL PRESENTATION

- Infants with CRS typically are born with low birth weight and are small for gestational age (SGA), often with congenital cataracts, microphthalmos, glaucoma, hearing loss, and congenital heart defects (usually peripheral pulmonary artery stenosis or patent ductus arteriosus).
- The presence of extramedullary dermal hematopoiesis produces a so-called blueberry muffin appearance (similar to CMV infection); long bone radiographs show irregular radiolucency (so-called celery stalking).
  - Late manifestations of CRS in older infants and children include thyroid disease, diabetes mellitus, and immunodeficiency.

DIAGNOSIS

- The classic triad of congenital cataracts, hearing loss, and congenital heart disease should suggest the diagnosis of CRS.
- Rubella virus may be detected by PCR amplification or viral culture of throat, blood, urine, or CSF specimens during the first year of life.

THERAPY

- None; CRS is preventable by ensuring that all pregnant women are screened for immunity to rubella by serologic testing.
- Pregnant women found to be nonimmune to rubella should be immunized during the immediate postpartum period.

Human Immunodeficiency Virus

BASIC INFORMATION

- HIV infection in the pregnant woman may be transmitted to the child during pregnancy (~30% of transmission), peripartum period (~60% of transmission), or breastfeeding (~10% of transmission). Breastfeeding is thus contraindicated for HIV-infected mothers in developed countries with clean water.

- The overall mother to child transmission (MTCT) rate for HIV in the untreated mother-infant pair is ~25% in the absence of breastfeeding and up to 35% with breastfeeding; however, with the tripartite treatment regimen of combination antiretroviral therapy for the pregnant women, a short course of antiretroviral prophylaxis for the neonate, and prevention of breastfeeding, MTCT rates of 0.5% or less are achievable (see Chapter 40).
- There are no symptoms or signs of perinatal HIV infection (no embryopathy).
- Diagnosis of perinatal HIV infection must be performed by PCR amplification.
  - HIV-exposed infants are seropositive at birth, whether truly infected or not, due to transplacental acquisition of maternal antibody (which can persist as long as 18 months after birth).
  - HIV RNA PCR or DNA PCR assays are sensitive and specific, but only ~40% of infected newborns will be diagnosed at birth; nearly 100% of infected infants can be diagnosed by 4–6 months of age, because test sensitivity increases with age
  - Serial PCR assays should be performed at 2 weeks, 1 month, and 4–6 months of age at minimum to diagnose HIV infection; some experts also test at birth.
- See Chapter 40 for preventive therapy in the HIV-exposed neonate.

Hepatitis B Virus

BASIC INFORMATION

- Perinatal transmission of HBV from infected mothers to neonates is highly efficient (>90%) and usually occurs from infected blood or body fluid exposures during labor and delivery; in utero transmission accounts for less than 2% of all vertically transmitted HBV infections.
- Chronic HBV infection occurs in up to 90% of infants infected with hepatitis B at birth; chronic HBV is life-threatening later in adulthood (~25% risk of fatal hepatocellular carcinoma or cirrhosis).
- Postexposure prophylaxis with HBV vaccine, or HBV vaccine and hepatitis B immune globulin (HBIG), is highly effective; see Chapter 40 for discussion of universal vaccination of neonates.
- HBV infection in neonates and infants is asymptomatic; diagnosis is established by finding HBV surface antigen serologically in the blood.
- Breastfeeding by an HBV-positive mother poses no additional risk of acquisition of HBV infection by the infant with the appropriate administration of hepatitis B vaccine and HBIG.

Hepatitis C Virus (HCV)

BASIC INFORMATION

- In contrast to the highly efficient vertical transmission of HBV from infected mothers (in the absence of neonatal immunization) and the modest vertical transmission of HIV (in the absence of combination antiretroviral therapy), vertical transmission of hepatitis C virus (HCV) is distinctly uncommon, ~5%.
- Vertical transmission of HCV may be elevated to ~10%–15% if the mother is dually infected with HIV and HCV.
- There is no available postexposure HCV prophylaxis for the neonate.
- HCV infection in neonates and infants is asymptomatic; diagnosis is established by positive HCV antibody testing at 18 months of age (by which time the high levels of maternal transplacental antibody should have been cleared) or, if earlier diagnosis is desired, by a positive PCR amplification test for HCV at ~3 to 4 months of age.
- Maternal HCV infection is not a contraindication to breastfeeding, although HCV-infected mothers should consider abstaining if their nipples are cracked or bleeding.

PROTOZOA

Toxoplasmosis

BASIC INFORMATION

- *Toxoplasma gondii* is an obligate intracellular parasite with worldwide distribution; it infects a wide range of mammals (cats are the definitive host), birds and, globally, up to ~30% of humans.
- Congenital toxoplasmosis occurs when a mother sustains a primary infection during pregnancy; conversely, immunocompetent women who have been infected prior to pregnancy (i.e., are seropositive already at the diagnosis of pregnancy) virtually never transmit toxoplasmosis to their neonate.
  - The seropositivity rate in US women of childbearing age is ~6% to 11%, with higher rates in those born overseas or living on farms (thus most US women of childbearing age are susceptible to primary infection during pregnancy).
  - The estimated overall vertical transmission rate of toxoplasmosis is ~25%.
  - The current estimated incidence of acute primary infection among pregnant women in the United States is 0.2 to 1.1/1000 pregnant women; a lower incidence of congenital toxoplasmosis in neonates has been reported, ~0.2 to 0.9/10,000 live births.
- The probability of fetal infection increases as the gestational age at primary maternal infection increases.

CLINICAL PRESENTATION

- Congenital toxoplasmosis is a severe disease, although it is thought that perhaps 60% of newborns are asymptomatic at birth; visual or hearing impairment, learning disabilities, or mental retardation will become apparent in a large proportion of congenitally infected children in several months to years of age.
- The major clinical signs of congenital toxoplasmosis include chorioretinitis, cerebral calcifications (throughout the brain, in contrast to the periventricular distribution of

those from congenital CMV infection), and hydrocephalus, alone or in combination.
  - The classic triad of chorioretinitis, calcifications, and hydrocephalus rarely is seen at birth but is highly suggestive of congenital toxoplasmosis and, eventually, if untreated, most infants will develop all the findings—>90% chorioretinitis, 80% calcifications, ~70% hydrocephalus, ~60% complete triad of findings.
  - Cerebral calcifications can be demonstrated by plain radiography, ultrasonography, or computed tomography (CT) imaging of the head.
- Additional signs of congenital toxoplasmosis at birth include microcephaly, seizures, hearing loss, strabismus, a maculopapular rash, generalized lymphadenopathy, hepatomegaly, splenomegaly, jaundice, pneumonitis, diarrhea, hypothermia, anemia, petechiae, and thrombocytopenia.

DIAGNOSIS

- Congenital toxoplasmosis should be considered in infants born to the following women: (1) women suspected of having or who have been diagnosed with primary *T. gondii* infection during gestation; (2) women infected within 3 months of conception; (3) immunocompromised women (HIV-infected or otherwise) with serologic evidence of past infection with *T. gondii*; or (4) any infant with clinical signs or laboratory abnormalities suggestive of congenital infection.
- Serologic tests are the primary means of diagnosing primary and latent infection in women and congenital infections in neonates; PCR testing of amniotic fluid may also be carried out.
- Neonatal diagnosis:
  - Congenital infection is confirmed serologically by persistently positive IgG titers beyond the first 12 months of life; transplacental IgG antibody to *T. gondii* usually becomes undetectable by 6 to 12 months of age.
- Maternal diagnosis:
  - IgG-specific antibodies peak 1 to 2 months after infection and remain positive indefinitely, but the vast majority will have decreased to low-positive levels by 6 months after the acute infection; the lack of *T. gondii*–specific IgM antibodies in a person with low-positive titers of IgG antibodies indicates infection of at least 6 months' duration.
  - A positive IgM test should be followed by confirmatory testing at a laboratory with special expertise in *Toxoplasma* serology when determining that the timing of infection is important clinically (e.g., in a pregnant woman), because false-positive reactions do occur or persist for unexpectedly long periods.
  - In pregnant women, for whom the timing of the infection is critical (i.e., long-standing infection with little risk or primary infection with risk of transmission), specialized tests such as an IgG avidity test, AC/HS or differential agglutination test, or IgA- and IgE-specific antibody tests may be done to date the infection better; consultation with an expert and use of an expert reference laboratory are advised.
- Congenital toxoplasmosis can also be definitively diagnosed prenatally by detecting parasite DNA in amniotic fluid by PCR assay.
  - Serial fetal ultrasonographic examinations should be performed in cases of suspected congenital infection to detect any increase in the size of the lateral ventricles of the CNS or other signs of fetal infection, such as brain, hepatic, or splenic calcifications.

THERAPY

See Chapter 40 for prevention.

- For both symptomatic and asymptomatic congenital infections, oral pyrimethamine combined with sulfadiazine (supplemented with folinic acid) is recommended as initial therapy.
- The duration of therapy is usually 1 year; the optimal dosage and duration have not been established definitively, and drug toxicity may occur—therapy should be pursued in consultation with an infectious diseases specialist.

Malaria

BASIC INFORMATION

- Congenital malaria is rare—~0.5% of babies born to pregnant women with malaria in endemic areas become infected; pregnant women who are less immune to malaria (Western travelers to malarious areas) have rates of congenital malaria up to 5%.

CLINICAL PRESENTATION

- Presents at 2 to 8 weeks of age
- Symptoms mimic sepsis—fever in ~90%, anemia in 36%, splenomegaly in 30%, hepatomegaly in 20%, and thrombocytopenia, jaundice, irritability, and vomiting, ~10% each

DIAGNOSIS

- Thin blood smears and rapid *Plasmodium* antigen detection tests; PCR testing becoming more available

THERAPY

- Congenital *P. falciparum* disease may be severe and chloroquine-resistant.
- If chloroquine susceptibility is expected (non–*falciparum* disease or falciparum from nonresistant geographic areas), chloroquine is used as in older infants.
- *P. falciparum* congenital malaria might require quinidine and clindamycin.

Suggested Readings

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40 Prevention of Infections and Immunization

GEOFFREY A. WEINBERG

Immunization

- Immunization of infants <37 weeks' gestation or <2500 g birth weight generally follows the identical, routine, universal immunization recommendations for term infants, with few exceptions.
  - Immunizations for premature infants should be given at appropriate chronologic ages and with full doses of recommended vaccines.
  - Medically stable preterm infants who remain in the hospital at 2 months of chronologic age should be given all inactivated vaccines recommended for that age—medically stable is defined as an infant who does not require ongoing management for serious infection, metabolic disease, or acute renal, cardiovascular, neurologic, or respiratory tract illness and who demonstrates a clinical course of sustained recovery and a pattern of steady growth.
  - The only immunization to routinely defer in a premature neonate in the neonatal intensive care unit (NICU) or nursery is oral rotavirus vaccine—to prevent the potential nosocomial spread of this live vaccine virus, although research is ongoing to determine whether such spread actually occurs. Premature infants can receive rotavirus vaccine at the time of hospital discharge if they are between 6 and 15 weeks, 0 days of chronologic age, and are medically stable.

Prevention of Specific Bacterial Infection

- Group B streptococci (GBS; *Streptococcus agalactiae*)
  - Universal chemoprophylaxis (intrapartum antibiotic prophylaxis [IAP]) is recommended by both the Centers for Disease Control and Prevention (CDC) and American Academy of Pediatrics (AAP) and has reduced the incidence of GBS early-onset sepsis by >75%.
  - However, late-onset GBS infection is not prevented by IAP.
  - All pregnant women are screened at 35–37 weeks' gestation for vaginal-rectal colonization.
  - IAP is given to the following pregnant women:
    - Those with a previous infant with invasive GBS disease (regardless of screening during current pregnancy)
    - Those with GBS bacteriuria or urinary tract infection (UTI) during the current pregnancy
    - Those with positive GBS vaginal-rectal screening (unless a cesarean delivery is performed before onset of labor with intact membranes)
    - Those with unknown GBS colonization status at onset of labor or rupture of membranes with gestation < 37 weeks, rupture of membrane ≥ 18 hours, or temperature ≥ 38.0°C
    - Those with an intrapartum nucleic acid amplification test positive for GBS, if such testing is available
  - Adequate IAP is defined as ≥4 hours of intravenous (IV) penicillin G or ampicillin, or for penicillin-allergic women without a history of anaphylaxis, IV cefazolin
    - For women with a history of anaphylaxis, angioedema, or respiratory distress and urticaria to penicillin or cephalosporins, clindamycin may be used if the GBS isolate is known to be susceptible, and vancomycin if not.
    - Dosing information (all IV): penicillin G, 5 million units initial loading dose, then 2.5–3.0 million units every 4 hours until delivery; ampicillin, 2-g initial dose, then 1 g every 4 hours until delivery; cefazolin, 2 g initially, then 1 g every 8 hours until delivery; clindamycin, 900 mg every 8 hours until delivery; vancomycin 1 g every 12 hours until delivery
  - Management of the newborn infant born to a woman receiving IAP is as shown in Fig. 40.1.

Prevention of Specific Fungal Infection

- *Candida albicans*
  - Several randomized clinical trials and retrospective cohort analyses have documented decreased invasive candidiasis among selected neonates who have been administered fluconazole prophylaxis, although doses, schedules, and target birth weights have varied across trials.
  - Fluconazole prophylaxis is recommended for the following:
    - Very-low-birth-weight (VLBW) (<1500 g) and extremely-low-birth-weight (ELBW) (<1000 g) neonates in a NICU who have invasive candidiasis rates of ≥5%–10%
    - Fluconazole administered IV, beginning at 48–72 hours of life for these neonates, at 3 to 6 mg/kg/dose twice weekly; when the infant can tolerate oral feeding, the same dose may be given orally.

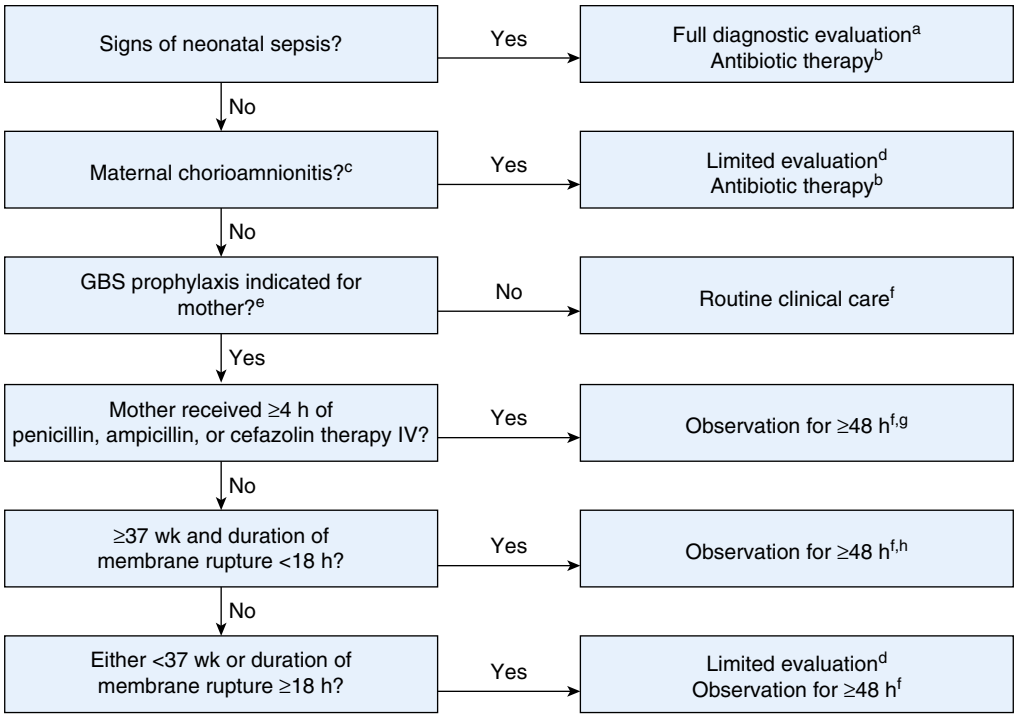

Fig. 40.1 Algorithm for the prevention of early-onset group B streptococcus (GBS) infection in the newborn. [a]A full diagnostic evaluation includes blood culture; complete blood cell (CBC) count, including white blood cell differential and platelet counts; chest radiograph (if respiratory abnormalities are present); and lumbar puncture (if the patient is stable enough to tolerate the procedure and sepsis is suspected). [b]Antibiotic therapy should be directed toward the most common causes of neonatal sepsis, including intravenous ampicillin therapy for GBS infection and coverage for infection by other organisms (including Escherichia *coli* and other gram-negative pathogens) and should take into account local antibiotic-resistance patterns. [c]Consultation with obstetric providers is important in determining the level of clinical suspicion for chorioamnionitis. [d]A limited evaluation includes blood culture (at birth) and CBC count with differential and platelet counts (at birth and/or at 6–12 hours after birth). [e]GBS prophylaxis is indicated if one or more of the following are true: (1) the mother is GBS-positive late in gestation and is not undergoing cesarean delivery before labor onset with intact amniotic membranes; (2) GBS status is unknown and there are one or more intrapartum risk factors, including less than 37 weeks' gestation, rupture of membranes for 18 hours or more, or temperature of 38.0°C or greater; (3) GBS bacteriuria during current pregnancy; or (4) history of an infant with GBS disease. [f]If signs of sepsis develop, a full diagnostic evaluation should be performed, and antibiotic therapy should be initiated. [g]If the stage is 37 weeks' gestation or later, observation may occur at home after 24 hours if other discharge criteria have been met, there is ready access to medical care, and a person who is able to comply fully with instructions for home observation will be present. If any of these conditions are not met, the newborn should be observed in the hospital for at least 48 hours and until discharge criteria have been achieved. [h]Some experts recommend a CBC count with differential and platelet counts at 6–12 hours of age. *IV*, Intravenously; *wk*, weeks. (From Centers for Disease Control and Prevention. Prevention of perinatal group B streptococcal disease - revised guidelines from CDC. *MMWR Recomm Rep*. 2010;59(RR-10):1–36, and Ferrieri P, Wallen LD. Newborn sepsis and meningitis. In: Gleason CA, Juul SE, eds. *Avery's Diseases of the Newborn*, 10th Ed. Philadelphia: Elsevier, 2018.)

- Duration of prophylaxis is until 42 days of age or when IV lines are discontinued

Prevention of Specific Viral Infection

- Hepatitis B virus (HBV)
  - About 1000 new cases of perinatal hepatitis B infection still occur annually in the United States, even though the overall case incidence has decreased by 90% since the vaccine's licensure in 1982.
    - Prevention of perinatal HBV infection relies on the proper and timely identification of infants born to mothers who are hepatitis B surface antigen (HBsAg) positive or of unknown status to ensure the administration of appropriate postexposure immunoprophylaxis with HBV vaccine and hepatitis B immune globulin (HBIG; Fig. 40.2).
    - All newborn infants with a birth weight ≥ 2000 g should receive HBV vaccine by 24 hours of age (birth dose).
    - All newborns < 2000 g born to women who are HBsAg-positive are given HBV vaccine at birth plus HBIG; those born to women of unknown status are given HBV and HBIG if the mother's status cannot be confirmed to be negative (see Fig. 40.2).
  - In addition, HBsAg-positive pregnant women with a high HBV viral load may be eligible for anti-HBV therapy with antiviral agents such as lamivudine and tenofovir; expert consultation is advised.
- Human immunodeficiency virus (HIV)
  - The most important risk factor for vertical transmission of HIV is the maternal plasma HIV RNA viral load.

- Thus vertical transmission of HIV is best prevented by a three-part strategy, requiring communication with the clinician(s) caring for the pregnant woman and possible consultation with experts in HIV medicine:
  - Ensuring that the mother is receiving a combination antiretroviral therapy regimen, and adhering to it
  - Ensuring that the woman receives intrapartum IV zidovudine during labor and delivery
  - Providing antiretroviral prophylaxis for the HIV-exposed neonate with zidovudine (and possibly one or two additional antiretroviral agents such as lamivudine and nevirapine, depending on the exact circumstances of the mother's therapy and the child's birth) beginning as soon as possible (preferably within 6–12 hours of birth) for 6 weeks
- Serial virologic testing with nucleic acid amplification tests is required for neonatal diagnosis in all HIV-exposed births because transplacental IgG antibodies will confound the interpretation of standard HIV antibody testing.
  - Virologic testing is performed three times, for a minimum at 2–3 weeks, 4–8 weeks, and 4–6 months of age; in high-risk infants (those with mothers who did not receive prenatal care or antepartum antiretroviral therapy, or who had HIV RNA of >1000 copies/mL near delivery, or who had acute HIV infection during

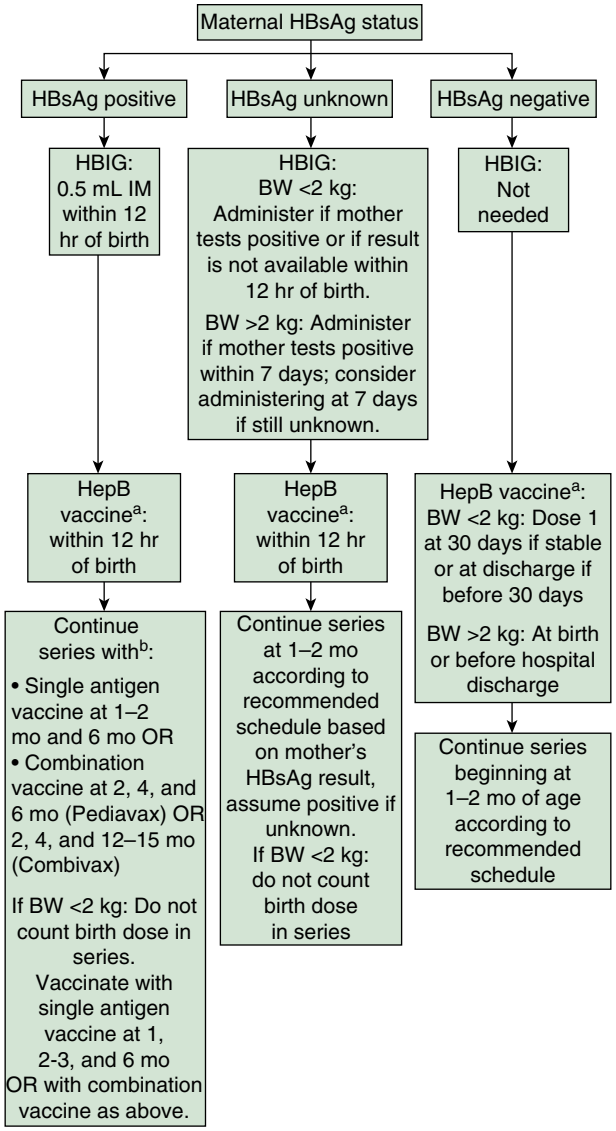

Fig. 40.2 Management of neonates born to mothers with unknown or positive hepatitis B surface antigen (HbsAg) status. *BW,* Birth weight; *HBIG,* hepatitis B immune globulin; *HepB,* hepatitis B virus. [a]Only single antigen vaccine should be used. [b]Reimmunization may be required based on anti-HBs; test for HBsAg and anti-HBs at age 9–12 months or 1–2 months after completion of HepB series if delayed. (Modified from American Academy of Pediatrics. *Red Book: 2015 Report of the Committee on Infectious Diseases*, 30th ed. Elk Grove Village, IL: AAP; 2015, and Ellison-Barnes A. Immunoprophylaxis. In: Hughes HK, Kahl LE. *The Harriet Lane Handbook -A Manual for Pediatric House Officers*, 21st ed. Philadelphia: Elsevier, 2016.)

pregnancy) should be tested additionally at birth and at 8–10 weeks (five tests).
  - In the United States, where safe infant feeding alternatives are available and are free for women in need, HIV-infected women should not breast-feed their infants.
  - Expert consultation should be obtained for women with HIV infection who are contemplating pregnancy, or who are pregnant already, and for HIV-exposed neonates. Consultation is available with local or regional HIV experts, or with the National Perinatal HIV Hotline (1-888-448-8765), or at the AIDS Info website (a service of the US Department of Health and Human Services), https://aidsinfo.nih.gov/guidelines.
- Herpes simplex virus (HSV)
  - During prenatal evaluations, all pregnant women should be asked about past or current signs and symptoms consistent with genital herpes infection in themselves and their sexual partners, but it should be recognized that the absence of previous signs and symptoms of genital herpes infections has poor sensitivity in determining the risk of genital HSV in pregnancy.
  - If a pregnant woman has had active recurrent genital herpes, the American College of Obstetricians and Gynecologists (ACOG) recommends suppressive antiviral therapy at or beyond 36 weeks of gestation for the woman, often with oral valacyclovir.
  - Neonates born to women with known recurrent genital infection, but no genital lesions at delivery, should be observed by the parents for signs of infection in the first 4–6 weeks of life (e.g., vesicular lesions of the skin, respiratory distress, seizures, or signs of sepsis) but do not require surface cultures or empiric acyclovir prophylaxis.
  - The management of neonates born to a pregnant woman with active genital lesions is complex; the risk of transmitting HSV to the newborn infant during delivery is influenced directly by the mother's classification of HSV infection, including whether she has primary or recurrent genital HSV infection, and perhaps also whether she has some cross-protective immunity from a previous nongenital HSV infection.
    - The risk of HSV transmission varies up to 30-fold more in primary infection than in semi-immune or recurrent infection.
    - If membranes are intact or ruptured for <4 hours, but active genital HSV lesions are seen at delivery, cesarean section is recommended to decrease the risk of HSV transmission.
    - Many experts also will use HSV-1– and HSV-2–specific serologic tests of the mother, in conjunction with surface cultures (performed at 24 hours of age) of the newborn's eyes, skin, mouth, and rectum in an attempt to help guide management of the neonate, with or without empiric prophylactic acyclovir for neonates judged to be at greatest risk of acquiring HSV (see the bibliography for an example of one approach [*Red Book 2018*]).
- Varicella zoster virus (VZV)
  - Varicella infection (chickenpox) has a higher case-fatality rate in infants when the mother develops varicella from 5 days before to 2 days after delivery because there is little opportunity for the development and transfer of antibody from mother to infant, and the infant's cellular immune system is immature.
  - When varicella develops in a mother >5 days before delivery and gestational age is 28 weeks or more, the severity of disease in the newborn infant is modified by the transplacental transfer of VZV-specific maternal IgG antibody.
  - If zoster (shingles) develops in a pregnant woman, the infant will not be at risk, because of the transplacental transfer of VZV-specific IgG, unless the neonate is born at <28 weeks.
  - Candidates for immunoprophylaxis with VariZIG, (a licensed varicella-zoster hyperimmune globulin) or IVIG (if VariZIG not available) include the following after a valid chickenpox exposure (e.g., household exposure or face to face exposure with a caretaker or staff in hospital):
    - Pregnant women without evidence of VZV immunity
    - Neonates born to women who develop chickenpox (but not zoster) within 5 days before delivery or within 2 days after delivery
    - Premature infants ≥ 28 weeks' gestation whose mother has no history of chickenpox or has no documented serologic immunity to VZV
    - Premature infants < 28 weeks' gestation or ≤1000 g birth weight, regardless of maternal history or immunity
  - Immunoprophylaxis, if used, should be given as soon as possible, within 10 days of the exposure.
  - Airborne and contact precautions are recommended for neonates born to mothers with varicella and, if still hospitalized, should be continued until 21 days of life or until 28 days of age if VariZIG or IGIV was administered.

Prevention of Specific Parasitic Infection

- Toxoplasmosis
  - Whether to routinely screen all pregnant women for toxoplasmosis is controversial; the preventive effect of such screening depends on the incidence of maternal infection, risk of transmission at different times in pregnancy, whether the transmission to the neonate of the identified infection in the mother is preventable by medical therapy, and receiver-operator characteristics of serologic screening tests.
    - Some European countries perform universal screening of pregnant women, but the lower incidence rates of maternal infection, and conflicting data on the cost-effectiveness of screening, has led to no universally agreed-on regimen in the United States.
  - There are other approaches to the prevention of toxoplasmosis, aside from serologic screening (Table 40.1):
    - Antepartum education should be given about avoiding *Toxoplasma gondii*–related exposures during pregnancy
    - There should special attention paid to meat handling and cooking, in addition to avoidance of cat feces.

Table 40.1 Measures for the Primary Prevention of Toxoplasmosis Infection in Pregnant Women

Transmission	Recommendations and Considerations
Meat and other edibles	■ Meat should be cooked up to at least 63°C (145°F) for whole cut meat (excluding poultry), up to at least 71°C (160°F) for ground meat (excluding poultry), and up to at least 74°C (165°F) for all poultry (whole cuts and ground) (a food thermometer should be used). ■ Meat should be frozen at -20°C (-4°F) for at least 48 hours. ■ Freezing and thawing at specific temperatures for a specific time can kill *T. gondii* tissue cysts. ■ Infected meat that has been smoked, cured in brine, or dried may still be infectious. ■ Contact with mucous membranes should be avoided when handling raw meat. ■ Gloves should be worn when handling raw meat, and hands should be thoroughly washed after handling raw meat. ■ Kitchen surfaces and utensils should be thoroughly washed after contact with raw meat. ■ Drinking unpasteurized goat milk should be avoided. ■ Eating raw oysters, clams, or mussels should be avoided. ■ Skinning or butchering animals without gloves should be avoided.
Untreated water	■ Drinking untreated water, including that from wells, or water with potential contamination by feces from domestic or wild cats should be avoided.
Cat feces and soil	■ Contact with material or soil potentially contaminated with cat feces, especially handling of cat litter or gardening, should be avoided. However, if not possible to be avoided, disposable gloves should be worn when gardening and, during any contact with soil or sand, hands should be washed with soap and warm water afterward. ■ Cats should be kept indoors. Stray cats should not be handled or adopted while the woman is pregnant. ■ The cat litter box should be changed daily because *T. gondii* does not become infectious until 1 to 5 days after it is shed in a cat's feces. ■ Cats should be fed canned or dried commercial food, not raw or undercooked meats.

Modified from Maldonado YA, Read JS; Committee on Infectious Diseases. Diagnosis, treatment, and prevention of congenital toxoplasmosis in the United States. *Pediatrics*. 2017;139(2):e20163860.

- Diagnosis of toxoplasmosis in a pregnant woman is complex and may include serologic testing by specialized reference laboratories, polymerase chain reaction (PCR) tests on amniotic fluid, and serial ultrasound monitoring (see Chapter 39 and AAP article [below]). Expert consultation is advised.
- Spiramycin is thought to prevent transmission of maternal toxoplasmosis to the fetus, but does not cross the placenta well, so does not treat an infected fetus reliably; pyrimethamine-sulfadiazine does cross the placenta and treats the fetal infection, and leucovorin (folinic acid) is used to lessen hematologic adverse effects.
- If a pregnant woman is suspected or confirmed to have acquired toxoplasmosis before the 18th week of the current pregnancy, oral spiramycin is given to the mother to prevent transmission to the fetus; amniocentesis is performed for PCR testing of the amniotic fluid as soon as possible at or after 18 weeks' gestation, and fetal ultrasonography is performed every 4 weeks.
  - If the PCR test result of the amniotic fluid is negative and the ultrasonography remains normal, spiramycin is continued until delivery.
  - If the amniotic fluid PCR test result is positive, and/or fetal ultrasonography is suggestive of congenital infection, then maternal therapy with oral pyrimethamine plus sulfadiazine plus leucovorin is given from ~18 weeks' gestation until delivery.
- If a pregnant woman is suspected or confirmed to have acquired toxoplasmosis after the 18th week of the current pregnancy, oral pyrimethamine plus sulfadiazine plus leucovorin is given to the woman through delivery.
- Spiramycin is not commercially available in the United States. It can be obtained at no cost (provided by Sanofi-Aventis) through consultation (with the Palo Alto Medical Foundation Toxoplasma Serology Laboratory, 1-650-853-4828, or the National Collaborative Chicago-Based Congenital Toxoplasmosis Study, 1-773-834-4152, or the US Food and Drug Administration, 1-301-796-1600).

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Questions:

1. Intrapartum antibiotic prophylaxis has significantly reduced the incidence of which of the following infections in the U.S.?
   a. Late-onset sepsis from group B streptococci (GBS)
   b. Both early-onset and late-onset sepsis from GBS
   c. Early-onset sepsis from GBS
   d. Syphilis

SECTION 11

Gastroenterology

REBECCA ABELL and MEGAN E. GABEL

41 Normal and Abnormal Gastrointestinal Development

REBECCA ABELL and MEGAN E. GABEL

Esophagus

- By week 4 of gestation, the primitive foregut is formed by folding of the endoderm and splanchnic mesoderm into a tubular structure.
- A complex process of in-folding and fusion of the lateral sides of the proximal foregut gives rise to the respiratory tube (ventral) and esophageal tube (dorsal).
- Incomplete fusion of the lateral grooves results in failure of separation of the dorsal and ventral tubes, leading to a tracheoesophageal fistula (TEF).
- The esophageal lumen is reestablished by week 10 of gestation.
- By the end of the first trimester, neuroblasts and circular muscle are present throughout the esophagus.
- By week 16, stratified squamous epithelium is present.
- Swallowing is first seen as early as week 16.
- The structure of the esophageal musculature is divided into three segments:
  - Upper third—striated muscle
  - Middle third—striated and smooth muscle
  - Lower third—smooth muscle
- Nonnutritive sucking can be seen as early as gestation week 20.
- Nutritive sucking does not appear until weeks 32–34.
- Superficial glands are present in the esophageal mucosa by week 20.
- Mucous and lingual lipases are secreted by squamous cells by week 28.
- The upper esophageal sphincter is present by week 32.
- By 40 weeks, the esophagus is approximately 8–10 cm in length.

Stomach

- It arises from the embryonic foregut.
- By week 4, it is recognized as a fusiform dilation.
- The endocrine chief, mucous, and parietal cells appear by week 12.
  - By week 16, all these cells are secreting hydrochloric acid, intrinsic factor, pepsin, gastrin, and mucus.
- It enlarges ventrodorsally and rotates 90 degrees clockwise on a longitudinal axis.
- The primitive gut is lined by endoderm.
- The mesoderm differentiates into smooth muscle layers.
- There are two functional zones of motor activity:
  - The proximal zone (fundus and proximal third of the body) is a reservoir that can distend to accommodate bolus feeding; it generates steady contractions stimulated by the vagus nerve.
  - The distal zone is responsible for mixing and breaking down food to allow food to empty into the duodenum.
- Term infants have a neutral gastric pH at birth but this drops within the first 48 hours of birth.
  - Premature infants have a prolonged period of alkaline pH.
  - Gastric acid plays a protective role against bacteria entering into the GI tract. Thus it protects the upper aerodigestive tract and modulates the intestinal microbiome.

Intestine

- This primitive gut tube forms by week 4, when a portion of the yolk sac incorporates into the embryo during craniofacial and lateral folding (Fig. 41.1).
- The lumen is occluded as third epithelial lining rapidly proliferates and then later recanalizes.
  - Failure to recanalize results in intestinal atresia or stenosis.
- It is divided into the foregut, midgut, and hindgut.
  - Caudal portion of foregut gives rise to upper duodenum
  - Midgut gives rise to lower duodenum, jejunum, ileum, appendix, ascending colon, and proximal two-thirds of the transverse colon
  - Hindgut gives rise to one-third of the transverse colon, descending colon, sigmoid colon, rectum, and superior part of anal canal
- The midgut loop herniates through the umbilical ring at week 6.
- Neuroblasts appear at week 7.
- At week 11, the midgut loop rotates counterclockwise around the superior mesenteric artery (SMA) as it returns to the abdominal cavity.
  - Failure of this loop to return to the abdomen results in omphalocele; gastroschisis results from a herniation through a defect in the abdominal wall musculature, typically to the right of the umbilical cord
  - If there is only partial intestinal rotation, malrotation ensues
- Myenteric muscle contractions are seen at week 32.
- At gestation week 24, lactase activity <25% of that found in term infants.

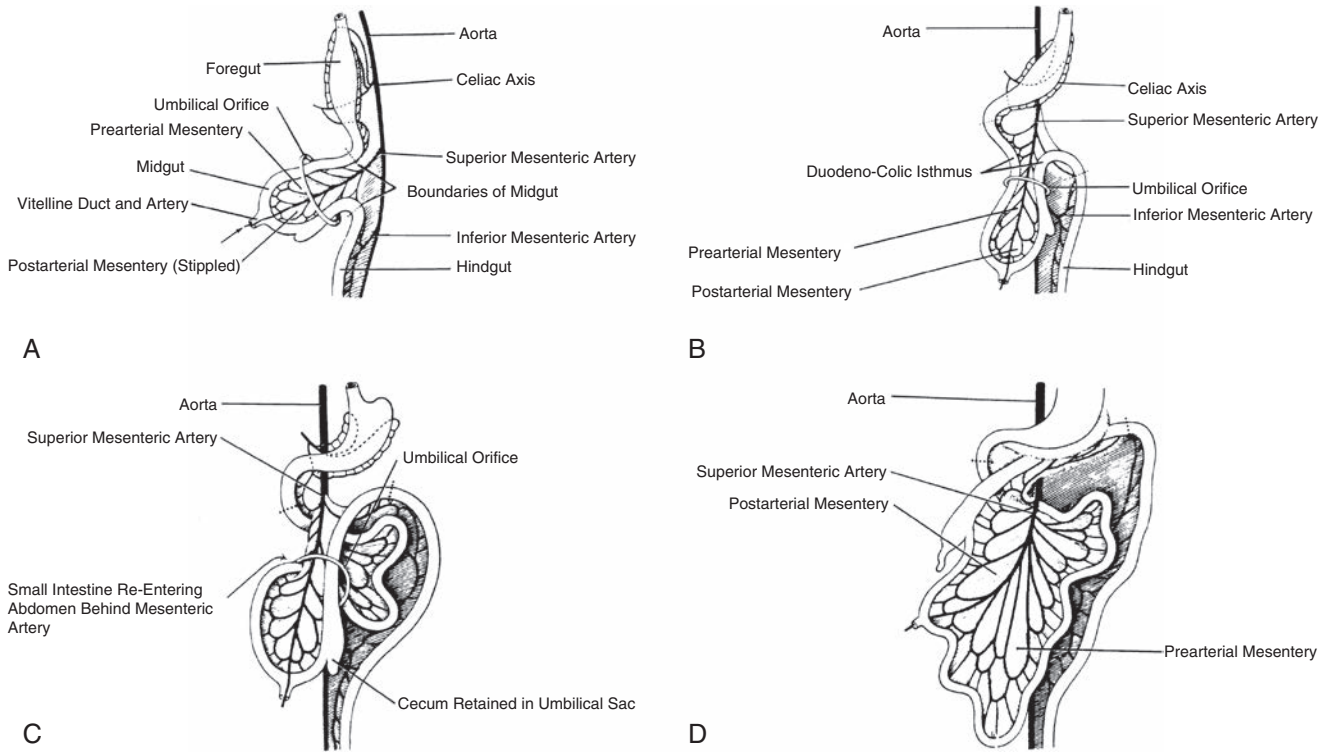

Fig. 41.1 Normal rotation of the alimentary tract. (A) Fifth week of intrauterine life, lateral view. The foregut, midgut, and hindgut are shown with their individual blood supply supported by the common dorsal mesentery in the sagittal plane. The midgut loop has been extruded into the umbilical cord. (B) Eighth week of intrauterine life, anteroposterior view. The first stage of rotation is being completed. Note the narrow duodenocolic isthmus from which the midgut loop depends and the right-sided position of the small intestine and left-sided position of the colon. Maintenance of this position within the abdomen after birth is termed nonrotation. (C) About the 10th week of intrauterine life, during the second stage of rotation, anteroposterior view. The bowel in the temporary umbilical hernia is in the process of reduction; the most proximal part of the prearterial segment entering the abdomen to the right of the superior mesenteric artery is held forward close to the cecum and ascending colon, permitting the bowel to pass under it. As the coils of small intestine collect within the abdomen, the hindgut is displaced to the left and upward. (D) Intrauterine life, week 11, at the end of the second stage of rotation. From its original sagittal position, the midgut has rotated 270 degrees in a counterclockwise direction about the origin of the superior mesenteric artery. The essentials of the permanent disposition of the viscera have been attained. Anomalies of intestinal rotation as a cause of intestinal obstruction: report of two personal observations, review of one hundred and three reported cases. The image is in Avery' Diseases on page 1072 of the 9th edition and they list it as (A-D, From Gardner CD Jr, Hart D: Arch Surg 29:942, 1934. Copyright 1934).

- Increase in lactase activity occurs at weeks 32–34.
- The small intestine typically measures between 200 and 300 cm at 40 weeks.
- Gut-associated lymphoid tissue (GALT) contributes significantly to the immune system.
  - Peyer patches are lymphoid follicles that are the sites of T and B cell activity.
  - Lamina propria lymphocytes are responsible for secreting immunoglobulin A (IgA), which binds and neutralizes intestinal bacteria.

Pancreas

- Dorsal and ventral pancreatic buds arise from the endoderm of the caudal foregut at weeks 4–5.
- Each bud communicates with the foregut through a duct.
- The duodenum rotates, resulting in movement of the ventral pancreatic bud posterior and inferior to the dorsal pancreatic bud.
- The two buds fuse to form the pancreas at week 7.
  - Ventral pancreatic bud forms inferior part of the head of pancreas and uncinated process
  - Dorsal pancreatic bud forms superior part of the head, body, and tail of pancreas
- The ductal systems of the two buds join at week 8.
- Differentiation of endocrine and exocrine structures is present by week 14.
  - By gestation week 14, insulin and pancreatic zymogen granules are present.
  - By gestation week 16, amylase is present.
  - By gestation week 31, trypsin, lipase, and amylase are secreted.
- The concentration of pancreatic enzymes is lower in preterm infants at birth.

Hepatobiliary Liver

- The liver is formed from the endoderm.
- The liver bud arises from the cranioventral portion of the endoderm.
- The liver grows in size and is encapsulated and lobulated, with bile ducts present by week 6.
- Hepatoblasts, which are precursors to hepatocytes, migrate into the septum transversum mesenchyme, with hematopoietic and endothelial precursors.

Table 41.1 Anatomic and Functional Maturation of the Gastrointestinal Tract

POSTCONCEPTIONAL AGE (WEEKS)					
15	**20**	**25**	**30**	**35**	**40**
Mouth	Salivary glands	Swallow	Lingual lipase	*Sucking*	
Esophagus	Muscle layers present	Striated epithelium present	*Poor lower esophageal sphincter tone*		
Stomach	Gastric glands present	G cells appear	*Gastric secretions present*	*Slow gastric emptying*	[a]
Pancreas	Exocrine and endocrine tissue differentiate	Zymogen present	*Reduced trypsin, lipase*		[a]
Liver	Lobules form	*Bile secreted*	*Fatty acids absorbed*		[a]
Intestine	Crypt and villus form	*Glucose transport present*	*Dipeptidase, sucrase, and maltase active*	*Lactase active*	
Colon		Crypts and villi recede		*Meconium passed*	

[a]Full functional maturation occurs postnatally. *Italics* indicate functional maturation.

Developmental anatomy and physiology of the gastrointestinal tract. In: Taeusch HW, Ballard R, Gleason C, eds. *Avery's Diseases of the Newborn*. 8th ed. Philadelphia: Elsevier; 2005:1071–1085.

- Bile acids are synthesized by week 12.
- Bile acids are secreted by week 22.
- The bile acid pool size in preterm infants is one-third of that seen in term infants.
- Due to immature processing of bile salts, preterm infants are at increased risk of developing cholestasis, especially after chronic parenteral nutrition.
- The lymphatic system develops by week 15.

Gallbladder and Biliary Tree

- The hepatic diverticulum gives rise to the hepatic parenchyma, intrahepatic biliary tree, and common bile duct.
- The cystic diverticulum gives rise to the cystic duct and the gallbladder.
- The cystic duct fuses with the common bile duct.
- Hepatoblasts in the mesenchyme near the portal vein form a layered structure called the *ductal plate*.
- The ductal plate cells form bile ducts in the intrahepatic portal tracts.
- Canaliculi are formed when hepatocytes join.
- By week 4, the intrahepatic biliary tree is formed.

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Questions

1. Nutritive sucking is evident at what gestational age?
   a. 20 weeks
   b. 28 weeks
   c. 32 weeks
   d. 36 weeks

2. Preterm infants have a prolonged period of gastric acidic pH.
   a. True
   b. False

3. Failure of the primitive gut tube to recanalize results in which of the following?
   a. Intestinal atresia
   b. Intestinal malrotation
   c. Intestinal duplication
   d. Gastroschisis

4. Which disaccharidase enzyme activity is reduced by 75% in preterm infants compared to term infants at birth?
   a. Sucrase
   b. Alpha-glucosidases
   c. Dipeptidases
   d. Lactase

5. Peyer patches found in the small intestine contribute to which of the following?
   a. IgA production
   b. Intestinal motility
   c. Bile acid reabsorption
   d. T and B cell activity

6. At what gestational age do the ductal systems of the two buds of the pancreas fuse?
   a. 6 weeks
   b. 8 weeks
   c. 12 weeks
   d. 16 weeks

7. Preterm infants are at increased risk to develop cholestasis due to which of the following?
   a. Sepsis
   b. Decreased bile acid pool
   c. Increased bile acid production
   d. a and b

8. The intrahepatic biliary tree is formed by which gestational week?
   a. 4
   b. 6
   c. 8
   d. 10

9. Omphalocele is the result of which of the following?
   a. Failure of recanalization of the primitive gut tube
   b. Failure of midgut loop to return to the abdominal cavity
   c. Partial rotation of the midgut loop around the superior mesenteric artery (SMA)
   d. Herniation of midgut loop through the abdominal ring

10. Incomplete fusion of the lateral grooves of the primitive foregut results in which of the following?
    a. Tracheoesophageal fistula (TEF)
    b. Duplication cyst
    c. Pancreatic divisum
    d. Biliary atresia

42 Developmental Anomalies

REBECCA ABELL and MEGAN E. GABEL

GI Developmental Anomalies

OROPHARYNX

- Epstein pearls
  - Small cystic lesions on hard palate present in 80% of newborns
  - Typically disappear within one month
  - Larger ones rarely require surgical excision
- Tumors of the mouth
  - Epignathus
    - Extremely rare, congenital teratoma of the upper jaw or palate
    - It is a benign tumor but is associated with morbidity because it can present with severe airway obstruction or feeding difficulty
    - Epignathus can be associated with other congenital malformations including cleft palate, bifid tongue, bifid uvula, congenital heart defects, and inguinal hernias
    - Treatment is surgical excision
  - Congenital epulis
    - Rare congenital benign neoplasm, also known as *granular cell tumor* or *congenital gingival granular cell tumor*
    - Arises from upper or lower jaw
    - May interfere with respiration or feeding

Salivary Gland

- Hemangiomas and lymphangiomas are most common tumors
- Benign lesions are confined to intracapsular portion of the gland
- Once histologic diagnosis is confirmed, treatment is observation

Esophagus

- Esophageal duplication cysts
  - Comprise 10%–15% of all gastrointestinal (GI) duplications
  - Can lead to esophageal obstruction
  - Neonates are typically asymptomatic but can present with respiratory or digestive difficulties
  - Diagnosis is made with chest radiograph and computed tomography (CT) demonstrating a mediastinal mass
  - Magnetic resonance imaging (MRI) is necessary to rule out a neurenteric cyst, which may have a connection to spinal canal
  - Treatment is surgical resection
- Tracheoesophageal fistula (TEF) (Fig. 42.1)
  - There are five common anatomic variants with Type C (esophageal atresia/distal TEF) accounting for 85% of cases
  - Develops before the eighth week of gestation as a result of abnormal division of dorsal and ventral foregut
  - Incidence 1/3000–4000 live births
  - Up to 7% of neonates have a chromosomal abnormality
  - Up to 70% will have at least one other congenital anomaly
  - Most commonly seen in association with VACTERL association (Vertebral, Anorectal, Cardiac, Tracheal, Esophageal, Renal/Genitourinary, Limb)
  - Can be seen with CHARGE syndrome (Coloboma, Heart defect, Atresia choanae, Restriction of growth/development, Genital hypoplasia, Ear defect/deafness)
  - Diagnosis
    - Prenatal history of polyhydramnios in one-third of cases, due to esophageal atresia
    - Shortly after birth infant presents with increased oral secretions, feeding difficulties, and respiratory distress
    - Gasless abdomen is suggestive of isolated esophageal atresia
    - Inability to pass NG (nasogastric) tube may help make diagnosis
    - Distal fistula may present with significant abdominal distention
    - H-type TEF may present outside of the newborn period with history of more mild respiratory issues associated with feeding or recurrent aspiration pneumonia
  - Treatment
    - Make infant NPO and initiate acid suppression and IV fluids
    - Decompression of esophageal pouch with suction catheter
    - Preoperative evaluation of associated congenital anomalies is necessary
    - Definitive treatment is corrective surgery
  - Postoperative complications
    - Anastomotic leak can occur in 10%–15% of cases
    - Esophageal stricture
    - Gastroesophageal reflux (GER)
    - Recurrent fistula
    - Tracheal obstruction
- Gastroesophageal reflux (GER)
  - A normal physiologic condition in the neonate due to a lower resting pressure of the lower esophageal sphincter (LES, 2–3 mm Hg)
  - Normal resting pressure (10–15 mm Hg) is obtained by 6 months of life
  - 82% of cases are related to transient relaxation of the LES

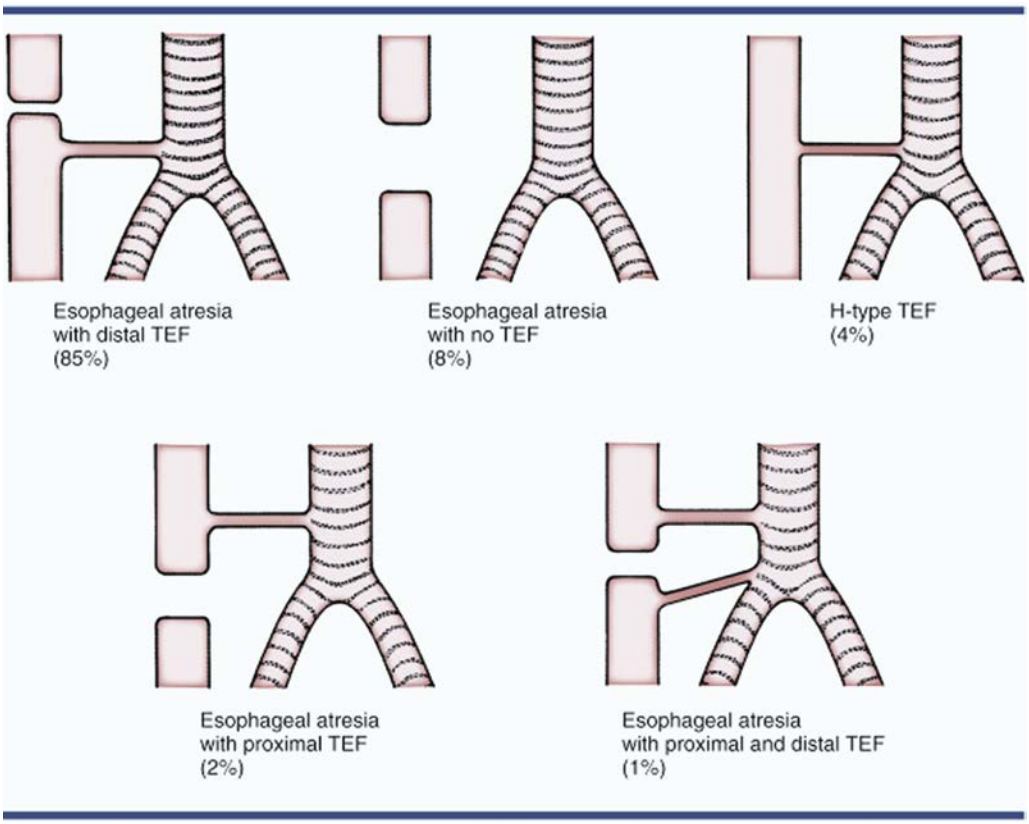

Fig. 42.1 Various types of tracheoesophageal fistulas (TEF) with relative frequency (%).

- Symptoms of pathologic GERD (gastroesophageal reflux disease) include poor weight gain, irritability, feeding aversion, apnea, cyanosis, bradycardia
- Barium swallow should be obtained to rule out underlying anatomic abnormalities but has low yield to diagnose GERD
- Gastric emptying studies may be helpful to identify delayed gastric emptying which may contribute to GER
- Impedance studies will identify acid as well as nonacid reflux, but there is only a weak association between results and presence of reflux complications
- Treatment
  - Inclined positioning
  - Addition of cereal to formula
  - Acid blockade (H2 blocker or proton pump inhibitor) will not decrease physiologic reflux but will decrease mucosal acid exposure
  - Prokinetic agents: erythromycin (risk of pyloric stenosis), metoclopramide (risk of irreversible tardive dyskinesia)
  - Surgical intervention: Nissen fundoplication in high risk patients that are refractory to medical treatment

Stomach

- Microgastria
  - Very rare congenital anomaly
  - Associated with mega-esophagus, malrotation, biliary anomalies, situs inversus, skeletal anomalies/defects, asplenia, and GERD
  - Presents with vomiting, failure to thrive, persistent diarrhea
  - Diagnosed by upper GI (UGI) contrast study
  - Treatment
    - Continuous enteral feeding with supplemental parenteral nutrition until gastric adaptation and able to transition to bolus feeding
    - If surgical intervention is necessary, the standard approach includes gastric augmentation with roux-en-Y jejunal reservoir
- Gastric volvulus
  - Can result from inadequate mesenteric fixation
  - Often associated with other defects such as malrotation, diaphragmatic defect, or asplenia
  - Symptoms are emesis (bilious/nonbilious) and abdominal distention
  - Abdominal radiograph will demonstrate massive gastric dilation
  - UGI will show transverse lie of the stomach and inversion of the greater curvature and pylorus
  - Treatment is emergent surgery
- Pyloric stenosis
  - Idiopathic hypertrophy of pyloric muscle resulting in narrowing and elongation of pyloric channel
  - Results in gastric outlet obstruction
  - Incidence is 1/1000–3/1000 live births
  - Male predominance is 4:1
  - Association between maternal and infant exposure to erythromycin
  - Typically presents between 3–6 weeks of age with progressive projectile vomiting

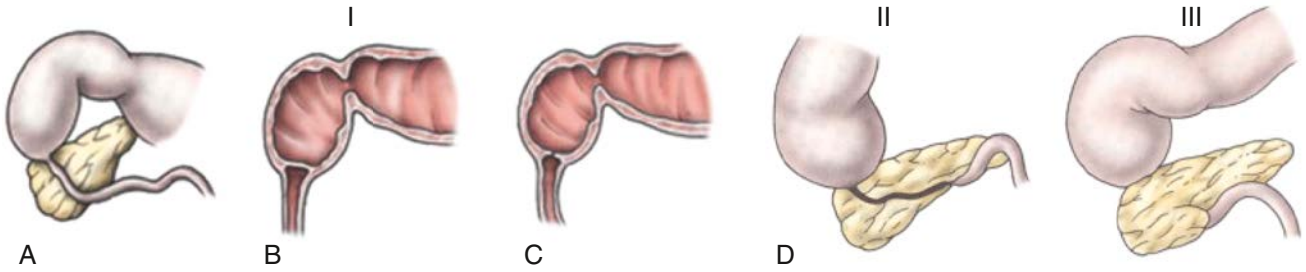

Fig. 42.2 Duodenal and intestinal atresia and stenosis.

- Hypochloremic hypokalemic contraction alkalosis is seen
- Hypoglycemia and indirect hyperbilirubinemia may be present
- Hallmark of physical exam is palpation of "olive" in the epigastric area
- Diagnosis is confirmed with ultrasound
- Treatment includes correction of metabolic derangement and surgical pyloromyotomy

- Pyloric atresia
  - Incidence is 3/100,000
  - Congenital partial or complete gastric obstruction involving the antrum or the pylorus
  - Associated with Down syndrome and junctional epidermolysis bullosa
  - Presents in the first few days of life with nonbilious emesis, feeding difficulties, and abdominal distention
  - Can have prenatal history of polyhydramnios
  - Can have stomach rupture within first 12 hours of life
  - Diagnosis is made with upper GI contrast study
  - Treatment includes correction of metabolic derangement and gastric decompression, followed by gastroduodenostomy

Small Intestine

- Duodenal atresia (DA) and stenosis (Fig. 42.2)
  - Atresia or stenosis occurs when duodenal segment does not recanalize during the 8th–10th weeks of gestation
  - Most infants with DA have other associated anomalies (Down syndrome, congenital heart disease, intestinal malrotation, esophageal atresia, or imperforate anus)
  - Often there is a history of prenatal polyhydramnios
  - Obstruction of the duodenal lumen can be complete, partial, intrinsic, or extrinsic
  - Extrinsic forms include malrotation with obstruction from Ladd bands or from twisting on a small mesenteric base, compression by an anterior or preduodenal portal vein, gastroduodenal duplication, cysts or pseudocyts of the pancreatic-biliary tree, or annular pancreas
  - Annular pancreas
    - Occurs when the ventral pancreatic bud does not rotate behind the duodenum, causing an extrinsic compression encircling the second portion of the duodenum
    - Can also be associated with intrinsic duodenal anomalies
  - Prenatal ultrasound may demonstrate two dilated, fluid-filled structures
  - Infant presents with bilious emesis within 24 hours of birth, without abdominal distention
  - Abdominal radiographs demonstrate classic "double bubble" sign (Fig. 42.3)
  - Treatment involves placement of NG for decompression, fluid and electrolyte stabilization, and evaluation for associated anomalies prior to surgical correction
- Duplications of the small intestine
  - Duodenal duplications are most commonly in the first or second portion and may be lined with gastric mucosa
  - They can cause pancreatitis due to compression of pancreatic duct
  - Hemorrhage or perforation are indications for emergent surgery
  - May be detected with prenatal ultrasound as a right upper quadrant cystic mass
  - UGI may demonstrate extrinsic compression but ultrasound and CT are needed for definitive diagnosis
  - Treatment is surgical resection
- Jejunoileal atresia (Fig. 42.4)
  - Occurs after 12th week of gestation
  - Due to mesenteric vascular disruption leading to ischemic necrosis
  - Classified into five subtypes
    - Type I: mucosal (membranous) web
    - Type II: blind ends connected by a fibrous cord
    - Type IIIa: blind ends separated by a V-shaped mesenteric defect
    - Type IIIb: apple-peel or Christmas-tree deformity (blind ends; distal small bowel segment forms corkscrew around ileocecal artery terminus)
    - Type IV: multiple atresias (string of sausages)
  - Prenatal ultrasound may show polyhydramnios and distended loops of fetal bowel
  - Infants present with bilious emesis, abdominal distention, failure to pass meconium, and jaundice
  - Abdominal radiographs demonstrate dilated, thumb-sized loops of bowel ("rule of thumb")
  - Contrast enema is diagnostic with presence of micro-colon
  - Treatment involves decompression of the stomach, fluid resuscitation, and subsequent surgical resection
- Malrotation and/or volvulus
  - Occurs between 6th and 12th weeks of gestation if counterclockwise rotations and fixation do not occur properly
  - Malrotation occurs in 1/100, but only 1/6000 are diagnosed, with 80% of those being in the newborn period since not symptomatic if not obstructed by Ladd bands or volvulus

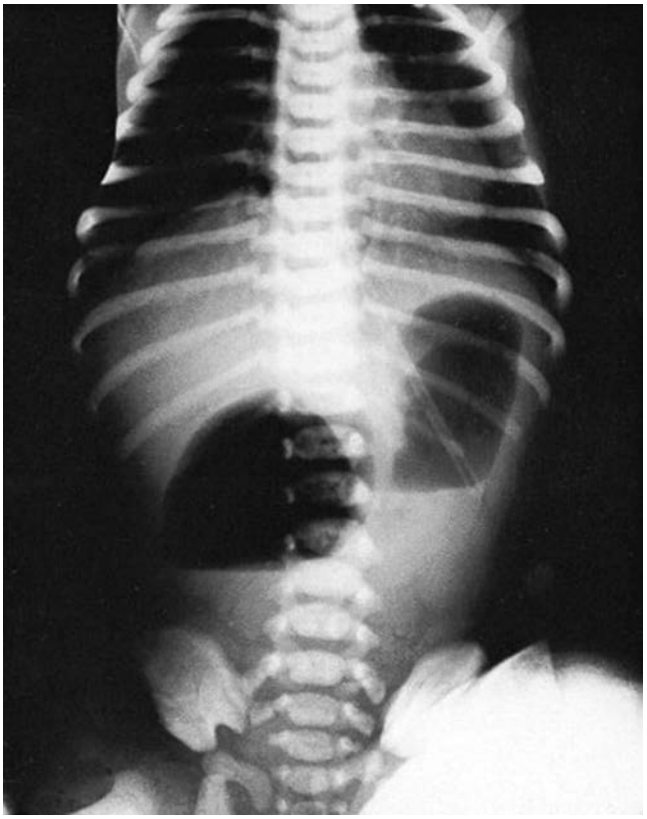

Fig. 42.3 "Double bubble" sign seen with duodenal atresia.

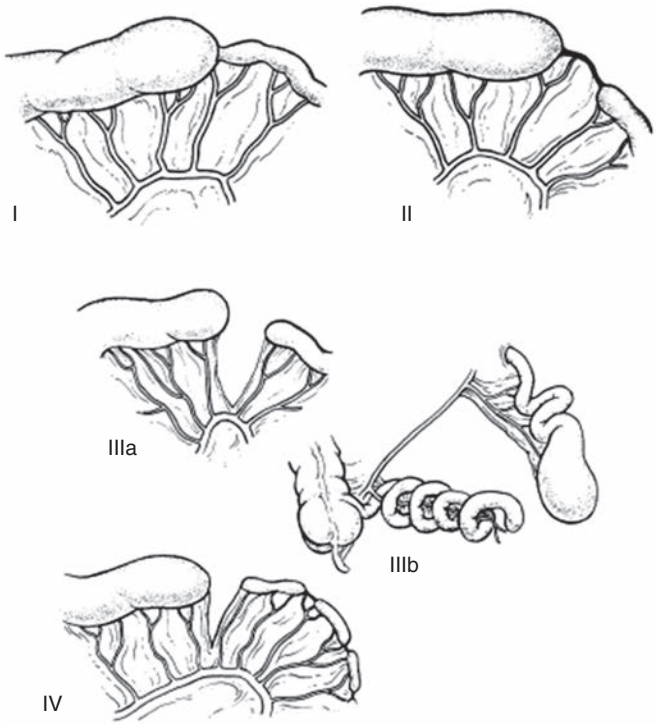

Fig. 42.4 Jejunoileal atresis and stenosis.

- Volvulus presents with sudden bilious emesis
- Upper GI should be obtained to look at position of ligament of Treitz which will not cross midline (Fig. 42.5)
- Surgical intervention is indicated emergently to avoid significant bowel ischemia and necrosis

Large Intestine

- Intestinal atresia
  - Less than 10% of intestinal atresia/stenosis occur in the colon
  - Etiology thought to be vascular compromise in utero, most likely along vascular watershed area of the hepatic flexure
  - Incidence approximately 1/20,000
  - Diagnosis may be suspected with dilated bowel on prenatal ultrasound
  - Infants develop abdominal distention within 24–28 hours of birth and there is often no passage of meconium
  - Diagnosis suggested by abdominal radiograph showing distended small bowel loops
  - Water-soluble contrast enema can establish diagnosis and differentiate from meconium plug syndrome, small left colon syndrome, or Hirschsprung disease
  - Treatment involves gastric decompression, IV antibiotics, and surgical correction
    - In stable patients without peritonitis, primary anastomosis is possible
    - Size discrepancy between dilated proximal colon and small distal colon may not allow for primary anastomosis; proximal ostomy and distal mucus fistula is created and anastomosis is done at a later time after dilated portion has decompressed
- Meconium plug syndrome (MPS)/small left colon syndrome
  - Functional immaturity of colon resulting in obstructive meconium plugs
  - Thought to be related to transient colonic hypomotility, more frequent in preterm infants, IDM (Infant of Diabetic Mother), and when there is history of maternal eclampsia
  - Hypomotility may be related to immaturity of myenteric plexus ganglia
  - Maternal magnesium sulfate administration can lead to neonatal hypermagnesemia, which will depress the function of intestinal smooth muscle, contributing to MPS
  - Neonatal hypoglycemia can also result in decreased intestinal motility
  - Diagnosis suggested by dilated loops of bowel on abdominal radiograph
  - Water-soluble contrast enema both diagnostic and therapeutic
    - Contrast enema with multiple filling defects which represent meconium plugs
    - Obstruction often resolved with contrast enema, infrequently surgical intervention is required
  - Further evaluation for cystic fibrosis or Hirschsprung disease may be indicated
- Consequences of surgical resection of distal ileum, cecum, and large intestine
  - Primary role of the colon is absorption of water and electrolytes
  - Terminal ileum is the only segment that reabsorbs bile salts actively

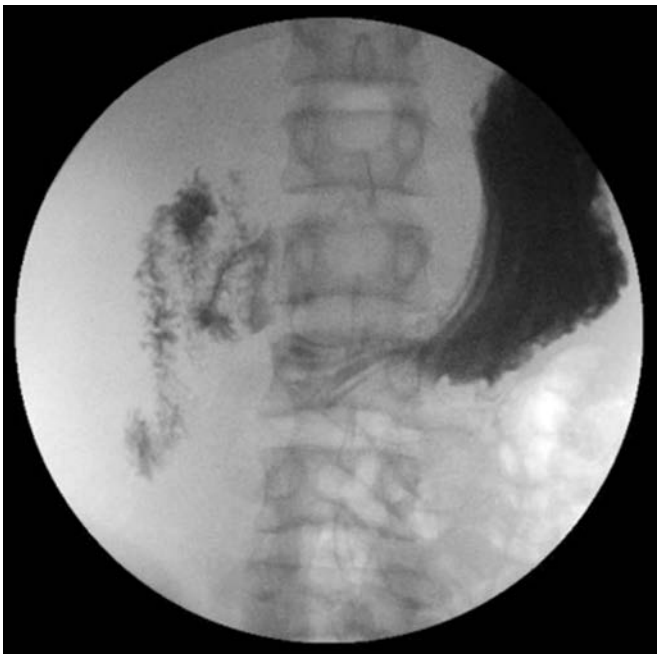

Fig. 42.5 Upper GI series demonstrating malrotation.

- If 50 cm or more of ileum are lost, bile salt synthesis by the liver cannot compensate for decrease in enterohepatic circulation.
  - Bile acids are necessary for the digestion and absorption of fats and fat-soluble vitamins
  - Inadequate lipid emulsification results and colonic fluid losses are increased
- Loss of ileum/ileocecal valve accelerates gastric emptying and small bowel motility and further reduces absorptive capability
  - Thought to be mediated by peptide PPY and GLP-1

Rectum and Anus

- Anorectal malformations
  - Imperforate anus
  - incidence: 1/5000 births
  - Slightly more common in males
  - Occurs when there is arrest of the caudal descent of the urorectal septum to the cloacal membrane during development
  - Diagnosis
    - Based on good perineal exam
    - Females may pass meconium through a perineal, vestibular, or vaginal fistula or may present as cloaca (rectum, vagina, and urinary tract meet and fuse, creating a single common channel)
    - Males, may have cutaneous fistula that tracks midline towards the penis which may present with meconium in the urine or air in the bladder
    - X-ray may demonstrate progressive distal bowel obstruction
    - Perineal ultrasound may be more helpful
  - Treatment
    - Low defects can be managed with surgery to restore anorectal canal
    - High and intermediate defects require colostomy and later elective repair
- Hirschsprung disease
  - Occurs in 1/5000 births
  - Male to female ratio 4:1
  - Caused by agenesis of ganglion cells in the myenteric and submucosal plexuses; decreased expression of nitric oxide synthase gene also adds to dysmotility
  - Multiple gene mutations have been identified but RET (receptor tyrosine kinase) is the most common
  - 20%–30% associated with congenital anomalies/syndromes
    - More commonly seen with trisomy 21, MEN2, Waardenburg syndrome, Smith-Lemli-Opitz syndrome, and central hypoventilation syndrome
  - Occurs when vagal neural crest cells do not migrate appropriately between weeks 5–12; the earlier this happens, the longer the segment of aganglionic bowel
  - Anus is always involved, amount of intestine involved can vary
  - Presenting symptoms vary
    - Failure to pass meconium within first 48 hours of life
    - Bilious vomiting
    - Constipation with abdominal distention, often suppository dependent
    - Failure to thrive
  - Hirschsprung-associated enterocolitis (HAEC)
    - Characterized clinically by fever, abdominal distention, bloody diarrhea, and sepsis
    - Leading cause of morbidity and mortality in children with Hirschsprung disease
  - Initial evaluation
    - Rectal exam demonstrates tight anus with empty rectal vault
    - Contrast enema demonstrates different caliber of small aganglionic segment and dilated proximal segment
    - This "transition zone" may not be apparent until 3 to 4 weeks of age
    - Continued presence of contrast in rectosigmoid 24 hours later is very suggestive of Hirschsprung disease
    - Will not be diagnostic in total colonic aganglionosis
  - Diagnosis
    - Rectal suction biopsy or full thickness biopsy taken at 2–4 cm above the anal verge
    - Demonstrates absence of ganglion cells and presence of acetylcholinesterase (AChE) with hypertrophic nerve fibers
  - Treatment: surgical resection of aganglionic bowel and anastomosis of anus to ganglionic bowel proximally
  - Risk of enterocolitis persists, even after surgery

Pancreas

- Pancreatic agenesis/hypoplasia
  - Rarely reported conditions that lead to endocrine/exocrine pancreatic insufficiency
  - Hypoplasia results from
    - Agenesis of the dorsal bud (typically provides 90% of pancreatic tissue)
    - Fatty replacement of the pancreatic tissue
  - Intrauterine growth restriction can result
  - Treatment is hormone and enzyme replacement

- Schwachman syndrome
  - Triad of pancreatic insufficiency, bone marrow dysfunction, and poor growth
  - 89% of patients have mutations mapped to chromosome 7q11
  - Defect is with enzyme secretion and acinar function
  - Clinical presentation: steatorrhea, neutropenia, +/- anemia or thrombocytopenia, and failure to thrive
  - Skeletal anomalies can be present
    - Progressive long-bone dysostosis or metaphyseal chondrodysplasia seen in 50%
    - Rib cage abnormalities are seen in one-third of patients
  - Treatment is pancreatic enzyme replacement and close monitoring for infection
  - Mortality is increased (30%) due to infections and increased risk of leukemia
- Cystic fibrosis
  - Genetic disease that can present in the newborn period with intestinal obstruction due to meconium plugs (meconium ileus)
    - Can lead to peritonitis, volvulus, or bowel necrosis
    - Microcolon may also result due to in utero intestinal obstruction and subsequent underdevelopment of the colon
- Clinical manifestations also include prolonged jaundice, liver disease, and failure to thrive
- Respiratory symptoms typically develop outside of the newborn period
- Caused by mutation of cystic fibrosis transmembrane regulator (CFTR) gene on chromosome 7
  - This gene encodes a protein that forms a chloride channel
  - More than 800 different mutations described, F508 deletion is the most common
  - Autosomal recessive
  - Prenatally
    - Ultrasound showing hyperechoic fetal bowel pattern, meconium peritonitis, abdominal calcifications suggestive of CF
    - Chorionic villus sampling or amniocentesis is diagnostic
  - Diagnosis is often made after birth by newborn screening
  - Confirmatory test is sweat testing for chloride concentration analysis
    - Sweat chloride > 60 mEq/dL is diagnostic
  - Testing for pancreatic insufficiency (stool elastase) can also suggest the diagnosis
  - Management requires a multidisciplinary approach with pulmonology, gastroenterology, nutrition, and social work
  - GI care in infancy is centered on providing adequate calories for growth, appropriately dosing pancreatic enzymes, and addressing acute issues with meconium ileus

Meconium Syndromes

- Meconium ileus
  - Almost always associated with cystic fibrosis (occurs in 10%–20% of patients with CF)
  - Inspissated meconium leads to obstruction in the distal small bowel
  - Presents with bowel obstruction at 24–48 hours of life
  - Signs include bilious emesis, abdominal distention, and failure to pass meconium
  - If bowel necrosis has occurred in utero, a pseudocyst may develop and can present as a palpable mass
  - Volvulus may also occur and present as an abdominal mass
  - Diagnosis: abdominal x-ray showing "soap-bubble appearance" due to air in meconium
  - Initial management includes hydration, gastric decompression, and antibiotics
  - Nonoperative treatment is indicated for uncomplicated cases and involves enema
  - Successful 50% of the time, but associated with 11% perforation rate
  - Operative treatment involves enterotomy and bowel irrigation with *N*-acetyl-cysteine
  - At times, it is necessary to divert the bowel to allow for continued bowel irrigation
- Meconium peritonitis
  - Intestinal obstruction can lead to bowel necrosis and perforation during the fetal period
  - Meconium in the peritoneal cavity leads to an inflammatory reaction
  - Results in calcification and scarring, termed *fibroadhesive peritonitis*, which seals off the perforation
  - Meconium ascites occurs when perforation allows liquid meconium to fill the peritoneal cavity just before birth
  - Infants can be asymptomatic, diagnosed due to calcifications on radiograph
  - If infants present with bowel obstruction, surgical intervention is indicated
  - Surgery often involves resection of necrotic bowel or intestinal diversion
- Meconium plug syndrome (also covered in large intestine section)
  - Also termed *functional inertia of prematurity* or *neonatal small left colon syndrome*
  - Typically occurs in preterm infants, also seen in infants of diabetic mothers
  - Thought to be due to immature intestinal motility leading to meconium obstruction in the colon
  - Contributing factors may be hypermagnesemia and hypoglycemia
  - Presents with abdominal distention and failure to pass meconium
  - Abdominal radiograph shows multiple dilated loops of bowel
  - Water-soluble contrast enema can be diagnostic and therapeutic
  - Surgical treatment is rarely required

Abdominal Wall Defects

- Gastroschisis
  - Herniation of abdominal contents through an abdominal wall defect
  - Etiology thought to be due to rupture of umbilical stalk during time of midgut herniation (5–10 weeks) or intrauterine vascular accident

- Risk factors include young maternal age, lower SES, and first-born infant
- Defect is typically on the right side of the umbilicus
- Diagnosis can be made prenatally via ultrasound; elevated levels of maternal AFP (Alpha-fetoprotein) as well as amniotic AFP are present.
- Bowel is not protected by peritoneal sac and is exposed to amniotic fluid leading to fibrous "peel" covering the exposed surface
- Intestinal atresia may also be present in 5%–25% of cases
- Other associated anomalies are infrequent (15%) and not associated with increased risk of abnormal chromosomes, in contrast to omphalocele
- At birth the entire gastrointestinal tract may be eviscerated
- Abdominal defect can be restrictive, leading to significant risk of vascular compromise
- Initial treatment includes placing infants' lower body in sterile bag, positioning to maintain blood flow to extraabdominal intestines (care must be taken to avoid kinking mesenteric vessels), keeping bowel moist, Replogle decompression, adequate fluid and hydration to account for accelerated losses, and broad spectrum antibiotics
- Primary closure of the defect is possible in 90% of cases.
- For larger defects, a staged reduction via silo system is necessary to avoid respiratory failure and abdominal compartment syndrome
- Infants typically have prolonged ileus and are at increased risk for NEC
- Long-term consequences include poor motility, feeding intolerance, and need for prolonged parenteral nutrition
- Survival rate is 90%–95%

- Omphalocele
  - Congenital defect in the central abdominal wall
  - Results from failure of lateral body folds and craniocaudal folds to converge and close the ventral abdominal wall
  - Typically occurs around the 10th week of gestation
  - Eviscerated intestinal contents are covered by mesenchymal membrane and are protected from amniotic fluid.
  - Liver may herniate through the abdominal wall defect
  - Omphalocele can be associated with other congenital abnormalities in 50%–75% of cases including congenital heart disease, VACTEL, Beckwith-Wiedemann syndrome, and trisomies 13,18, and 21
  - Diagnosis can be made by ultrasound at 19 weeks' gestation
  - Due to association with cardiac and chromosomal disorders, amniocentesis and fetal echocardiogram are recommended
  - Initial treatment includes wrapping bowel in sterile saline-soaked gauze, Replogle decompression, adequate fluid and hydration, and broad-spectrum antibiotics.
  - Operative repair performed as soon as possible after birth
  - For larger defects, a staged reduction via silo system is necessary to avoid respiratory failure and abdominal compartment syndrome
  - Survival rate is 30%–80%, largely due to associated anomalies

Syndromes Associated With Gastrointestinal Malformation

- Pentalogy of Cantrell: sternal, diaphragmatic, and pericardial defects, upper abdominal omphalocele, ectopia cordis
- Beckwith-Wiedemann syndrome: macrosomia, visceromegaly, hemihypertrophy, hypoglycemia, renal pathology
- EEC syndrome: ectodermal dysplasia, cleft palate, ectrodactyly
- OEIS complex: omphalocele, exstrophy, imperforate anus, spinal defect

Suggested Readings

Textbook: Avery's Diseases of the Newborn, 8th ed. Chapters 70, 71, 72.
Textbook: Fanaroff and Martin's Neonatal-Perinatal Medicine, Diseases of the Fetus and Infant. 8th ed. Martin, Fanaroff, Walsh. Chapter 45, pp 1357–1417.
Textbook: Review of Pediatric Gastrointestinal Disease and Nutrition. 4th ed. Editors: Huang, Walker. 2005. Kindle edition. Section 1,2,3.
Textbook: Pediatric Gastrointestinal and Liver Disease; Pathophysiology/Diagnosis/Management. 3rd ed. Wyllie, Hyams. Chapters 21, 22.

Questions

1. Epstein pearls
   a. Typically require surgical excision
   b. Can lead to respiratory and/or feeding difficulties
   c. Disappear within one month
   d. Involve the soft palate

2. Which one of the following is not a cause of bilious vomiting?
   a. Intestinal obstruction
   b. GERD
   c. Pyloric stenosis
   d. Intussusception

3. Which is not a cause of delayed passage of meconium?
   a. CF
   b. Small left colon syndrome
   c. Hirschsprung disease
   d. Milk protein intolerance

4. In infants with TEF, coexisting congenital anomalies occur in
   a. 5%
   b. 30%
   c. 70%
   d. 90%

5. Which is the most common form of TEF?
   a. Esophageal atresia with distal TEF
   b. Esophageal atresia with no TEF
   c. H-type TEF
   d. Esophageal atresia with proximal TEF

6. What causes reflux in infants?
   a. Low resting pressure of the upper esophageal sphincter
   b. Immature esophageal peristalsis
   c. Increased gastric acidity
   d. Transient relaxation of the lower esophageal sphincter

7. Which is most consistent with pyloric stenosis?
   a. Hypochloremic alkalosis
   b. Hyperchloremic acidosis
   c. Hypochloremic acidosis
   d. Hyperchloremic acidosis

8. With what syndrome would you most commonly see double bubble?
   a. Trisomy 21
   b. Beckwith-Wiedemann syndrome
   c. Smith-Lemli-Opitz syndrome
   d. Trisomy 18

9. A 3-day-old infant has not yet stooled. What is the next step in management?
   a. UGI with SBFT
   b. Abdominal ultrasound
   c. Rectal suction biopsy
   d. Barium enema

10. Poor motility is a long-term consequence of which condition?
    a. Gastroschisis
    b. Omphalocele
    c. Intestinal atresia
    d. Pyloric stenosis

43 Acquired Disorders of the Gastrointestinal Tract

REBECCA ABELL and MEGAN E. GABEL

Gastrointestinal Bleeding

See Table 43.1.

NECROTIZING ENTEROCOLITIS

- Necrotizing enterocolitis (NEC) most common gastrointestinal (GI) emergency in premature infants
- Clinical features
  - Incidence, ~12% of infants born at <1500 g, 30% mortality
  - Postnatal age of onset and incidence inversely related to birth weight and gestational age
  - 90% of infants with NEC premature
  - Term, late preterm infants infrequently develop NEC; risk factors (associated with bowel ischemia) include intrauterine growth restriction (IUGR) and small for gestational age (SGA), birth asphyxia, congenital heart disease, gastroschisis, polycythemia, hypoglycemia, sepsis, exchange transfusion, ± umbilical lines
  - Can occur in epidemics
  - Occurs more frequently in African-American infants than white infants
- More common following initiation of enteral feeds
- Breast milk and established feeding guidelines—protective factors
- 50% require surgery

Table 43.1 Causes of Gastrointestinal (GI) Bleeding in the Neonate

Upper GI Bleeding	Lower GI Bleeding
Swallowed maternal blood	Milk protein allergy, allergic colitis
Vitamin K deficiency	Hirschsprung disease
Stress gastritis or ulcer	Necrotizing enterocolitis
Acid-Peptic Disease	Intussusception
Vascular anomaly	Gastrointestinal duplication
Coagulopathy	Duodenal web
Mallory-Weiss tear	Anal fissure
Bowel obstruction	Coagulopathy
Milk protein allergy	Volvulus
	Infectious colitis
	Meckel diverticulum
Presentation of Upper GI Bleeding	**Presentation of Lower GI Bleeding**
Hematemesis	Bright red blood in the stool
Coffee ground emesis	Tarry stools
Melena	

- Predictor of neurodevelopmental morbidity
- Positive blood cultures in one-third
- Likely multiple risk factors—bowel ischemia, immaturity of immune system, enteral feeding
- Clinical presentation
  - Lethargy, apnea, abdominal distention, erythema, decreased bowel sounds, metabolic acidosis from lactate accumulation, peaceful tachypnea due to abdominal distention and metabolic acidosis, poor perfusion with delayed capillary refill
- Diagnosis
  - Suspect with clinical features; laboratory values can reveal neutropenia, thrombocytopenia, hyponatremia.
  - Abdominal x-ray—can reveal fixed loop, stacking of loops, pneumatosis, portal venous air, perforation
- Treatment
  - NPO, decompress GI tract with Replogle tube, fluid resuscitation, avoid dopamine (can worsen bowel necrosis from vasoconstriction), broad-spectrum antibiotics, respiratory support if apneic, surgical resection of necrotic bowel

SHORT BOWEL SYNDROME

- Occurs following bowel resection to treat NEC (most common), midgut volvulus, omphalocele, aganglionosis, jejunal or ileal atresia, gastroschisis
- Most frequent cause of intestinal failure in neonates
- Clinical features depend on length of remaining bowel, location of lost bowel
- Complications
  - Malabsorption of nutrients
  - Gastric hypersecretion
  - Small bowel bacterial overgrowth
  - Intestinal adaptation difficulties
  - Cholestatic liver disease typically from chronic use of parenteral nutrition
  - Catheter-related complications
  - Enterocolitis
- Management
  - Parenteral nutrition to supply adequate calories
  - H2 blockers or proton pump inhibitors to suppress acid secretion
  - Intermittent treatment with antibiotics for bacterial overgrowth
  - Enteral feeds to help with intestinal growth and adaptation—small volumes of elemental formula with medium-chain triglycerides
  - If missing ileocecal valve at high risk for diarrhea, fat and vitamin B_{12} malabsorption, need vitamin B_{12} supplementation

- Surgical management includes bowel-lengthening procedures or intestinal transplantation

NEONATAL INTUSSUSCEPTION

- Extremely rare
- Often missed diagnosis and confused with NEC
- Most cases involve small bowel
- Clinical presentation
  - Abdominal distention, feeding intolerance, vomiting, bloody stools
- Diagnosis
  - Ultrasound is gold standard
  - X-rays—may be unremarkable or may see dilation of bowel loops or gas-fluid levels
  - Contrast enema if colonic involvement

ALLERGIC ENTERITIS AND COLITIS—MILK PROTEIN ALLERGY

- It is caused by immunologic hypersensitivity to milk protein.
- The frequency is 2%–6% but only 0.5% in breastfed infants.
- 30%–60% can also have allergy to soy protein.
- Acute gastroenteritis is a risk factor.
- Symptoms
  - 50%–60% have gastrointestinal or skin symptoms.
  - 30% have respiratory symptoms.
- Diagnosis is based on clinical improvement with a milk-free diet or recurrence of symptoms with the reintroduction of milk.
- There are no diagnostic biochemical tests.
- The most sensitive and specific test to predict if a reaction to cow's milk will occur is a cow's milk–specific immunoglobulin E (IgE) and an index of lymphocyte stimulation with beta-lactoglobulin.
- Biopsies are not needed for diagnosis but demonstrate partial or total villous atrophy, with an increase in eosinophils.
- Treatment is removal of cow's milk protein,
  - Formulas containing hydrolyzed proteins or amino acid–based formulas can be used.
  - Breastfed infants require removal of dairy from the mother's diet.
  - 28% of children can tolerate milk protein by the age of 2 years and 78% by 6 years.

Malabsorption Syndromes

DISORDERS OF CARBOHYDRATE ABSORPTION

- Enterocytes lining the small intestine produce enzymes that convert disaccharides and oligosaccharides into monosaccharides.
  - Enzymes are maltase-glucoamylase (MGA), sucrose-isomaltase (SI), and lactase phlorizin hydrolase.
  - Monosaccharides are absorbed via transport proteins.
- Carbohydrate malabsorption can occur due to deficiency of these enzymes or a defect in a transport protein involved in absorption.
- Patients present with severe, watery, osmotic diarrhea.
- Diarrhea regresses when the infant receives nutrition NPO.
- Diagnosis is often made based on the age of the patient and what foods are present in the diet (Table 43.2).

ENZYME DEFICIENCIES

Congenital Sucrase-Isomaltase Deficiency

- Congenital sucrase-isomaltase deficiency (CSID) most common
- Mapped to chromosome 3
- Presents around age 3–6 months when baby is introduced to foods containing sucrose
- Severe watery diarrhea, acidosis, abdominal distention, cramping, failure to thrive (FTT)
- Stool pH < 7 due to fermentation of sugars by colonic bacteria
- Reducing substances negative (sucrose is nonreducing sugar)
- Endoscopy with biopsy for disaccharidase activity is gold standard for diagnosis
- Treatment: avoidance of sucrose

Congenital Lactase Deficiency

- Congenital lactase deficiency (CLD) very rare
- Autosomal recessive, most cases described in Finland
- Presents with introduction of lactose (breast milk, lactose-based formula)
- Severe watery diarrhea, vomiting, FTT, lactosuria, aminoaciduria, lethargy
- Diagnosis made by failure of blood glucose to rise after administration of lactose
- Gold standard: endoscopy with biopsy for disaccharidase activity
- Treatment: lactose-free diet

Maltase-Glucoamylase Deficiency

- Maltase-glucoamylase deficiency (MGA) very rare
- MGA has 60% homology to SI
- Not uncommon to see MGA and CSID co-occur
- Presents with diarrhea and distention
- Symptoms begin with introduction of starch into diet
- Endoscopy with biopsy for disaccharidase activity is gold standard for diagnosis
- Treatment: lactose-free formula and starch elimination

Table 43.2 Age of Onset of Different Malabsorption Syndromes

Age of Onset	Disorder
Immediate neonatal period	Glucose-galactose malabsorption (GGM) Congenital lactase deficiency
Weaning age	Glucoamylase deficiency Congenital sucrose-isomaltase deficiency (CSID)

Adapted from Martin RJ, Fanaroff AA, Walsh MC. *Fanaroff and Martin's Neonatal-Perinatal Medicine.* 10th ed. Philadelphia: Elsevier; 2015.

Transport Defects

GLUCOSE-GALACTOSE MALABSORPTION

- Glucose-galactose malabsorption (GGM) is very rare
- Autosomal recessive, chromosome 22
- Leads to defect in sodium-glucose linked transporter (SGLT) protein
- Severe watery diarrhea in newborn period can lead to death
- Occurs when infant is fed breast milk or glucose-containing formula
- Diagnosis made by stools positive for reducing substances
- Oral glucose test does not lead to rise in serum glucose
- Diarrhea stops when NPO
- Intestinal biopsies normal
- Treatment: formula with fructose as carbohydrate component

Disorders of Protein Absorption

PRIMARY INTESTINAL ENTEROPEPTIDASE DEFICIENCY

- Very rare
- Enteropeptidase converts trypsinogen to trypsin, which then activates other pancreatic enzymes
- Presenting symptoms: diarrhea, FTT, protein-losing enteropathy, significant serum hypoalbuminemia
  - Diagnosis by biopsy with enzyme quantification or measurement of enzyme level in duodenal fluid
  - Treatment: protein-hydrolysate formula

Disorders of Fat Absorption

HYPOBETALIPOPROTEINEMIA AND ABETALIPOPROTEINEMIA

- Autosomal dominant disorder
- Low or absent plasma concentrations of apolipoprotein B lipoproteins and low-density-lipoprotein (LDL) cholesterol
- In heterozygotes, typically clinically asymptomatic
- Homozygous patients—have complete absence of beta-lipoproteins; present with fat malabsorption, acanthocytosis, retinitis pigmentosa, neuromuscular degeneration
- Abetalipoproteinemia (autosomal recessive [AR])—presents with same symptoms due to absence of beta-lipoproteins
- Treatment: low-fat diet and fat-soluble vitamin supplementation

CHYLOMICRON RETENTION DISEASE (ANDERSON DISEASE)

- Autosomal recessive disorder of lipoprotein assembly
- Presenting symptoms
  - Hypocholesterolemia
  - Fat malabsorption
  - FTT
- Clinical presentation similar to abetalipoproteinemia, but extra intestinal manifestations are less severe
- Treatment: low-fat diet and fat-soluble vitamin supplementation

PRIMARY BILE ACID MALABSORPTION

- Due to disruption in enterohepatic circulation of bile
- Presenting symptoms
  - Diarrhea
  - Steatorrhea
  - Decreased serum cholesterol
- Treatment: cholestyramine and low-fat diet

Disorders of Electrolyte Absorption

CONGENITAL CHLORIDE DIARRHEA

- Congenital chloride diarrhea (CCD)—most common cause of congenital secretory diarrhea with intact mucosal histopathology
- AR transmission, defect in intestinal brush border chloride–bicarbonate exchange
- Severe watery diarrhea high in chloride beginning in immediate neonatal period
- Persists when NPO
- Patients have hyponatremia, hypokalemia, hypochloremia, metabolic alkalosis
- Treatment: includes oral chloride, potassium supplements, suppression of gastric acid

CONGENITAL SODIUM DIARRHEA

- Congenital sodium diarrhea (CSD)—AR transmission
- Exceedingly rare
- Due to defect in sodium-hydrogen exchanger in jejunal brush border
- Presents similarly to CCD but with high sodium content in diarrhea
- Can also present with abdominal distention and failure to pass meconium
- Laboratory tests will show hyponatremia, metabolic acidosis, hypokalemia
- Treatment: fluid and electrolyte replacement

Disorders of Villous Architecture

MICROVILLUS INCLUSION DISEASE

- Microvillus inclusion disease (MVID)—congenital defect of intestinal brush border
- Presents with severe diarrhea (up to 500 mL/kg/day)
- Persists when NPO
- Diagnosis made via duodenal biopsy specimens that show villous atrophy
- Treatment: options are lifelong parenteral nutrition or small bowel transplantation

TUFTING ENTEROPATHY

- Presents in first weeks of life with severe life-threatening diarrhea
- Duodenal biopsy shows epithelial shedding
- Treatment: options are lifelong parenteral nutrition or small bowel transplantation

Suggested Readings

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Questions

1. Which is true of sucrose-isomaltase deficiency?
   a. It presents after the introduction of standard infant formula.
   b. It presents with bloody diarrhea.
   c. It presents when secondary foods are introduced.
   d. Treatment is use of an amino acid–based formula.

2. Which is true of congenital lactase deficiency?
   a. It presents after introduction of standard infant formula.
   b. It presents with bloody diarrhea.
   c. It presents when secondary foods are introduced.
   d. Treatment is use of amino acid–based formula.

3. A 2-week-old female infant presents with severe watery diarrhea, acidosis, and lethargy. The work-up reveals that stools are positive for reducing substances, intestinal biopsies are normal, and diarrhea resolves when the infant is made NPO. This disorder is due to which of the following?
   a. Defect found on chromosome 3
   b. Defect in sodium-glucose linked transporter (SGLT) protein
   c. Autosomal recessive disorder of lipoprotein assembly
   d. Defect in sodium-hydrogen exchanger in jejunal brush border

4. Treatment of hypobetalipoproteinemia involves which of the following?
   a. Low-fat diet
   b. High-fat diet
   c. Supplementation with docosahexaenoic acid (DHA)
   d. Supplementation with zinc

5. A 6-hour-old infant is admitted to the NICU with severe watery diarrhea that persists when the infant is made NPO. The infant is found to have hyponatremia, hypochloremia, and metabolic alkalosis. The likely diagnosis is which of the following?
   a. Microvillous inclusion disease
   b. Tufting enteropathy
   c. Congenital sodium diarrhea
   d. Congenital chloride diarrhea

6. Which one of the following is not a risk factor for necrotizing enterocolitis (NEC)?
   a. Bowel ischemia
   b. Immaturity of the immune system
   c. Enteral feeding
   d. Exposure to antibiotics

7. Which is not a complication of short bowel syndrome?
   a. Gastric hypersecretion
   b. Small bowel intestinal overgrowth
   c. Enterocolitis
   d. Stricture

8. Appropriate management of small bowel syndrome consists of all but which of the following?
   a. Acid suppression
   b. Chronic antibiotic use to treat for bacterial overgrowth
   c. Total parenteral nutrition (TPN)
   d. Enteral feeds with MCT (Medium Chain Triglycerides)

9. A 3-week-old breastfed infant presents with irritability and bright red blood in the stool. The complete blood count (CBC) reveals white blood cell count (WBC), 7,000/μL, hematocrit (Hct), 13%, and Platelets (Plt), 300,000/μL. Electrolytes are within normal limits. Weight gain has been stable but mother reports recent feeding refusal. The most likely diagnosis is which of the following?
   a. NEC
   b. Gastroesophageal reflux disease (GERD)
   c. Infection
   d. Milk protein allergy

10. Which of the following is true regarding cases of neonatal intussusception?
    a. Most involve the small bowel
    b. Most involve large bowel
    c. Very common
    d. Always require surgical intervention

44 Liver Disease, Abdominal Masses, and Ascites in the Newborn Infant

REBECCA ABELL and MEGAN E. GABEL

Congenital Malformations of the Liver and Bile Ducts

CHOLEDOCHAL CYSTS

- Cystic dilation of hepatobiliary tree
- Incidence 1/100,000–150,000 in Western countries
- More common in Asian countries
- Four times more common in females
- Proposed etiology: regurgitation of pancreatic secretions in to the biliary tree at the time of pancreaticobiliary duct fusion, resulting in weakening and dilation of the duct
- Can coincide with biliary atresia
- Clinical presentation
  - Jaundice
  - Elevated liver enzymes
  - Direct hyperbilirubinemia and elevated gamma-glutamyltransferase (GGT)
  - Obstructive symptoms such as cholangitis, pancreatitis, hepatitis, cirrhosis, and/or portal hypertension if not treated
- Diagnosis
  - Ultrasound
  - Can be diagnosed prenatally
  - Classified (types I–VI) based on Todani criteria, presence of multiple saccular or cystic dilations of the intrahepatic ducts (known as *Caroli disease*)
- Treatment
  - Surgical resection
  - Risk of malignancy if not removed

INTRAHEPATIC BILIARY HYPOPLASIA: ALAGILLE SYNDROME

- Autosomal dominant
- Paucity of intralobular ducts
- Occurs in 1/30,000 live births
- Mutations in the *JAG1* and *NOTCH2* genes
- Clinical presentation
  - Triangular facies
  - Posterior embryotoxon (iris strands)
  - Butterfly vertebrae
  - Renal disease
  - Cardiac defects (peripheral pulmonic stenosis, tetralogy of Fallot)
  - Direct hyperbilirubinemia
  - May have acholic stool
  - Elevated ALT
  - Elevated bile acids
  - Very elevated GGT—may be up to 20 times the normal value
- Diagnosis made by liver biopsy

EXTRAHEPATIC BILIARY ATRESIA

- Occurs in 1/15,000–18,000 live births
- Most common cause of prolonged conjugated hyperbilirubinemia in neonates
- Perinatal or embryonic form
- Progressive fibroinflammatory cholangiopathy
- Obliteration of extrahepatic biliary tree, resulting in obstruction and cirrhosis of liver
- Clinical presentation
  - Appear well at birth
  - Direct bilirubin typically < 7 mg/dL
  - Hepatosplenomegaly
  - GGT elevated
- Pathogenesis
  - Defect in morphogenesis of biliary tract
  - Defect in fetal or prenatal circulation
  - Environmental toxin exposure
  - Viral infection
- Immunologic or inflammatory dysregulation
- Diagnosis
  - Ultrasound
- Absence of gallbladder suggestive, but presence of gallbladder does not rule it out; triangular cord sign suggestive of biliary atresia
  - Scintigraphy—HIDA scan
- Measures hepatic uptake and excretion of analogues of iminodiacetic acid into intestines
- Pretreatment—phenobarbital 5 mg/kg per day for 5 days prior to study
  - Liver biopsy demonstrates bile plugging, proliferated ducts, edema, fibrosis
  - Exploratory laparotomy with cholangiography
- Treatment: Kasai procedure
  - Roux-en-Y jejunostomy
  - Better prognosis if done before 60 days of age

Cholestasis of the Neonate

See Table 44.1 for causes.
Refer to Chapter 39 for a review of Neonatal Hepatitis

ABDOMINAL MASSES

See Box 44.1.

Neonatal Ascites

See Table 44.2.

- Chylous ascites
  - Most common type
  - Occurs more often in males
  - Most often due to congenital failure of lymphatic channels to communicate
  - May accompany intestinal malrotation and incomplete volvulus
  - Often refractory to therapy; can cause malnutrition and immunodeficiency due to extravasation of protein and lymphocytes
  - Treatment: paracentesis and formula containing medium-chain triglycerides (MCTs)
- Urinary ascites
  - 25% of neonatal ascites
  - Caused by obstructive uropathy
  - Most commonly posterior urethral valves but can also be from ureteroceles, urethral atresia, bladder neck obstruction, neurogenic bladder, bladder hematoma
  - Need to look for abnormalities in urinary tract and collecting system
  - Treatment—surgical decompression or correction of underlying issue
- Biliary ascites
  - Caused by spontaneous perforation of biliary tree
  - 68% of cases perforation is in the main biliary tree
  - Two forms of biliary ascites
    - Acute: abdominal distention, vomiting, lack of bowel signs, may not have jaundice
    - Chronic form: early jaundice, gradual abdominal distention
- 80% of cases
- Diagnosis confirmed by scintigraphy or ultrasound
- Treatment: laparotomy with biliary drainage
- Pancreatic ascites
  - Extremely rare
  - May be due to pancreatic duct anomaly
  - Only symptom is abdominal distention
  - Urine and serum amylase levels—can be normal
  - Treatment requires surgical drainage
- Ruptured ovarian cyst
  - Presents with hemoperitoneum in addition to ascites

Suggested Readings

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Table 44.1 Metabolic and Genetic Causes of Neonatal Cholestasis

Disease Process	Presentation	Diagnosis
Biliary atresia	Dark urine, acholic stools	Ultrasound, HIDA scan, liver biopsy, intraoperative cholangiography
Alagille syndrome	Characteristic facies, cardiac findings, vertebral anomalies	Chest x-ray (butterfly vertebrae), ophthalmology, echo, GGT, cholesterol level increased, decreased levels of fat-soluble vitamins, liver biopsy
Choledochal cyst	Abdominal mass	Cyst seen on ultrasound, ERCP, MRCP
Caroli disease, syndrome	Bacterial cholangitis, portal hypertension	Ultrasound of liver and kidneys, ERCP, MRCP if >1 year old, *PKHD1* gene (ARPKD)
Gallstones or biliary sludge	May have acholic stools	Ultrasound, ERCP, GGT, LFTs elevated
Idiopathic neonatal giant cell hepatitis	Prolonged jaundice	Histologic diagnosis after other causes excluded
Neonatal sclerosing cholangitis	Dark urine, acholic stools	GGT often > 800 IU/L, ERCP, liver biopsy with small duct destruction, intraoperative cholangiogram shows pruning of small bile ducts
Progressive familial intrahepatic cholestasis (PFIC)	Severe cholestasis, intractable pruritus, possible coagulopathy	GGT decreased or normal in types 1 and 2, GGT increased in type 3, liver biopsy, genetic testing
A1AT deficiency	Neonatal jaundice	GGT often high, A1AT level low, A1AT PI phenotype analysis (ZZ, SZ, MZ)
Cystic fibrosis	Jaundice and hepatomegaly, steatorrhea, failure to thrive, meconium ileus	Newborn screening with high IRT, stool elastase low, sweat test with elevated sweat chloride, genetic testing

Table 44.1 Metabolic and Genetic Causes of Neonatal Cholestasis—cont'd

Disease Process	Presentation	Diagnosis
Gaucher disease	Splenomegaly, hepatomegaly, thrombocytopenia, anemia, bleeding, osteopenia	β-Glucocerebrosidase decreased, chitotriosidase increased, alkaline phosphatase increased; bone marrow biopsy with "crinkled paper" cytoplasm, glycolipid-laden macrophages, foam cells
Niemann-Pick type C	Splenomegaly	Filipin-positive reaction (detection of cholesterol in fibroblasts), increase in chitotriosidase, genetic testing
Wolman disease, LAL deficiency	Hepatomegaly, neonatal liver failure	Hyperechoic liver, lysosomal lipase acid decreased in peripheral blood mononuclear cell
Mitochondrial disorders	Lethargy, vomiting, hypotonia, seizures, hypoglycemia, coagulopathy, lactic acidosis.	Genetic testing, fasting and postprandial lactate, INR, plasma lactate-to-pyruvate ratio > 20
Tyrosinemia	Cholestasis and coagulopathy, Fanconi-related nephropathy or seizures	Newborn screening, urinary excretion of succinylacetone is increased, 4-hydroxy-phenylketones and γ-aminolevulinic acid increased, genetic testing
Galactosemia	Vomiting, diarrhea, renal tubular acidosis, cataracts, FTT, coagulopathy.	Newborn screening, presence of reducing substances in urine, galactose-1-phosphate uridyltransferase activity in red blood cells decreased
Congenital disorders of glycosylation	Dysmorphic facies, MR, seizures, dystrophy, hepatomegaly, cyclic vomiting, diarrhea, hypoalbuminemia, protein-losing enteropathy	Triglycerides increased, ATIII decreased, factor XI decreased, proteins C and S decreased
Hypothyroidism	Jaundice	Newborn screening, TSH and free T_4 elevated
Panhypopituitarism	Hypoglycemia, prolonged jaundice, micropenis	Glucose, cortisol, TSH, free T_4, IGF-1 and IGF-BP decreased, hypercalcemia, liver biopsy with bile duct paucity, MRI may show microadenoma or absent sella
ARC syndrome	Limb contractures, arthrogryposis multiplex congenita, facial dysmorphia, rental tubular acidosis, cholestasis, platelet dysfunction, ichthyosis	Genetic testing

A1AT, Alpha-1-antitrypsin; *ARC,* arthrogryposis-renal dysfunction-cholestasis syndrome; *ARPKD,* autosomal recessive polycystic kidney disease; *ERCP,* endoscopic retrograde cholangiopancreatography; *FTT,* failure to thrive; *GGT,* gamma-glutamyl transferase; *HIDA,* hepatobiliary iminodiacetic-based acid scan; *IGF-1,* insulin-like growth factor 1; *IGF-BP,* insulin-like growth factor binding protein; *INR,* international normalized ratio; *IRT,* immunoreactive trypsinogen; *LAL,* lysosomal acid lipase; *LFT,* liver function test; *MR,* ; *MRCP,* magnetic resonance cholangiopancreatography; *T_4,* thyroxine; *TSH,* thyroid-stimulating hormone.

Box 44.1 Neonatal Abdominal Masses

Retroperitoneal—kidney

Hydronephrosis
Multicystic dysplastic kidney
Autosomal recessive polycystic kidney disease
Autosomal dominant polycystic kidney disease
Mesoblastic nephroma
Renal vein thrombosis

Retroperitoneal—other

Adrenal abscess
Fetus in fetu
Pelvic
Hydrometrocolpos
Ovarian cyst

Gastrointestinal

Intestinal duplication
Malrotation
Obstruction
Sacrococcygeal teratoma

Table 44.2 Neonatal Ascites

Type of Ascites	Features
Chylous	Clear or milky fluid; high triglyceride level and leukocyte count; protein content variable
Urinary	Urine—elevated urea, creatinine, and potassium; low or normal sodium and chloride
Biliary	Bilirubin > 4 g/dL
Pancreatic	May have elevated amylase, fat, and protein
Others	Neonatal hydrops; congestive heart failure; rupture of large ovarian cyst

Questions

1. A 5-week-old infant is found to have direct hyperbilirubinemia, heart murmur, and triangular facies. This syndrome is:
   a. More common in females
   b. Inherited in an autosomal recessive fashion
   c. Due to mutation in *FIC1* gene
   d. Due to mutation in *JAG1* gene

2. Symptoms concerning for biliary atresia include all the following except:
   a. Acholic stools
   b. Triangular facies
   c. Hepatosplenomegaly
   d. Prolonged jaundice

3. Treatment of chylous ascites in the neonate typically includes:
   a. Surgical decompression
   b. Dietary restriction of protein
   c. Dietary restriction of long chain triglycerides
   d. Biliary drainage

4. With extrahepatic biliary atresia, the goal is to perform the Kasai procedure:
   a. Before 60 days old
   b. Before 90 days old
   c. Before direct bilirubin reaches 8 mg/dL
   d. Before direct bilirubin reaches 10 mg/dL

5. The distinguishing laboratory finding of progressive familial intrahepatic cholestasis type 2 (PFIC2) as opposed to PFIC1 or PFIC3 is:
   a. Elevated gamma-glutamyltransferase (GGT)
   b. Low GGT
   c. Elevated aspartate aminotransferase (AST)
   d. Elevated alanine aminotransferase (ALT)

6. Which of the following is not a presentation seen with Alagille syndrome?
   a. Triangular facies
   b. Butterfly vertebrae
   c. Cardiac defects
   d. Low GGT

7. Which of the following laboratory values are you most likely to find with biliary ascites?
   a. High triglyceride count
   b. Bilirubin > 4 g/dL
   c. Low sodium level
   d. Elevated urea level

8. Which of the following can occur if a choledochal cyst goes without treatment?
   a. Biliary atresia
   b. Pancreatitis
   c. Cirrhosis
   d. b and c

9. All the following are mechanisms for pathogenesis of biliary atresia except:
   a. Defect in morphogenesis of biliary tract
   b. Regurgitation of pancreatic secretions in to the biliary tree
   c. Viral infection
   d. Defect in fetal or prenatal circulation

10. Which of the following is most likely to be present in a neonate with alpha-1 antitrypsin deficiency?
    a. High levels of alpha-1 antitrypsin
    b. MM phenotype
    c. High GGT levels
    d. Normal ALT and AST levels

SECTION 12

Hyperbilirubinemia

AARTI RAGHAVAN

45 Bilirubin Biochemistry Metabolism and Measurement

AARTI RAGHAVAN

Bilirubin Biochemistry

- Life span of red blood cells (RBCs) in the newborn is 1.5 to 3 months.
- Bilirubin is a yellow-orange pigment (4Z, 15Z, bilirubin; IX, alpha isomer) formed by the degradation of hemoglobin in mammals. This provides 80% of the bilirubin in neonates.
- Other sources include degradation of myoglobin from muscles, cytochromes, and catalase activity.
- Biliverdin is formed as an intermediate step, and carbon monoxide is a byproduct.
- Due to the shorter life span of RBCs, bilirubin production in neonates is 8.5 mg/kg/day compared with 4 mg/kg/day in adults.
- Other factors leading to increased bilirubin production in newborns compared with adults:
  - Increased cytochrome turnover
  - Increased enterohepatic circulation

Bilirubin Physiology, Pathways of Synthesis, Transport, and Metabolism in the Newborn

BILIRUBIN PRODUCTION

- Heme is produced by the degradation of RBCs in the reticuloendothelial system.
- Heme breaks down into biliverdin (IX alpha) by the action of heme oxygenase, with iron and carbon monoxide produced as byproducts. Carbon monoxide combined with hemoglobin forms carboxyhemoglobin, which is released through the lungs.
- Biliverdin is converted into bilirubin (IX alpha) by the action of bilirubin reductase.
- The degradation of 1 g of hemoglobin = 34 g of bilirubin.

TRANSPORT AND PROTEIN BINDING

- Unconjugated bilirubin is water-insoluble and is transported in plasma bound to albumin.
- 7–8 mg/dL binds to one molecule of albumin.
- Binding occurs via two sites: primary high-affinity binding site and secondary low-affinity binding site. Other binding sites exist but are not clinically significant.
- Due to tight binding with albumin, bilirubin only occurs in its free unbound form in a low nanomolar range, even in cases of hyperbilirubinemia.
- When the molar concentration of bilirubin exceeds the albumin-binding capacity, levels of free unbound bilirubin increase.
- Bilirubin binding to albumin increases with postnatal age and decreases in sick infants and in the presence of binding competitors such as ampicillin, sulfa drugs, ceftriaxone, free fatty acids, and benzyl alcohol.

UPTAKE AND CONJUGATION

- The bilirubin-albumin complex travels to hepatocytes via plasma.
- Bilirubin is transported into the hepatocytes by carriers such as ligandin or glutathione S-transferase.
- Increased uptake of bilirubin occurs when ligandin concentrations are increased.
- Ligandin concentrations reach adult levels 1 to 2 weeks after birth. Concentrations are also increased by drugs such as phenobarbital.
- Glucuronyl transferase (uridine diphosphate [UDP] - glucuronyl transferase) catalyzes the binding of glucuronic acid to bilirubin, resulting in water-soluble bilirubin glucuronide (polar form) that can be excreted in bile.
- Bilirubin monoglucuronide is formed in the endoplasmic reticulum of microsomes (25%); diglucuronide formation occurs at the cell membrane (60%).
- Conjugation of bilirubin converts water-insoluble to water-soluble molecules, resulting in decreased intestinal absorption because hydrophilic molecules do not get absorbed easily.

EXCRETION

- Conjugated bilirubin is excreted into bile by an energy-dependent mechanism against a concentration gradient.
- Due to this energy-dependent mechanism, the clearance of bilirubin from the hepatocyte is a saturable process and is a rate-limiting step after the first week of postnatal life.
- Bile is secreted into the intestines and then is reduced to stercobilinogen and urobilinogen and excreted into stool.
- Alternatively, deconjugation in the small intestine is mediated by beta-glucuronidase in the brush border of the intestine.

Unconjugated bilirubin is reabsorbed into the circulation. This cycle of conjugation, excretion, deconjugation, and absorption is known as *enterohepatic circulation.*

- Relatively low levels of bacterial flora also prevent conversion to urobilinogen, increasing intestinal absorption.
- Enterohepatic circulation in neonates is slightly slower due to decreased nutrient intake and decreased intestinal transit time.

BILIRUBIN PHYSIOLOGY IN THE FETUS

- Fetal bilirubin production is approximately 150% that of adults.
- Heme degradation results in the formation of bilirubin IX alpha, heme oxygen, and biliverdin.
- The rate-limiting step in bilirubin metabolism is the reduced levels of UDP glucuronyl transferase, which is at low levels until 30 weeks' gestation and increases to 1% of adult levels at term.
- Bilirubin appears in the fetus from 14 weeks' gestation.
- At 16 weeks, unconjugated bilirubin IX alpha appears in bile.
- By 38 weeks' gestation, the primary isomer is bilirubin IX alpha.
- Although amniotic fluid does contain bilirubin in early gestation, it is not seen near term.
- Unconjugated bilirubin in the fetus is eliminated by crossing the placenta or via the liver into bile.
- Biliverdin and bilirubin conjugates do not cross the placenta.
- Conjugation and excretion into bile are confirmed by the accumulation of bilirubin in meconium, up to 5–10 times the daily neonatal production.
- Beta-glucuronidase activity in the meconium converts conjugated bilirubin to its unconjugated form, allowing absorption into the portal circulation.
- Reabsorbed bilirubin may be reconjugated in the liver or may cross the placenta into the maternal circulation.
- Due to the efficient elimination of unconjugated and conjugated bilirubin from the fetus, the fetal bilirubin level rarely rises to severe levels, even with hemolytic disease, where anemia is the overriding concern.

Measurement

- Principle of traditional method: reaction with the diazo agent, resulting in colored bilirubin derivatives, which are quantified by spectrophotometry
  - Directly reacting bilirubin (direct bilirubin): conjugated bilirubin reacts directly with the diazo agent to yield colored derivatives.
  - Indirectly acting bilirubin (indirect bilirubin): when the reaction is catalyzed by caffeine or DMSO, unconjugated bilirubin is energized to react with the diazo agent, forming colored derivatives.
  - Total bilirubin = indirect derivatives + direct bilirubin derivatives.
  - Other less reliable methods used for measurement include fluorimetry and high-pressure liquid chromatography.
  - Spectrophotometry is most commonly used.
  - Other methods are often influenced by the products of bilirubin and glucuronide metabolism, which are found in an age-dependent and subject-dependent manner.
  - The administration of drugs, nutrition, and treatments such as phototherapy or exchange transfusions affect the concentration of bilirubin.
- Measurement of free bilirubin (i.e., unbound to albumin)
  - This method is not widely available for clinical use.
  - It is of interest due to the neurotoxic potential of free bilirubin.
  - Most bilirubin is bound to albumin, so free levels are expected to be low.
  - When bilirubin levels are high, levels exceed albumin-binding sites, resulting in high free bilirubin levels.
  - Because free bilirubin measurement tools are not well established, the serum bilirubin-to-albumin ratio is used as a surrogate marker.
- Noninvasive measurement of bilirubin
  - Transcutaneous measurement of yellow-orange pigment in the skin using optical technology
  - Provides an index of total bilirubin
  - Useful for serial measurements and measurement of trends
  - Serves as a screen; need confirmatory blood sampling and testing

How to Use Predischarge Bilirubin Measurement to Predict Risk of Severe Hyperbilirubinemia

- Bilirubin rises in an hourly fashion over the first few days of life, typically peaking at 4–5 days of life.
- Infants discharged at approximately 48 hours of life have only started to demonstrate increasing bilirubin.
- For this reason, all newborns must have follow-up soon after discharge (1–3 days after discharge).
- The timing of discharge should be determined based on risk factors such as feeding history, race and ethnicity (East Asian ethnicity higher risk), previous sibling with hyperbilirubinemia, cephalohematoma, and bruising.
- The American Academy of Pediatrics recommends routine screening for bilirubin and risk evaluation based on hours of life prior to discharge.
- Predischarge bilirubin level and gestational age are the most sensitive factors to assess risk.
- Complete absence of hyperbilirubinemia is highly predictive of low-risk infants.

Suggested Readings

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Questions

1. All the following are true statements about bilirubin metabolism except:
   a. Bilirubin is formed from biliverdin catalyzed by biliverdin reductase.
   b. Carbon monoxide is produced during the conversion of bilirubin to biliverdin.
   c. Bilirubin is converted back to biliverdin by reactive oxygen species.
   d. Iron eliminated from heme oxidation catalyzed by heme oxygenase is recycled.

2. Which of the following substances is lipophilic and crosses the placenta from the fetus?
   a. Conjugated bilirubin
   b. Unconjugated bilirubin
   c. Lumirubin
   d. Biliverdin

3. All the following are measures of bilirubin except:
   a. Serum bilirubin
   b. Transcutaneous bilirubin
   c. ETCO
   d. Reticulocyte count

4. All the following are risk factors for hyperbilirubinemia except:
   a. Formula feeding
   b. Ethnicity
   c. Gestational age
   d. Bruising

5. Which of the following enzymes are involved in bilirubin conjugation?
   a. Heme oxygenase
   b. Beta-glucuronidase
   c. UDP glucuronyl transferase
   d. All the above
   e. A and B
   f. B and C

6. All the following contribute to an increased propensity for hyperbilirubinemia in neonates compared with adults except:
   a. Increased RBC turnover
   b. Immature conjugating enzymes
   c. Decreased enterohepatic circulation
   d. Relatively high bacterial flora

7. Factors affecting albumin to bilirubin binding include:
   a. Low serum albumin level
   b. Acidosis
   c. Medications such as ceftriaxone
   d. All of the above

8. The rate-limiting step in bilirubin metabolism in a preterm infant is:
   a. Heme oxygenase activity
   b. UDP glucuronyl transferase activity
   c. Beta-glucuronidase activity
   d. All of the above
   e. None of the above

9. Bilirubin is transported from the bilirubin-albumin complex into hepatocytes by which of the following?
   a. Ligandin
   b. Glucuronyl S-transferase
   c. All of the above
   d. None of the above

10. Which of the following methods is most commonly used to measure the serum bilirubin levels?
    a. Spectrophotometry
    b. Fluorimetry
    c. High-pressure liquid chromatography
    d. All of the above
    e. None of the above

46 Bilirubin Toxicity

AARTI RAGHAVAN

Basic Information

- Severe jaundice in the newborn can cause bilirubin toxicity.
- In most patients, elevated serum bilirubin has no long-term sequelae.
- Elevated free unbound bilirubin can cross the blood-brain barrier and affect the brain.
- Typical areas of brain that are affected include the basal ganglia, cranial nerve nuclei, and hippocampus, which are stained yellow on pathologic examination.
- Staining correlates with neuronal necrosis and loss and gliosis.
- The level of free bilirubin is determined by its binding to serum albumin.
- Factors affecting bilirubin binding to albumin are detailed in Table 46.1.

Acute Bilirubin Encephalopathy

DEFINITION

- Acute manifestation of bilirubin-induced neurologic dysfunction (BIND)

CLINICAL FEATURES

- Elevated serum bilirubin
  - Early bilirubin toxicity—transient and reversible
  - Increasing lethargy, with concomitant increase in serum bilirubin concentrations, with reversal of lethargy following interventions such as double-volume exchange transfusion

Table 46.1 Factors Decreasing Bilirubin Binding to Albumin

Condition	Mechanism
Low serum albumin ▪ Preterm Infant ▪ Sick Infant	Low albumin binding site availability
Drugs ▪ Sulfisoxazole ▪ Moxalactam ▪ Ceftriaxone ▪ Indomethacin ▪ Salicylates ▪ Ampicillin (rapid infusion)	Competitively displaces bilirubin from albumin
Acidosis (pH < 7.4)	Increases movement of bilirubin into tissues, including brain
Increased free fatty acids (e.g., IV lipid infusion, hypoxemia)	Displaces bilirubin
Benzyl alcohol	Inhibits albumin-bilirubin binding

DIAGNOSIS AND EVALUATION

- The exact bilirubin level to cause BIND is unknown, although the risk appears greater with other risks such as prematurity and concomitant illness.
- Serum bilirubin should be used as part of a dynamic process of monitoring over time because bilirubin metabolism varies over time.
- The brainstem auditory evoked response (BAER) demonstrates changes in wave latency and magnitude, especially prolongation of latencies of waves III and IV-V and interpeak I-III and I-V, suggestive of brainstem conduction interference.
- BAER findings at this stage are typically reversible.
- An abnormal BAER may be due to cranial nerve VIII injury.
- Because cochlear function may be normal, otoacoustic emission (OAE) tests are not sufficient to screen for neuropathy.
- MRI scans show focal changes in the globus pallidus and hippocampus.

Kernicterus

DEFINITION

- Worsening encephalopathy due to hyperbilirubinemia, with pathologic findings of yellow staining and necrosis of neurons in basal ganglia, hippocampus, subthalamic nuclei, and cerebellum, with subsequent gliosis in these areas
- Cerebral cortex typically spared.
- Extraneural sequelae seen in >50% of affected infants—necrosis of renal tubular cells, intestinal mucosa and pancreatic cells, accumulation of bilirubin crystals

PATHOGENESIS

- Bilirubin enters the brain because of any of the following reasons:
  - Increased production of bilirubin that overwhelms normal conjugation mechanisms.
  - Low serum albumin or decreased albumin-binding capacity (seen in sick or preterm infants), resulting in increased free serum bilirubin; other factors affecting bilirubin-albumin binding detailed in Table 46.1
    - Disruption of blood-brain barrier:
    - Increased serum osmolarity, hypoxemia, meningitis—all contribute
  - Increased in situ production of bilirubin.
    - Hemeoxygenase 1 and 2 (HO 1 and 2) break down hemoglobin outside the reticuloendothelial system in the brain and are upregulated under stress.

  - Biliverdin reductase converts biliverdin to bilirubin, which is cleared by bilirubin oxidase and transported out of the central nervous system (CNS).
  - All these enzymes are developmentally regulated.
  - The breakdown of transport increases in situ accumulation of bilirubin.
- Postulated theories of CNS neuronal injury include the following:
  - Passage through lipid moieties of cell membranes into subcellular organelle such as mitochondria, interfering with energy metabolism
  - Binding to cytoplasmic protein and inhibiting function
  - Interference with DNA function

CLINICAL FEATURES

Several Phases

- Phase 1: jaundice, poor suck, hypotonia, drowsiness
- Phase 2: hypertonia, fever, torticollis, with or without opisthotonus
- Phase 3: reduced hypertonia, high-pitched cry, hearing and visual abnormalities, poor feeding, athetosis, seizures
- Typical duration of symptoms: 24 hours
- Mortality: 50%
- Long-term sequelae: choreoathetoid cerebral palsy, upward gaze palsy, sensorineural hearing loss, dental dysplasia, may have normal intellect
- Long-term sequelae: may be seen in infants with no evidence of bilirubin encephalopathy or kernicterus.
- Presentation in preterm infants less typical, bilirubin level for risk may be lower

RISK FACTORS FOR KERNICTERUS

- Prematurity
  - Clinical presentation less typical
  - May cross blood-brain barrier at lower levels
  - May not stain the brain like a term infant due to difference in CNS permeability and bilirubin metabolism
  - Mortality due to kernicterus higher than in term infant
- Sepsis
- Rapid rate of rise of bilirubin, such as with hemolytic diseases
- Asphyxia
- Hyperosmolar states—hyperglycemia, hypernatremia, dehydration, uremia due to renal failure
- Hypoxia
- Hypercarbia

EVALUATION AND DIAGNOSIS

- Diagnosis is based on
  - Clinical evaluation, findings as above
  - Extremely elevated serum bilirubin values
- Evaluation includes
  - Impact of kernicterus
    - MRI of the brain
    - BAER (serial)
- Assessment of the cause of kernicterus includes the following:
  - Infant blood type and Coombs test
  - Maternal blood type
  - Complete blood count with reticulocyte count
  - Liver function tests (with total and fractionated bilirubin)
  - Peripheral smear (assess hemolysis)
  - Osmotic fragility
  - Glucose-6-phosphate dehydrogenase levels
  - Blood cultures (sepsis increases risk of direct hyperbilirubinemia)
  - Thyroid function tests

TREATMENT

- Phototherapy
  - Mechanism of action
    - Light energy converts subcutaneous bilirubin (4Z-15Z bilirubin) to photoisomers (E configuration instead of Z configuration = lumirubin), which are also unconjugated but less lipophilic, can be excreted in urine or bile
  - Efficacy dependent on the following:
    - Wavelength (420–490 μm, blue range)
    - Surface area for exposure
    - Distance to baby (more effective when closer)
    - Irradiation (at least 30 $\mu W/cm^2$)
  - Side effects
    - Dehydration
    - Rash
    - Retinal injury
    - Gonadal injury
  - Contraindications
    - Bronze baby syndrome (bronzing of skin and urine) when phototherapy used in patients with conjugated hyperbilirubinemia
    - Acute intermittent porphyria—causes bullae formation and death
- Double-volume exchange transfusion
  - Indications
    - Based on American Academy of Pediatrics recommendations for management of hyperbilirubinemia in infants older than 35 weeks
    - Bilirubin levels in combination with risk factors, such as postnatal age, gestational age, glucose-6-phosphate dehydrogenase deficiency, asphyxia, acidosis
  - Exchange transfusion to be considered at bilirubin levels of 20–25 mg/dL
  - Technique
    - Red blood cells (RBCs) reconstituted with 5% albumin or fresh-frozen plasma
    - Citrate used as an anticoagulant in the blood increases risk for hypocalcemia
  - Side effects
    - Umbilical and portal vein thrombosis
    - Thrombocytopenia
    - Necrotizing enterocolitis
    - Hypocalcemia
    - Respiratory and metabolic acidosis
    - Graft-versus-host disease
    - Infections such as HIV, hepatitis C (very low risk)
  - Relatively lower risk when performed in intensive care unit by experienced, trained professionals

- Intravenous immunoglobulin
  - Useful in ABO and Rh incompatibility when response to phototherapy is suboptimal
  - More useful with ABO incompatibility than Rh incompatibility
  - Competitively binds to antigen and prevents antibody binding, preventing hemolysis
  - Dose: 500–1000 mg/kg IV over 2–4 hours
  - May reduce the need for exchange transfusion
  - Higher dose may be given again if limited response seen

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Watchko JF. Hyperbilirubinemia and bilirubin toxicity in the late preterm infant. *Clin Perinatol.* 2006;33(4):839–852.

Questions

1. All the following parts of the brain are typically affected in bilirubin toxicity except the:
   a. Hippocampus
   b. Cranial nerve nuclei
   c. Cerebral cortex
   d. Basal ganglia

2. Which of the following are features of acute bilirubin encephalopathy?
   a. Severely elevated serum bilirubin
   b. Abnormal brainstem auditory evoked response
   c. Abnormal otoacoustic emission test
   d. Abnormal MRI
   e. All of the above
   f. a, b, d

3. Which of the following are mechanisms contributing to bilirubin toxicity?
   a. Increased bilirubin production
   b. Alteration of the blood-brain barrier
   c. Decreased serum albumin
   d. Increased in situ bilirubin production
   e. All of the above
   f. None of the above

4. Extraneural injuries due to bilirubin include:
   a. Intestinal necrosis
   b. Renal tubular necrosis
   c. Pancreatic necrosis
   d. None of the above
   e. All of the above

5. Long-term sequelae of kernicterus include:
   a. Cerebral palsy
   b. Abnormal gaze
   c. Dental dysplasias
   d. Normal intellect
   e. All of the above
   f. None of the above

6. Efficacy of phototherapy depends on:
   a. Wavelength
   b. Irradiance
   c. Distance from surface
   d. Surface area of exposure
   e. All of the above
   f. None of the above

7. Of the following diagnoses, which is the most common complication of exchange transfusion
   a. Hypocalcemia
   b. Stroke
   c. Renal failure
   d. Intraventricular hemorrhage (IVH)

8. Which of the following is not a known side effect of phototherapy?
   a. Rash
   b. Acute intermittent porphyria
   c. Bronze baby syndrome
   d. Hypocalcemia

47 Physiologic and Breast Milk Jaundice

AARTI RAGHAVAN

Basic Information

- Normal serum bilirubin levels in children and adults are <0.9 mg/dL unconjugated bilirubin and <0.4 mg/dL conjugated bilirubin.
- Almost every newborn has a serum bilirubin above these values.
- This can occur due to various factors, such as newborn physiology (increased red blood cell [RBC] turnover, shortened RBC life span, immature hepatic function), race, inadequate feeding leading to dehydration, and age.
- Such forms of exaggerated physiology resulting in hyperbilirubinemia are known as *physiologic hyperbilirubinemia.*
- Factors influencing the severity of physiologic jaundice include
  - Gestational age
  - Effectiveness of feeding
  - Polycythemia
  - Maternal medications such as diazepam
- Jaundice may be classified as physiologic based on the risk factors and potential causes.

Breast-feeding Jaundice

DEFINITION

- Hyperbilirubinemia due to insufficient breast feeding, typically within the first 2 weeks of life

INFLUENCING FACTORS

- Maternal factors: ineffective technique, insufficient milk production, cracked nipples, fatigue
- Infant factors: poor latch, poor suck

MECHANISM

- Inadequate infant intake, resulting in dehydration
- Also effects of age, race, and ethnicity, on serum bilirubin

PATHOGENESIS

- Maternal and neonatal factors as mentioned above may reduce the oral intake of breast milk in the first weeks.
- This is particularly significant during the first few days, when colostrum is produced in small volumes.
- Reduced latch or milk let-down reduces stimulation and milk production, resulting in a further decrease of oral intake.
- Early formula supplementation may further lead to reduced milk production due to reduced let-down and stimulus.
- Poor oral intake may lead to delayed meconium passage and intestinal stasis, leading to increased enterohepatic circulation and to increased bilirubin load to the liver exceeding its conjugation capacity.

CLINICAL PRESENTATION

- Signs of dehydration—history of poor oral intake, decreased urine output, delayed capillary refill time, poor skin turgor, sunken fontanel, dry mucosa, weight loss.
- Decreased physical activity
- Icterus—may or may not be present

DIAGNOSIS AND EVALUATION

- Physical examination consistent with dehydration
- Screening with transcutaneous serum bilirubin
- Elevated serum bilirubin
- Urinalysis—increased specific gravity (premature less able to concentrate urine)

TREATMENT

- Prevention
  - Supplementation with water, glucose solutions, or formula avoided
  - Frequent breastfeeding, 8–12 times per day
  - Evaluation of breastfeeding technique, with maternal access to lactation consultant
  - Close monitoring of exclusively breastfed neonates for signs of dehydration, decreased urination or passage of meconium, development of jaundice, inappropriate weight loss, or poor weight gain prior to discharge
  - Close follow-up postdischarge
- Treatment
  - Phototherapy
  - Intravenous rehydration, as indicated

Breast Milk Jaundice

DEFINITION

- Indirect hyperbilirubinemia typically seen after first 7 days in breastfed infants

INCIDENCE

- 10%–30% in breastfed infants

INFLUENCING FACTORS

- Breast milk intake

PATHOGENESIS

- Various substances have been implicated in the development of breast milk jaundice. They include the following:
  - Presence of high concentrations of beta-glucuronidase in maternal milk, which deconjugates bilirubin and increases enterohepatic reabsorption of bilirubin, resulting in increased bilirubin delivery to the liver;
  - Factors in breast milk such as metal ions, steroids, nucleotides could control uridine diphosphate glucuronyl transferase, which could reduce bilirubin excretion and cause hyperbilirubinemia;
  - Serum elevation of bile acids or taurine-glycine conjugates—may be related to the cause.

CLINICAL PRESENTATION

- Breastfed infants
- Typically vigorous, healthy infants with normal weight gain and gastrointestinal elimination
- Peak presentation, 5–15 days
- Most peak at levels of 5–10 mg/dL; severe cases—may reach 25–30 mg/dL
- Duration to resolution: weeks to months (mean, 9 weeks)
- No identifiable disease to cause hyperbilirubinemia except association with breast milk

DIAGNOSIS AND EVALUATION

- Although transcutaneous bilirubin can be used for screening, care should be exercised, given the narrow range of sensitivity.
- Elevated levels should be confirmed by serum bilirubin level measurement.
- Total and direct bilirubin should be measured to rule out conjugated hyperbilirubinemia.
- Complete blood count should be done to rule out a hemolytic process.
- Blood culture, urinalysis, and urine culture should be done to rule out urosepsis and thyroid function test to rule out thyroid dysfunction, as clinically indicated.

TREATMENT

- Close monitoring is essential.
- Phototherapy remains the mainstay of treatment of elevated bilirubin.
- For very high levels of serum bilirubin, interruption of breastfeeding with formula supplementation for 24 hours can lower serum bilirubin levels quickly and confirm the diagnosis.

Suggested Readings

Ballard RA, Gleason CA, Avery ME. *Avery's Diseases of the Newborn.* 5th ed. Philadelphia: Elsevier Health Sciences; 2012.

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Questions

1. A 6-day-old term infant presents to the emergency room with a history of exclusive breastfeeding, clinical jaundice, and decreased urination. The physical examination reveals a clinically jaundiced infant, with dry mucous membranes and poor skin turgor. Vital signs show a heart rate of 180 beats/min, temperature normal, blood pressure 55/32 mm Hg. The serum bilirubin drawn in the emergency room is 21 mg/dL. The first step in the management of this infant is:
   a. Draw complete blood count with a reticulocyte count.
   b. Start an IV, and give a normal saline bolus.
   c. Start intensive phototherapy.
   d. Prepare for an exchange transfusion.

2. A 10-day-old exclusively breastfed infant presents to the clinic for a well child visit. The mother reports frequent breastfeeding, with six to eight wet diapers per day and one or two stools per day. The physical examination reveals normal vital signs, a jaundiced infant, and no palpable hepatosplenomegaly. Serum bilirubin drawn in clinic = 22 mg/dL. The first step in the management of this infant is
   a. Suspension of breastfeeding and supplementation with formula
   b. IV fluid hydration
   c. Intensive phototherapy
   d. Exchange transfusion

3. Factors contributing to breast milk jaundice include the following:
   a. Presence of high concentrations of beta-glucuronidase in maternal milk
   b. Factors in breast milk such as metal ions, steroids, nucleotides, which could control uridine diphosphatase glucuronyl transferase
   c. Serum elevation of bile acids or taurine-glycine conjugates may be related to cause
   d. All of the above
   e. None of the above

4. Breast milk jaundice peaks at:
   a. 1–3 days
   b. 7–14 days
   c. 5–15 days
   d. 2–6 days

5. All the following are factors that contribute to breastfeeding jaundice except:
   a. Cleft lip
   b. Engorgement
   c. Cracked nipples
   d. Maternal age

6. Evaluation of hyperbilirubinemia may include:
   a. Fractionated serum bilirubin
   b. Complete blood count with reticulocyte count
   c. Serum electrolytes
   d. Urine culture
   e. All of the above
   f. None of the above

7. Factors influencing severity of physiologic jaundice include:
   a. Delayed cord clamping
   b. Maternal medications such as diazepam
   c. Gestational age
   d. Delayed feeding
   e. All of the above
   f. None of the above

SECTION 13

Skin Disorders

TOLA OYESANYA, JACQUELINE SELPH and BERNARD A. COHEN

48 Skin Development and Function

TOLA OYESANYA, JACQUELINE SELPH, and BERNARD A. COHEN

- Embryology and development of skin (Table 48.1)
- Differences between preterm and full-term skin (Table 48.2)
  - Preterm babies—skin is thinner, has fewer keratinocyte attachments, has less pigment, less hair, less sweat, and more sun sensitivity.
  - Thinner skin increases transepidermal water loss (loss of water from inside the body to the surrounding environment through the epidermis via evaporation and diffusion) and increases the permeability of medications or toxic substances.
    - Avoid topical medications in newborns if systemic absorption would be harmful, particularly topical lidocaine, mydriatic agents, and antiseptic agents.
  - Decreased epidermal and dermal thickness result in increased heat loss from radiation and conduction.
    - Minimize heat loss by swaddling the child, increasing ambient humidity and temperature, and covering the child with a plastic bubble.
  - Newborns are not as well equipped to handle thermal stress and sunlight due to underdeveloped eccrine glands.
    - Avoid prolonged sun exposure and wear protective clothing if outdoors.
  - Newborns are more likely to develop blisters or erosions in response to heat, chemical irritants, mechanical trauma, and inflammatory skin conditions.
    - Avoid application of monitors, adhesives, and harsh chemicals and cleansing agents because these may compromise the skin barrier in neonates.
- Common skin injuries of neonates
  - IV infiltration
    - Skin infiltration by IV fluids can cause inflammation and subsequent necrosis. Infiltration of hypertonic

Table 48.1 Neonatal Skin Embryology

Gestational Age (weeks)	Epidermal Development	Hair, Nail, and Gland Development
3–4	Single layer of ectoderm	
6	Outer periderm and inner germinal (basal) layer	Basal layer → epidermis
9–12	Epidermal stratification and appearance of anchoring filaments, hemidesmosomes	Hair follicles and nail primordia seen
12–14	Fingerprints form	Eccrine and sebaceous glands develop
12–24	Melanin production (12–16 weeks); melanosome transfer (20 weeks)	Hair follicle differentiation
24	Mature epidermis complete	All layers of epidermis keratinized

Adapted from Jain S, ed. *Dermatology: Illustrated Study Guide and Comprehensive Board Review.* Springer: New York; 2005:2.

Table 48.2 Structural and Functional Differences of Adult, Term, and Preterm Infant Skin

Parameter	Adult	Term	Preterm (30 week)	Significance
Epidermal thickness	50 μm	50 μm	27.4 μm	Permeability to topical agents; ↑ transepidermal water loss[a]
Cell attachments (desmosome, hemidesmosome)	Normal	Normal	Fewer	↑ Tendency to blister
Dermis	Normal	↓ Collagen and elastic fibers	⇊ Collagen and elastic fibers	↓ Elasticity ↑ Blistering
Melanosomes	Normal	Fewer; delayed activity for 1–7 days	1/3 of term infants	↑ Photosensitivity
Eccrine glands	Normal	↓ Neurologic control for 2–3 years	Total anhidrosis	↓ Response to thermal stress
Sebaceous glands	Normal	Normal	Normal	Barrier properties? Lubricant? Antibacterial?
Hair	Normal	↓ Terminal hair	Persistent lanugo	Helpful in assessing gestational age

[a]Transepidermal water loss (TEWL) is the loss of water from inside the body to the surrounding environment through the epidermis via evaporation and diffusion. TEWL increases permeability to topical agents such as medications.

Adapted from Puttgen K, Cohen BA. Neonatal dermatology. In: Cohen BA, ed. *Cohen's Pediatric Dermatology.* 4th ed. Philadelphia: Saunders/Elsevier; 2013:14.

fluids such as glucose and calcium may result in full-thickness sloughing of the skin and later contractures.
- Ensure proper placement of IV lines and watch for swelling or erythema near the IV site; discontinue IVs immediately if there is clinical suspicion.
  - Treatment may require splinting, physical therapy, and surgical repair, particularly if infiltration occurred over a joint.

- Chemical burns
  - Topical agents, such as iodophors, soaps, detergents, and solvents, may produce severe irritant reactions, particularly in premature infants
    - Treat with application of a bland emollient and consider a mild-potency topical steroid to soothe inflammation.
- Thermal burns
  - Heated water beds, radiant warmers, transcutaneous oxygen monitors, and heated humidified air can cause thermal burns.
    - Prevention is key! Monitor the temperature of these devices.
- Heel stick nodules
  - Often occur from repeated needlesticks (common sites include the heel)
  - Become clinically apparent as tiny whitish papules or nodules resembling milia after several months and eventually calcify.
  - Spontaneously resolve by age 18–30 months; no treatment needed

Suggested Readings

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49 Neonatal Skin Lesions

TOLA OYESANYA, JACQUELINE SELPH and BERNARD COHEN

Newborn Dermatoses

Table 49.1 Newborn Dermatoses

	Epidemiology	Clinical Features	Histology/Pathology Findings	Prognosis & Treatment	DDX (Differential Diagnosis)
Erythema Toxicum Neonatorum (see Fig. 49.1)	One-half of full-term newborns, less frequent in preterm	Healthy infants, erythematous macules evolving into yellow-white pustules on trunk, appear between days 1–3 of life, "flea-bitten" appearance	Eosinophils in Wright-stained smear	Asymptomatic, resolves spontaneously in several days	Transient neonatal pustular melanosis Miliaria Infantile acropustulosis. Eosinophilic pustular folliculitis
Transient Neonatal Pustular Melanosis (see Fig. 49.2)	5% of black newborns, 1% white infants	Small pustules that rupture leaving collarette of fine scale and significant postinflammatory hyperpigmentation, can involve palms and soles, may be present at birth	Neutrophils in Wright-stained smear, no organisms	Asymptomatic, pustules resolve within 48 hours, hyperpigmentation can last months	Same as above
Congenital Milia	Up to 40% full-term infants If >2 mm and large number especially of face and scalp consider oral facial digital syndrome	1 to 2 mm white smooth papules usually on cheeks, forehead, chin	Tiny epidermal inclusion cysts arising from vellus hair	Resolve over months without treatment	Epstein pearls occur on midline hard palate Bohn nodules appear at gum margin Sebaceous hyperplasia (smaller and more yellow)
Miliaria Neonatorum	Healthy infants, caused by obstruction of immature eccrine ducts	Four clinical variants depending on depth of occlusion All resolve with cooling and avoidance of occlusive clothing ▪ *Crystallina:* superficial, clear, noninflammatory vesicles within stratum corneum ▪ *Rubra:* erythematous grouped fine papules in skinfolds (see Fig. 49.3) ▪ *Pustulosa:* erythematous grouped pustules with possible bacterial infection ▪ *Profunda:* papular eruption within the deeper eccrine duct			
Neonatal acne (see Fig. 49.4)	20% healthy infants, more common in boys	Comedones, inflammatory papules and pustules. Neonatal acne appears at 1–2 weeks. Infantile acne appears at 3–6 months	Comedones	Infantile resolves by 3 months. Infantile can persist for years. 2.5% benzoyl peroxide daily. If severe systemic erythromycin can be added.	Cephalic pustulosis with uniform 2–3 mm pustules is a variant in which *Malassesia* is implicated No other disorders should feature comedones
Diaper Dermatitis	25% of infants	Redness/mild scaling of gluteal crease/buttocks/pubic area. May become erosive. Caused by irritants including urine, feces, cleansing materials	Spongiosis in the epidermis	Resolves with removing irritants, gentle skin care, zinc oxide paste as barrier ± mild potency topical steroid. If does not resolve, consider other Dx	Seborrheic dermatitis, allergic contact dermatitis, psoriasis (see Fig. 49.6), Langerhans cell histiocytosis, acrodermatitis enteropathica. *Candida:* intense erythema with satellite lesions and pustules, staphylococcus l and streptococcal infections

Fig. 49.1 Erythema toxicum neonatorum. Numerous yellow papules and pustules surrounded by large erythematous rings on the trunk. (Courtesy Dr. Bernard Cohen. Dr. Cohen retains copyright of this figure.)

Fig. 49.2 Neonatal pustular melanosis. Numerous tiny pustules dot the trunk, with healing pustules leaving hyperpigmentation. (Courtesy Dr. Bernard Cohen. Dr. Cohen retains copyright of this figure.)

Fig. 49.3 Miliaria rubra. Erythematous grouped fine papules visible on this infant. (From Puttgen K and Cohen BA. Neonatal Dermatology. In Cohen, BA. ed. *Pediatric Dermatology*. 4th ed. Philadelphia: Elsevier; 2013 [p. 21, Fig. 2.17].)

Fig. 49.4 Neonatal acne. Red papules mixed with pustules diffusely over face (A) and face and trunk (B) of infant. (From Puttgen K and Cohen BA. Neonatal Dermatology. In Cohen, BA, ed. *Pediatric Dermatology*. 4th ed. Philadelphia: Elsevier; 2013 [p. 22, Fig. 2.19].)

Papulosquamous Disorders in Neonates

SEBORRHEIC DERMATITIS

Clinical Findings

- Occurs within first 2 months of life
- Greasy yellow scales on erythematous base on face, scalp, or diaper area
- Hypopigmentation can develop in dark-skinned individuals

Diagnosis & Treatment

- Clinical diagnosis
- Resolves spontaneously by end of first year of life.
- Treatments such as ketoconazole, zinc pyrithione, or selenium sulfide shampoos ± 1% hydrocortisone

ACRODERMATITIS ENTEROPATHICA

Basic Information

- Caused by zinc deficiency which can be genetic or acquired.
- Genetic: autosomal recessive defect in intestinal absorption of zinc → zinc malabsorption.
  - Presents as breastfed infants are weaned off breast milk.
- Acquired: premature infants who carry the mutation that are exclusively formula fed.

Clinical Presentation

- Erosive periorificial, acral, and diaper rash with red, hemorrhagic crusted patches and plaques ± flaccid bullae (see Fig. 49.5)

Diagnosis and Treatment

- Low serum zinc and alkaline phosphatase (which is zinc dependent)
- High dose oral or IV zinc

NEONATAL LUPUS

Clinical Findings

- Subtle scarring, atrophic annular plaques commonly periocular, forehead, scalp but may be more widespread with prominent telangiectasiate (see Fig. 49.8)
- Associated with congenital heart block in up to 30% patients, which may be picked up before delivery

Diagnosis and Treatment

- Associated with transplacental passage of anti-Ro/SSA, U1 RNP antibodies → check antibody profile
- Check complete blood count (CBC [risk of thrombocytopenia]), check LFTs (risk of hepatobiliary disease), and electrocardiogram (EKG)
- Skin lesions often resolve with subtle scarring, dyspigmentation, and/or residual telangiectasias so may consider short course of topical steroids
- Heart block can be irreversible (mortality in 30% of cases), requires pacemaker
- Mother has 25% recurrence rate in subsequent pregnancies; consider oral hydroxychloroquine for mother in subsequent pregnancies

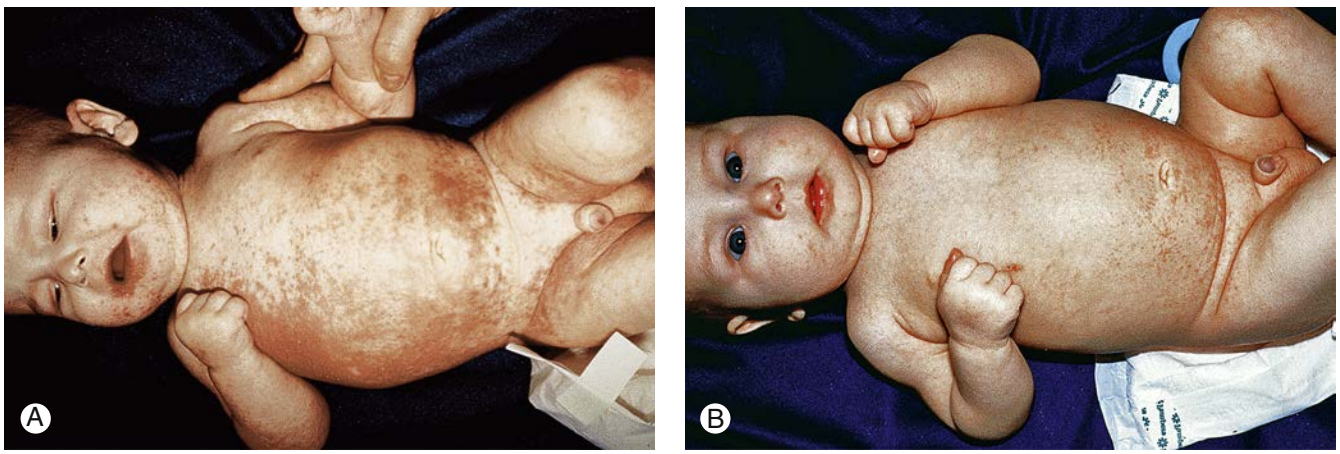

Fig. 49.5 Acrodermatitis enteropathica. (A) A bright, red, scaling dermatitis spread to the intertriginous areas, face, and extremities of this 4-week-old infant. (B) After 4 days of zinc supplementation, many lesions were healing with desquamation. (From Puttgen K and Cohen BA. Neonatal Dermatology. In Cohen, BA, ed. *Pediatric Dermatology*. 4th ed. Philadelphia: Elsevier; 2013 [p. 35, Fig. 2.39A].)

Fig. 49.6 Psoriasis. Beefy red diaper dermatitis involving skinfolds, which fails to respond to typical routine therapy. (A), (B) and (C) Represent different presentations. (From Puttgen K and Cohen BA. Neonatal Dermatology. In Cohen, BA, ed. *Pediatric Dermatology*. 4th ed. Philadelphia: Elsevier; 2013 [p. 33, Fig. 2.43].)

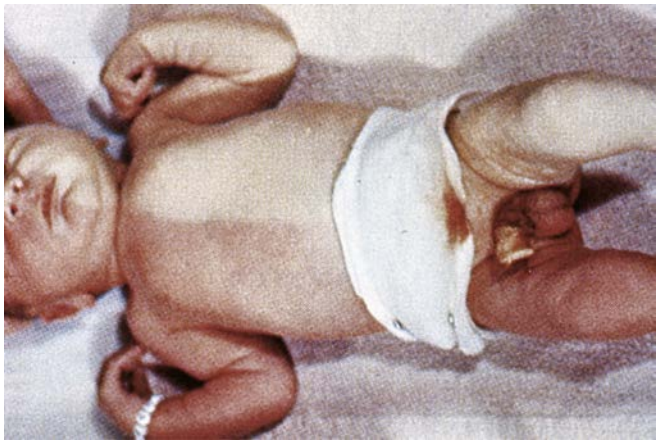

Fig. 49.7 Harlequin color change. (From Puttgen K and Cohen BA. Neonatal Dermatology. In Cohen, BA, ed. *Pediatric Dermatology*. 4th ed. Philadelphia: Elsevier; 2013 [p. 19, Fig. 2.10].)

Fig. 49.8 Neonatal lupus: characteristic erythematous annular plaques on the lateral forehead and temple. (Courtesy Dr. Bernard Cohen. Dr. Cohen retains copyright of this figure.)

Congenital Infections of the Newborn

Table 49.2 Congenital Infections of the Newborn

Infection	Epidemiology	Clinical Findings	Extracutaneous Findings	Diagnosis	Prognosis and Treatment	Dx
Cytomegalovirus (CMV)	Presents at birth; transmitted from mother who contracted CMV during pregnancy	Petechiae, purpura, blueberry muffin lesions	IUGR, deafness (most common infectious cause), chorioretinitis (common in HIV) microcephaly	CMV-IgM antibody, PCR for CMV-DNA in plasma and tissue fluids	Supportive care. IV ganciclovir can shorten duration of symptoms	Rubella Toxoplasmosis
Herpes Simplex Virus (HSV) (see Fig. 49.9)	Neonates from mothers who acquired primary HSV2 are at greatest risk; presents at birth to 48 hours later	Grouped or diffuse vesicles, bullae, erosions, scarring, lethargy, fever	Prematurity, microcephaly, chorioretinitis, encephalitis (temporal lobes), seizures, multiorgan failure	Tzanck prep with multinucleate giant cells, HSVDFA from vesicle, viral dx	Supportive care. IV acyclovir for 14–21 days can shorten symptoms	Epidermolysis bullosa Incontinentia pigmenti Varicella/VZV Bullous impetigo
Toxoplasmosis	Maternal infection in second or third trimester; later infection- lower risk	Blueberry muffin lesions on trunk.	Chorioretinitis, hydrocephalus, blindness, deafness, MR, seizures, intracranial calcifications.	IgM/IgG *T. gondii; T. gondii* PCR; CT/ultrasound of brain with ring enhancing lesions	Pyrimethamine Sulfadiazine	Disseminated CMV or HSV, rubella
Varicella	2% of neonates from mothers infected with the virus before 20 weeks gestation	Cutaneous scarring, limb hypoplasia, if zoster may see dermatomal lesions	Ocular abnormalities (chorioretinitis, cataracts), seizures, MR (can present without skin findings)	IgM/IgG VZV of mother or neonate, VZV PCR of fetal blood/amniotic fluid, lesions in dermatomal distribution	Supportive at birth. Nonimmune pregnant women with recent contact should get PEP with varicella-zoster IG	Toxoplasmosis, HSV, rubella
Syphilis, Early	Infection with T. Pallidum from mother, occurs before 2-years of age	Reddish-brown macules on face, buttocks, arms, legs ± diffuse acral scaling, condyloma lata	Snuffles, HSM, LAD, hemolytic anemia, thrombocytopenia, IUGR, periostitis	Nontreponemal serologic test (RPR or VDRL) performed on infant serum, clinical findings, positive darkfield test or PCR	IV Penicillin G	Rubella, CMV
Rubella	Nonimmune mothers transmit virus to fetus; severe defects within first 16 weeks gestation	Blueberry muffin lesions, petechiae, Forchheimer sign in 20% (pinpoint petechia on palate)	Cataracts, deafness (50%), congenital heart disease, CNS (microcephaly, hydrocephaly)	Viral dx from oropharynx where viral particles are shed, echocardiogram	Supportive care only.	CMV, toxoplasmosis, HSV

CNS, Central nervous system; *CT,* computed tomography; *HSM,* hepatosplenomegaly; *IgG,* immunoglobulin G; *IgM,* immunoglobulin M; *IUGR,* intrauterine growth restriction, *LAD,* lymphadenopathy; *PCR, PEP,* post exposure prophylaxis; *RPR,* rapid plasma reagin; *VDRL,* Venereal Disease Research Laboratory.

Fig. 49.9 Herpes simplex virus. Numerous clustered and coalescing vesicles with overlying serous exudate on the face of an intubated newborn. (Courtesy Dr. Bernard Cohen. Dr. Cohen retains copyright of this figure.)

Vascular Anomalies (Vascular Tumors and Vascular Malformations)

Table 49.3 Vascular Malformations

Vascular Malformation	Clinical Features	Diagnosis	Treatment	Extracutaneous Conditions	Other
Infantile Hemangioma	10% infants. Red macules that rapidly grow into bright red soft tumors	Clinical. Ultrasound or MRI if considering visceral involvement or extracutaneous syndromes	Regression expected. If large, disfiguring, or function is impaired, prednisone, timolol drops, propanol	May have visceral involvement (if >5 hemangiomas, rule out liver involvement with ultrasound, UA, CBC, stool guaiac	Large face/scalp IH → consider PHACE syndrome (posterior fossa brain malformations, hemangiomas, arterial anomalies, cardiac defects, and eye defects) Lumbosacral IH may have associated GU/spine, renal abnormalities (lumbar/sacral/pelvic syndromes)
Cavernous Hemangiomas (venous malformation)	Bluish papules or nodules made of dilated vessels in the dermis/fat.	Ultrasound/MRI may be helpful to delineate extent of lesion	Sclerotherapy, Nd-YAG laser, or surgical excision	Can be associated with pain, swelling, or functional impairment of joints	—
Stork bite/salmon patches)	Salmon patches: faint pink macules or patches usually located on the nape of neck (stork bite), glabella, forehead (angel kiss), upper eyelids, or sacrum	Clinical	Most regress with time	None.	Darken with crying, breath holding, or exertion
Port wine stain	Well demarcated red patch or plaque, typically unilateral. Most common on head and neck, but any body part can be involved. Does not regress	Clinical	Pulsed dye laser	If involving V1, obtain an MRI which may show tram-track calcifications and delineate extent of neurological involvement	Sturge-Weber syndrome: port-wine stain involving V1 distribution associated with an ipsilateral vascular malformation of the meninges, cortex, and eye (may develop HA, seizures, LD, hemiparalysis)
Kasabach-Merritt Syndrome	Large vascular or bulging nodules, plaques, or masses, purpura, with consumptive coagulopathy & low platelets	CBC, serum fibrinogen, D-dimers	Control consumptive coagulopathy. Systemic steroids may be helpful	Vascular tumors may be retro-peritoneal	Can be life threatening/fatal
Lymphatic Malformation (cystic hygroma, cavernous lymphangiomas)	Skin-colored nodules made of dilated lymphatic vessels on the oral mucosa, head/neck, trunk, axillae, proximal extremities	Ultrasound/MRI may be helpful to delineate extent of lesion	Observation	Can be deep on the head and neck, compressing important structures in the neck	—

CBC, Complete blood count; *HA,* headache; *IH,* infantile hemangioma; *LD,* learning disabilities; *MRI,* magnetic resonance imaging; *UA,* .

Aplasia Cutis Congenita

BASIC INFORMATION

- Congenital absence of the skin. May be sporadic or may be autosomal dominant.
- May also be associated with limb abnormalities, central nervous system (CNS) dysraphism, and syndromes.
- Perinatal trauma from scalp electrodes or forceps may create similarly appearing lesions.

CLINICAL PRESENTATION

- One or several erosions/ulcerations on the vertex scalp with overlying crust or thin membrane. Heals with a depressed, hairless scar over 3–6 months (see Fig. 49.10). Bullous forms are seen.
- Trunk or extremities may have similar findings; multiple, large, and nonvertex scalp lesions are more likely to be associated with extracutaneous lesions.
- May be associated with a lipoma or vascular stain (which may be a sign of CNS involvement).
- Distinguish from hair collar sign: dark hairs noted circumferentially around a central papule or round plaque which contains meningeal tissue. Usually solitary lesion but may rarely be associated with neural tube defect.

DIAGNOSIS AND TREATMENT

- Rule out neonatal lupus, HSV if lesions are ulcerated.
- Consider MRI if +hair collar sign, lipoma, vascular patch, or for large lesions to evaluate for connection to brain/bone.

Fig. 49.10 Aplasia cutis congenita. This child and his father had similar hairless, atrophic plaques on the scalp. A thin, hemorrhagic membrane was noted at birth. (Courtesy Dr. Bernard Cohen. Dr. Cohen retains copyright of this figure.)

Disorders of the Umbilical Cord

- Normally, the umbilical cord dries and separates from the umbilicus in 7–14 days with healing completed in 4 weeks. Refer to Table 49.4 for disorders of the umbilical cord.

Fig. 49.11 Omphalitis. Omphalitis developed in this 10-day-old infant shortly after the cord separated from the umbilicus. The infection cleared after a 10-day course of parenteral antibiotics. (From Puttgen K and Cohen BA. Neonatal Dermatology. In Cohen, BA, ed: *Pediatric Dermatology*. 4th ed. Philadelphia: Elsevier; 2013 [p. 25, Fig. 2.26].)

Table 49.4 Disorders of the Umbilical Cord

Disorder	Etiology	Clinical Presentation	Diagnosis/Treatment
Umbilical granuloma	Excessive moisture ± low-grade infection	Pink friable or firm papule on umbilicus	Silver nitrate cauterization; if persistent, excise
Umbilical polyp	Persistent vitelline duct (GI mucosa) or patent urachus (urinary tract mucosa)	Firm bright-red papule on umbilicus with chronic mucoid or watery discharge weeks to months after birth	Excision of patent urachus or persistent vitelline duct
Omphalitis (see Fig. 49.11)	Polymicrobial infection of umbilical stump. Risk factors: instrumentation, low birth weight, premature rupture of membranes	Periumbilical erythema, tenderness and/or foul-smelling purulent discharge from the umbilicus → sepsis	Obtain culture/sensitivities and IV antibiotics

Pigmented Lesions

Table 49.5 Pigmented Lesions

Diagnosis	Etiology	Clinical Presentation	Dx	Associations
Café au lait macule	Increased number of melanocytes.	Light to dark brown macule (>0.5 mm) or patch. May be solitary (10%–20% neonates) or multiple	Transient neonatal pustulosis, lentigines	More than six spots: NF1/2, Legius syndrome, McCune-Albright syndrome, tuberous sclerosis, others
Congenital smooth muscle hamartoma (hairy epidermal nevus)	Hamartomas made of smooth muscle and hair follicles (no nevus cells)	Tan/brown plaques on the trunk ± hair growth, approx. 1–5 cm in diameter	Epidermal nevus, Medium/large congenital nevi	No risk of malignancy
Congenital nevi (see Fig. 49.12)	Onset at birth or first year of life (1%–2% neonates). Nevus cells from neural crest→produce melanin	Pigmented macules or plaques, often with dense hair growth; may be tan initially and then darken. Can be over 20 cm/10% BSA (giant congenital nevus)	Hairy epidermal nevus	Giant congenital nevi → 2%–6% lifetime risk of melanoma. If over scalp, neck, or back, consider MRI to eval for neurocutaneous melanosis
Congenital dermal melanocytosis (Mongolian spot)	Dendritic melanocytes in the dermis; common in neonates with darker skin	Irregular blue-gray macules or patches, usually over lumbosacral area or buttocks	Nevus of Ota (usually periorbital)	May fade over time or persist

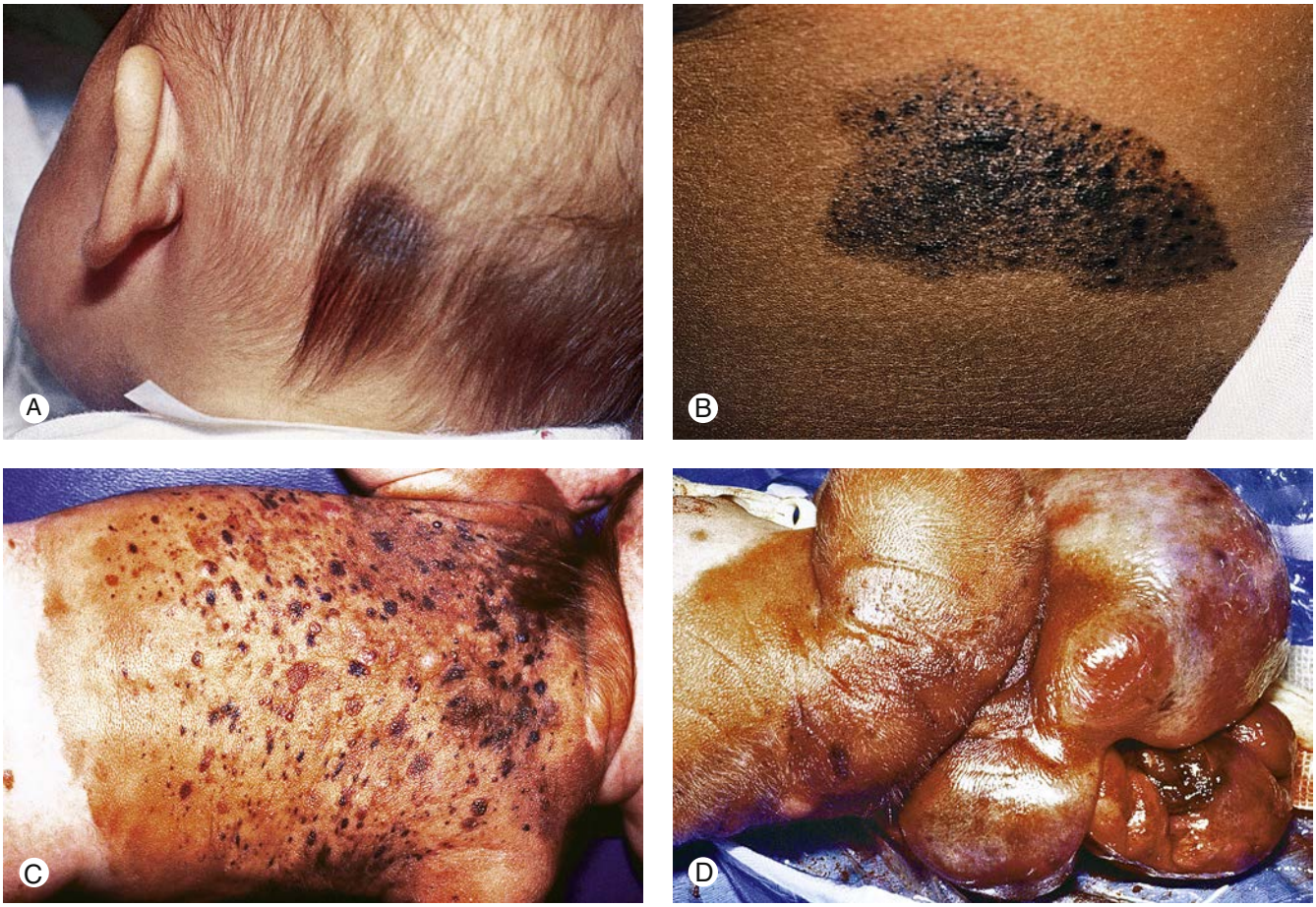

Fig. 49.12 Congenital nevi. Congenital pigmented nevi. (A) An innocent medium-size 5 cm by 3 cm nevus uniformly studded with dark brown papules on a male infant, present since birth. (B) A giant pigmented nevus with numerous darkly pigmented nodules. This child had neurocutaneous involvement and developed a malignant melanoma in the central nervous system. (From Puttgen K and Cohen BA. Neonatal Dermatology. In: Cohen, BA, ed. *Pediatric Dermatology*. 4th ed. Philadelphia: Elsevier; 2013 [p. 57, Fig. 2.85].)

Infectious Disease

- *Staphylococcus aureus* infections

STAPHYLOCOCCAL SCALDED SKIN SYNDROME (SSSS)

Basic Information

- Generalized blistering eruption due to strains of *S. aureus* that produce circulating toxin.

Clinical Presentation

- Abrupt onset of fever, irritability, and generalized skin redness. Neonates will have facial swelling, conjunctivitis, and crusting around the eyes, nose, and mouth.
- Flaccid, delicate bullae often form followed by widespread desquamation of all skin within 2-3 days (see Fig. 49.13).
- Must be distinguished from toxic epidermal necrolysis (TEN), which causes full thickness tissue necrosis, typically from a drug reaction.

Diagnosis and Treatment

- Clinical suspicion.
- Bacterial cultures from common sites of primary infection (nasopharynx, umbilicus, conjunctiva) with sensitivities to help guide antibiotic choice.
  - Skin lesions should be culture negative.
  - Gram stain from sites of common infection (nasopharynx, conjunctiva, umbilicus) will be positive for gram-positive cocci in clusters.
- IV penicillinase-resistant antistaphylococcal antibiotics (nafcillin or methicillin).
- Supportive care: fluid and electrolyte replacement, bland emollient if needed.

CANDIDA INFECTIONS

Basic Information

- *Candida albicans* is a pathogen of the female genitalia and is frequently noted in pregnancy.
- *C. albicans* also colonizes the oral cavity and GI tract of most newborns.

SYSTEMIC/DISSEMINATED CANDIDIASIS

Basic Information

- Systemic candidiasis (with blood, urine, or CSF involvement) affects LBW/premature infants more than full-term infants.
- *C. albicans* and *C. parapsilosis* are implicated.
- May be congenital (acquired in utero), due to untreated localized candidal infection, or from nosocomial spread.
- Risk factors: birth weight <1500 g, indwelling catheters, broad spectrum antibiotic use, systemic steroid use, history of instrumentation, premature (<27 weeks), and TPN.

Fig. 49.13 Staph scalded skin syndrome. Staphylococcal scalded skin syndrome developed in this neonate a few days after his brother was diagnosed with impetigo. Erosive patches were most marked on the (A) face and (B) diaper areas. (From Puttgen K and Cohen BA. Neonatal Dermatology. In: Cohen, BA, ed. *Pediatric Dermatology*. 4th ed. Philadelphia: Elsevier; 2013 [p. 38, Fig. 2.47].)

Fig. 49.14 Cutaneous candidiasis. Numerous inflammatory papules and pustules are scattered on the trunk and extremities, even the palms. (Courtesy Dr. Bernard Cohen. Dr. Cohen retains copyright of this figure.)

- Systemic involvement is secondary to hematogenous or lymphatic spread.
- Mortality is 40%–75%; early recognition is paramount.

Clinical Presentation

- Inflammatory papules or vesicopustules on a deeply erythematous base. May be sparse or diffuse on the body (see Fig. 49.14). Face and oral mucosa is usually spared.
- Progressive diaper dermatitis with papules, pustules, and abscesses.
- Systemic findings: respiratory distress, bradycardia, temperature instability, hypotension, pneumonia, and elevated white blood cells (WBCs), ± left shift all may suggest sepsis.

Diagnosis and Treatment

- KOH prep from affected skin will demonstrate hyphae.
- Skin biopsy for tissue culture.
- Chest x-ray and cerebrospinal fluid may be helpful.
- IV antifungal therapy (e.g., amphotericin B) if clinical suspicion for disseminated disease given clinical findings and above stated risk factors.

HERPES SIMPLEX VIRUS (HSV)

Basic Information

- Often caused by vertical transmission via contact with mother's genital mucosa during delivery. Two-thirds of cases are HSV-2 and one-third of cases are HSV-1.
- Categorized by skin-eye-mucosa (SEM) disease (40%), CNS disease (35%), and disseminated disease (25%).
- One-third of neonates have skin disease at initial presentation. Other presentations include sepsis, new onset seizures, liver dysfunction, coagulopathy, and respiratory distress.
  - If disseminated disease, 60% mortality rate and 40% risk of neurologic impairment.

Clinical Presentation

- Isolated or grouped vesicles on an erythematous base which evolve into pustules, crusts, or erosions.
- If infected in utero, skin lesions will be present at birth as diffuse erosions, bullae, and scars ± chorioretinitis, microcephaly, and microphthalmia.

Diagnosis and Treatment

- Unroof a fresh vesicle to obtain viral culture, HSV polymerase chain reaction (PCR) or Tzanck smear that will show multinucleated giant cells.
- Consider lumbar puncture for evaluation of CSF if concerned for disseminated disease.
- Treat empirically with IV acyclovir.
- C-section delivery for moms with prodromal or active lesions at delivery and/or prophylactic antiviral therapy for mothers with known HSV history.
- Low-dose prophylactic oral therapy for first 6 months of life reduces risk of recurrence and improves neurodevelopmental scores.

Genetic Neonatal Syndromes

Table 49.6 Disorders of Hypopigmentation and Hyperpigmentation

	Cause	Clinical Findings	Diagnosis, Treatment, Prognosis
Oculocutaneous Albinism	OCA1a	Near lack of pigment starting at birth, reduced visual acuity	- Genetic testing to distinguish subtypes - Refer to ophthalmology because of risk of photophobia, nystagmus, and reduced visual acuity - Refer to dermatology because increased risk of basal cell and squamous cell carcinoma; OCA1 also has increased risk of melanoma
	OCA1b	No pigment at birth but develop pigment over time	
	OCA2	Most common type, Africans, some pigment but variable	
	OCA3	Reddish-bronze skin and red hair, very rare	
	OCA4	Variable, very rare, seen in Japan	
Chédiak-Higashi		- Infancy presents with decreased skin, eye and hair pigment - Silvery hair with pigment clumping in hair shaft - Bleeding diatheses - Increased infections of skin, gut, lungs	- Look for giant granules within cells - Death typically by age 10 from lymphoproliferative syndrome - Severe neurologic degeneration
Phenylketonuria	Deficiency of phenylalanine hydroxylase	- Diffuse pigmentation dilution - Sweat with a musty odor - Progressive developmental delay	- Inborn error of metabolism, but because of screening very rare - Without treatment accumulation of phenylalanine leads to profound mental retardation, seizures - Refer to nutritionist
Waardenburg syndrome	Mutations in *PAX3*, *MITF*, *EDNRB/EDN3/SOX10*	- Skin: depigmented patch on the forehead with white forelock - Eyes: heterochromic irides, synophrys, dystopia cantorum	- Referral to audiology/ENT for congenital deafness - Normal life span
Piebaldism	c-Kit (AD)	- Associated with white forelock - Congenital patches of spotty hypopigmentation	- Results in defective migration of melanoblasts - Stable, permanent depigmentation but otherwise benign course
Incontinentia Pigmenti (see Fig. 49.15)	NEMO (X-linked dominant)	1) Vesicular—birth to 1 month along lines of Blaschko 2) Verrucous—warty papules from 8 weeks to 2 years 3) Hyperpigmented—up to adolescence 4) Hypopigmented—may persist through adulthood	- Affected patient can have seizures, developmental delay, and blindness
Tuberous Sclerosis	*TSC1* (hamartia), *TSC2* (tuberis)	Major features: - ≥ 3 angiofibromas, ≥ 3 ash-leaf macules, ≥ 2 ungual fibromas, shagreen patch, retinal hamartomas, cortical dysplasia, giant cell astrocytoma, cardiac rhabdomyomas, lymphangioleiomyomatosis, ≥ 2 angiomyolipomas	- At least one major or 2 minor criteria - Definitive diagnosis with genetic testing - Complications related to seizures and renal disease and the most common causes of mortality
Peutz-Jeghers Syndrome	SKT11 (AD)	- Pigmented macules on lips, buccal mucosa, digits seen by age 20 - GI polyps in jejunum and ileum → may lead to intussusception	- Number of melanocytic macules not related to number of GI polyps - Regular colonoscopy to assess polyposis - Pigmented macules may fade with time - Over 90% develop cancer (GI most common) before age 65
McCune-Albright Syndrome	*GNAS1* (somatic mutation)	Triad: 1) Café au lait macules (large "coast of Maine-like") 2) Polyostotic fibrous dysplasia 3) Endocrine dysfunction (especially precocious puberty and hypophosphatemic rickets)	- Pathologic fractures, gait abnormalities, and endocrine abnormalities need to be treated, but otherwise normal life span

Fig. 49.15 Incontinentia pigmenti. (A) and (B) Vesicles along erythematous base following lines of Blaschko. (C) Progression to warty papules. (D) Resolving with hyperpigmentation. (E) and (F) Additional examples. (From Puttgen K and Cohen BA. Neonatal Dermatology. In: Cohen, BA. *Pediatric Dermatology*. 4th ed. Philadelphia: Elsevier; 2013 [p. 47, Fig. 2.62].)

INHERITED ICHTHYOSES

- Spectrum of disorders linked by abnormal epidermal differentiation.
- Treatment of all is generally supportive care, aimed at maintaining fluid balance and decreasing risk of infections.

Harlequin Ichthyosis

- Clinical: most severe ichthyosis; presents at birth with thick plates of scale with deep bright red fissures, extreme ectropion, eclabium.
- Autosomal recessive: *ABCA12.*
- Diagnosis: genetic testing.
- Prognosis: often neonatal death from sepsis. Death usually within first few days of life.

Congenital Ichthyosiform Erythroderma (CIE) (See Fig. 49.16)

- Clinical: CIE is the number one cause of collodion membrane. After collodion membrane, infants have fine white scale.
  - Collodion membrane: thickened parchment-like skin, with distorting facial features such as ectropion and eclabium (see Fig. 49.17). Temperature instability, defective barrier function, insensible water loss.
- Autosomal recessive: *ALOXE3*, *ALOX12B.*
- Diagnosis: genetic testing, fetal skin sampling similar to lamellar ichthyosis.

Lamellar Ichthyosis

- Clinical: frequently collodion membrane at birth, followed by thick plate-like generalized brown scale.
- Autosomal recessive: transglutaminase 1 *(TGM1)*, most frequently reported.
- Diagnosis: in situ *TGM1* expression; genetic testing.

Steroid Sulfatase Deficiency (X-linked Ichthyosis)

- Clinical: presents in infancy with dark brown adherent scales, spares flexures.
- Associations: comma-shaped corneal opacities, cryptorchidism (which portends increased risk of testicular cancer), prolonged labor because of placental sulfatase deficiency.
- X-linked recessive: steroid sulfatase gene.
- Diagnosis: plasma cholesterol sulfate increased, decreased steroid sulfatase in leukocytes genetic testing, triple/quad screen will show decreased serum estriol.

Ichthyosis Vulgaris

- Clinical: most benign ichthyosis; begins in later infancy; fine white adherent scale, mostly on lower extremities; keratosis pilaris and hyperlinear palms. Associated with atopic dermatitis.
- Autosomal dominant: defect in filaggrin.
- Diagnosis: clinical diagnosis is sufficient, but genetic testing can be used.

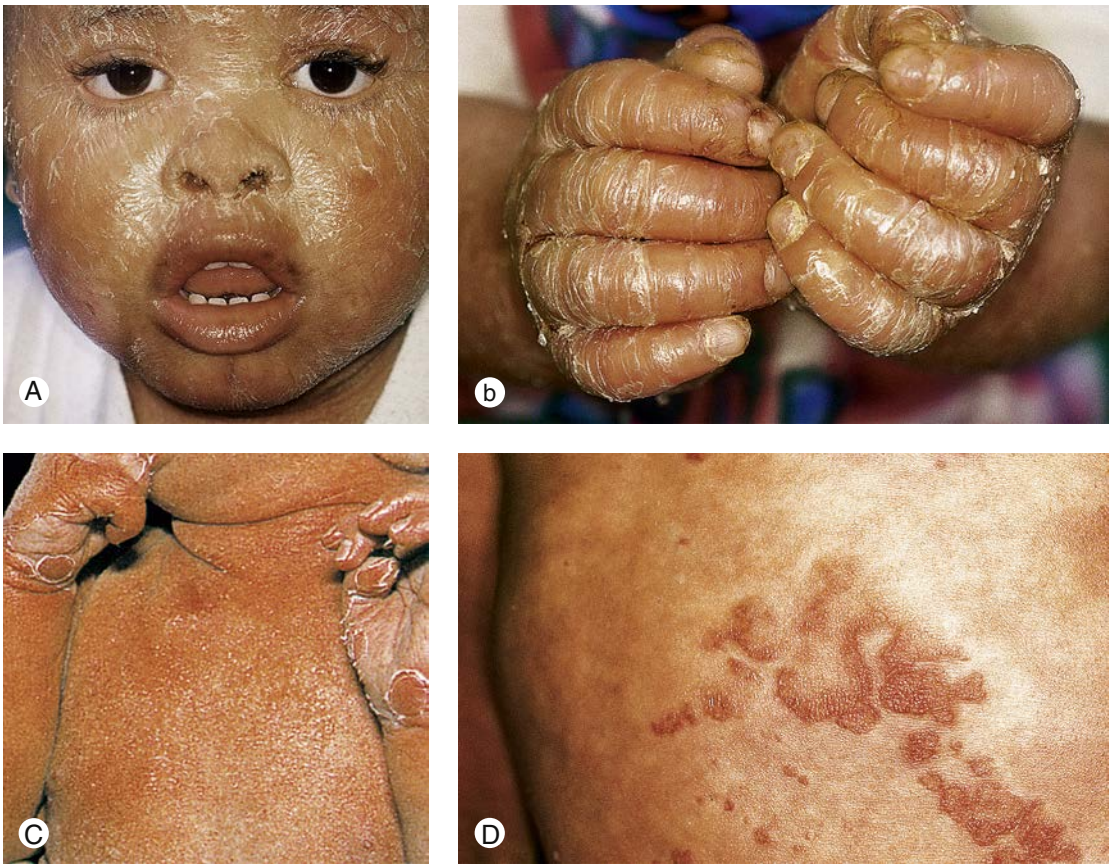

Fig. 49.16 Congenital ichthyosiform erythroderma. (A) and (B) Persistence of congenital erythroderma with marked fine white scale, especially on hands. (C) and (D) Additional presentations. (From Puttgen K and Cohen BA. Neonatal Dermatology. In Cohen, BA, ed. *Pediatric Dermatology*. 4th ed. Philadelphia: Elsevier; 2013 [p. 28, Fig. 2.31].)

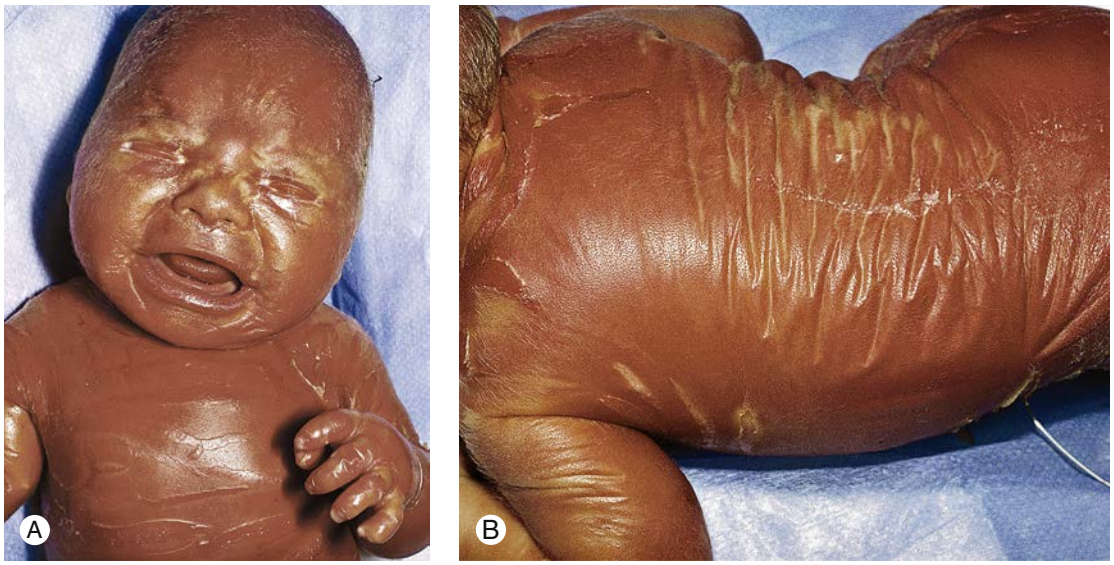

Fig. 49.17 Collodion membrane. Shiny transparent membrane covering baby at birth. Present in multiple conditions but most common in congenital ichthyosiform erythroderma. (A) Face, chest and hand, (B) truck involvement. (From Puttgen K and Cohen BA. *Neonatal Dermatology*. In Cohen, BA, ed. *Pediatric Dermatology*. 4th ed. Philadelphia: Elsevier; 2013 [p. 26, Fig. 2.29].)

Epidermolytic Hyperkeratosis

- Clinical: widespread blistering and erythroderma at birth; later generalized hyperkeratosis with malodor and prominent flexural involvement.
- Autosomal dominant: keratin 1 and 10.
- Diagnosis: genetic testing.

OTHER ICHTHYOSIFORM SYNDROMES

- All are diagnosed by genetic testing unless otherwise noted.

Netherton Syndrome

- Clinical: erythema, scale, and hypernatremia at birth; later in infancy more atopic dermatitis-like with the addition of polycyclic erythematous scaling plaques (ichthyosis linearis circumflexa), trichorrhexis invaginata of hair.
- Autosomal recessive: *SPINK5* gene.

Keratitis-Ichthyosis-Deafness (KID) Syndrome

- Clinical: mild hyperkeratosis, especially on face and extremities, palmoplantar keratoderma, recurrent bacterial and fungal infections, alopecia.
- Associations: nonprogressive sensorineural deafness, vascularized keratitis.
- Mostly sporadic, some autosomal dominant: *GJB2* gene (connexin 26).

Fig. 49.18 Epidermolysis bullosa simplex. Blisters form primarily in areas of pressure such as hands and feet. (From Puttgen K and Cohen BA. Neonatal Dermatology. In: Cohen, BA, ed. *Pediatric Dermatology*. 4th ed. Philadelphia: Elsevier; 2013 [p. 41, Fig. 2.50].)

EPIDERMOLYSIS BULLOSA

- Heterogeneous group of inherited bullous disorders with very fragile skin and blistering that heals with atrophic scarring, often quite painful and deforming. Nail and teeth dysplasia may be seen. Often causes early demise (see Figs. 49.18–20).
- Diagnosis is made clinically and confirmed with biopsy.
- Definitive diagnosis can be done through genetic analysis.

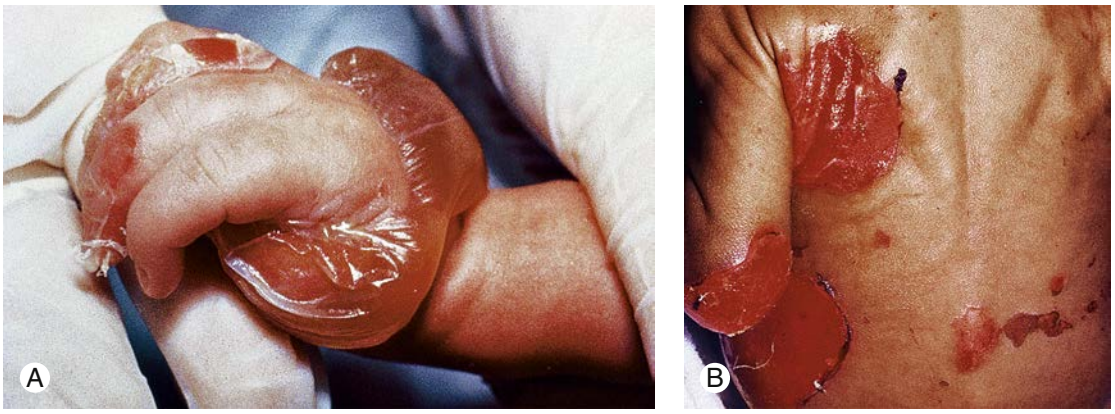

Fig. 49.19 Junctional epidermolysis bullosa. Widespread blisters at birth with erosions and denuded areas. (A) Hand, (B) Trunk involvement. (From Puttgen K and Cohen BA. Neonatal Dermatology. In: Cohen, BA, ed. *Pediatric Dermatology*. 4th ed. Philadelphia: Elsevier; 2013 [p. 39, Fig. 2.51].)

Fig. 49.20 Dystrophic epidermolysis bullosa. Blisters heal with hundreds of milia, especially on the hands and feet of this infant. (A-D) Represent various stages of healing. (From Puttgen K and Cohen BA. Neonatal Dermatology. In: Cohen, BA, ed. *Pediatric Dermatology*. 4th ed. Philadelphia: Elsevier; 2013 [p. 41, Fig. 2.52].)

Suggested Readings

Kollmann TR, Mailman TL, Bortolussi R. Listeriosis. In: Wilson CB, Nizet V, Maldonado Y, Remington JS, Klein JO, eds. *Infectious Diseases of the Fetus and Newborn*. 8th ed. Philadelphia: Elsevier Saunders; 2015:457–474.

Puttgen K, Cohen BA. *Neonatal Dermatology in Cohen's Pediatric Dermatology*. 4th ed. Philadelphia: Elsevier; 2013.

Questions

1. Which congenital infection of the newborn presents at delivery with prominent scarring on the body?
   a. Cytomegalovirus
   b. Toxoplasmosis
   c. Varicella
   d. Rubella
   e. Syphilis

2. Which syndrome describes a vascular tumor with associated ophthalmologic defects, posterior fossa brain malformations, and arterial/cardiac defects?
   A. PHACES syndrome
   B. SACRAL syndrome
   C. LUMBAR syndrome
   D. PELVIS syndrome
   E. LAMB syndrome

3. You are working in the newborn nursery when you are called to see a neonate with diffuse redness, crusting around the eyes and mouth, and desquamation of the neck, axilla, antecubital fossa, and inguinal folds. You suspect staphylococcal scalded skin syndrome. To further help evaluate this neonate, where should you obtain bacterial cultures from?
   a. Conjunctiva
   b. Umbilical stump
   c. Circumcision wound
   d. Nasopharynx
   e. All of the above

4. You are seeing a neonate in clinic who was born with a giant congenital nevus. You counsel the patient that there is approximately ___ chance of malignant transformation of the nevus.
   a. 1%–3%
   b. 2%–6%
   c. 10%–15%
   d. 15%–20%
   e. 20%–25%

5. You are seeing a neonate in pediatric clinic who has a stubborn diaper rash with red, hemorrhagic plaques and some flaccid bullae, along with a red rash around the mouth as well as the hands and feet. What is the most likely diagnosis?
   A. Langerhans cell histiocytosis
   B. Irritant dermatitis
   C. Psoriasis
   D. Acrodermatitis enteropathica
   E. None of the above

6. Which of the following is FALSE regarding the difference between neonatal pustular melanosis and erythema toxicum neonatorum?
   a. Erythema toxicum neonatorum presents in up to half of all full-term newborns.
   b. Transient neonatal pustular melanosis appears more commonly in blacks.
   c. Erythema toxicum neonatorum usually is not present at birth.
   d. Transient neonatal pustular melanosis is characterized by eosinophils on Wright-stained smear.
   e. Transient neonatal pustular melanosis resolves with hyperpigmentation.

7. What is the most sensitive marker of neonatal lupus?
   a. Anti-dsDNA
   b. Anti-Ro/SSA
   c. Anti-La/SSB
   d. U1-RNP
   e. ANA

8. Which of the following is the most likely cause of collodion membrane at birth?
   a. Netherton syndrome
   b. Ichthyosis vulgaris
   c. Epidermolysis bullosa simplex
   d. Lamellar ichthyosis
   e. Congenital ichthyosis erythroderma

9. What mutation causes the mitten deformity seen in dystrophic epidermolysis bullosa?
   a. Missense mutation in Collagen VII
   b. Mutation in Keratin 5
   c. Mutation in Keratin 14
   d. Mutation in Pectin
   e. Mutation in Laminin 332

10. Which congenital ichthyosis is associated with prolonged labor?
    a. Ichthyosis vulgaris
    b. Lamellar ichthyosis
    c. Steroid sulfatase deficiency
    d. Epidermolytic hyperkeratosis
    e. Sjögren-Larson syndrome

SECTION 14

Hematology/Oncology

LAURIE STEINER and JEFFREY R. ANDOLINA

50 Erythrocytes

LAURIE STEINER

Sites of Erythropoiesis in the Embryo, Fetus, and Neonate

- Sites of embryonic, fetal and neonatal erythropoiesis are shown in Fig. 50.1.
- Primitive red blood cells (RBCs) emerge from the yolk by 2–3 weeks after conception and support the growth of the embryo during the first trimester.
- Erythropoiesis shifts to the fetal liver during the late first trimester and continues to be a source of erythropoiesis through birth.
- By the end of the second trimester, the bone marrow is the primary site of erythropoiesis.

Developmental Biology of Hemoglobin

- Hemoglobin is a tetramer comprised of 2 α-type chains and 2 β-type chains. As erythropoiesis transitions from the yolk sac to the fetal liver and ultimately to the bone marrow, there are changes in the composition of the hemoglobin expressed. This process is termed *hemoglobin switching* and is illustrated in Fig. 50.1.
- Embryonic hemoglobins (Hb Gower 1 [ζ2ε2], [α2ε2]; and Hb Portland [ζ2γ2]) are expressed during the first trimester in primitive RBCs that come from yolk sac hematopoiesis.
- Fetal hemoglobin (Hb F; α2 γ2) is the predominant hemoglobin of the fetus and newborn. Of note, there are 2 isoforms of γ globin; $^{G}\gamma$ and $^{A}\gamma$, which differ by only one amino acid and are functionally similar. Fetal hemoglobin does not efficiently bind 2,3-DPG and therefore has a higher affinity for oxygen than adult hemoglobin (Fig. 50.2).
- The major form of adult hemoglobin (Hb A; α2β2) increases in expression rapidly after birth. The minor form of adult hemoglobin (HbA2; α2δ2) also increases in expression after birth. Adult hemoglobin has a lower oxygen affinity than either embryonic or fetal hemoglobin.
- By 6 months of age, the majority of infants express primarily adult globin and <1% of hemoglobin is Hb F.

Red Cell Indices During Development

- The RBC count, hemoglobin, and hematocrit increase steadily throughout development (Table 50.1).
- Fetal and neonatal RBCs are larger than adult cells. The MCV (mean corpuscular volume) declines gradually with increasing gestational and postnatal age.
- Fetal and neonatal RBCs have a shorter life span than adult RBCs. Adult RBCs have a life span of 120 days. Term RBCs survive only 60–80 days with even lower RBC survival times in preterm infants.

Erythropoietin, Regulation of Erythropoiesis, and Physiologic Anemia of Infancy

- Erythropoietin (EPO) is a glycoprotein hormone essential for the production of red blood cells.
- In the fetus, EPO is produced mainly in the liver, with production shifting to the kidney near the time of birth.
- EPO does not cross the placenta; therefore erythropoiesis is primarily under the control of the fetus.
- Intrauterine conditions that result in fetal hypoxia, such as placental insufficiency or cigarette smoking, can result in increased EPO production by the fetus and subsequent polycythemia.
- EPO levels in cord blood are higher than EPO levels in adults, due to the relatively hypoxic intrauterine environment. EPO production declines rapidly after birth, contributing to the physiologic anemia of infancy.
- Physiologic anemia of infancy occurs in term infants at approximately 8–12 weeks of life, with an average hemoglobin nadir of 11 g/dL.

Anemia of Prematurity

OVERVIEW

- Anemia of prematurity (AOP) is an earlier and more dramatic physiologic anemia that occurs in preterm infants, often occurring by 6 weeks of age and reaching hemoglobin nadirs of 7–10 g/dL.
- AOP is a multifactorial disorder. Contributing factors include:
  - The shorter life span of preterm erythrocytes.
  - Frequent blood sampling.
  - Decreased EPO production in response to hypoxia compared to term infants, which may be due to developmental differences in the site of EPO production (liver vs. kidney).
  - Suppression of erythropoiesis due to systemic illness.

SYMPTOMS

- Some infants are asymptomatic, while others develop symptoms including tachypnea, pallor, poor feeding, and suboptimal weight gain that necessitate treatment with red cell transfusion.

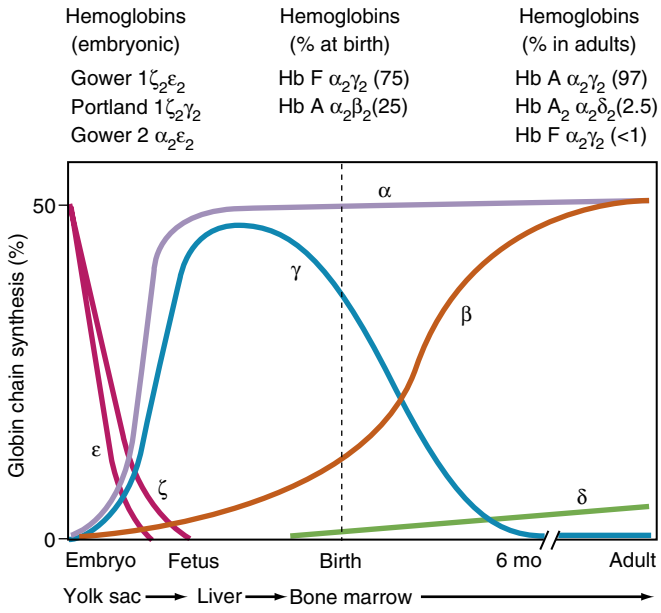

Fig. 50.1 Sites of erythropoiesis and pattern of hemoglobin expression during embryonic, fetal, and adult development. (From Steinberg MH, Benz EJ Jr., Adewoye HA, et al. Pathobiology of the human erythrocyte and its hemoglobins. In: Hoffman R, Benz EJ, Shattil SJ, eds. *Hematology: Basic Principles and Practice.* 7th ed. Philadelphia: Elsevier; 2018 [pp. 447–457, Fig. 33.8].)

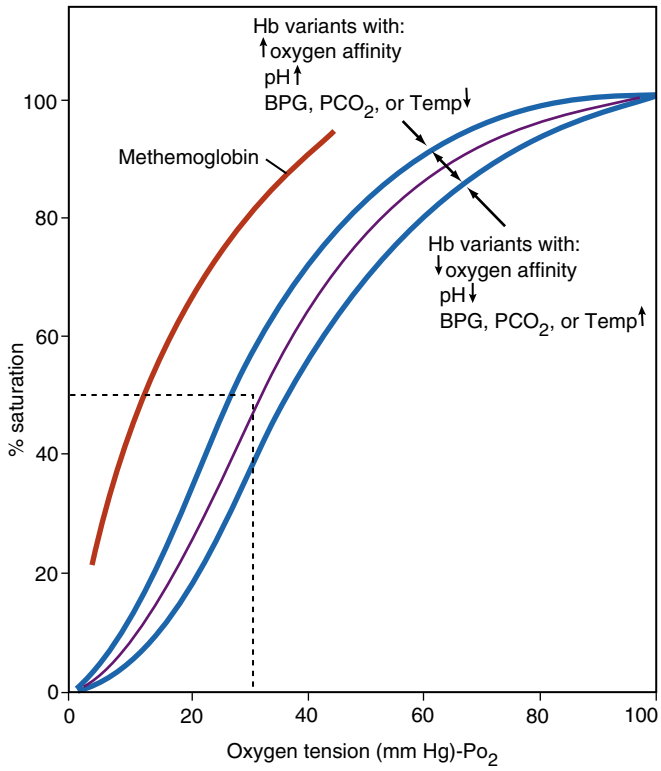

Fig. 50.2 The hemoglobin oxygen dissociation curve. Fetal hemoglobin shifts the P50 (the oxygen tension at which the hemoglobin is one-half saturated) to the left. (From Steinberg M, Benz E, Adewoye A, and Ebert B. Pathobiology of the human erythrocyte. In: Hoffman R, Benz EJ, Shattil SJ, eds. *Hematology: Basic Principles and Practice.* Philadelphia: Elsevier; 2018 [pp. 447–457, Fig. 33.3].)

TREATMENT

- Standard treatment for AOP is with red cell transfusion.
- The use of EPO to treat anemia of prematurity is an area of active research and debate. EPO treatment can reduce, but not eliminate, the need for transfusions. In some studies, EPO treatment has been associated with an increased risk for retinopathy of prematurity.

Red Blood Cell Antigens

THE ABO BLOOD GROUP

- There are four major ABO blood groups that are distinguished by the type of oligosaccharide present on the red cell surface.
- The ABO blood groups are encoded by the ABO gene locus. The A and B alleles encode enzymes (glycosyltransferases) that catalyze the final step of the synthesis of the A and B antigen, respectively. The O allele encodes a catalytically inactive enzyme that does not place an antigen on the red cell surface.
- One allele from the ABO group is inherited from the mother and one is inherited from the father. The inheritance pattern for the ABO blood group is shown in Table 50.2.

THE RH LOCUS

- The Rh antigens are encoded by a linked group of two genes, *RHD* and *RHCE*. People are Rh positive or negative based on the presence or absence of the D antigen.

ABO Incompatibility

OVERVIEW

- ABO incompatibility refers to a mother with blood type O who has a feus with blood type A, B, or AB. Hemolysis due to ABO incompatibility occurs when a woman with type O blood has antibodies that cross the placenta and interact with A or B antigens on the fetal erythrocytes.
- Maternal and fetal ABO incompatibility are common; however, hemolysis occurs in only a small fraction (~10%) of ABO incompatible pregnancies.
- The first pregnancy can be affected. Hemolysis does not worsen with subsequent pregnancies.

SYMPTOMS AND DIAGNOSIS

- Jaundice, often in the first 24 hours of life
- Positive direct Coombs test
- Evidence of neonatal hemolysis
  - Anemia with elevated reticulocyte count
  - Hyperbilirubinemia

TREATMENT

- Mainstay of treatment is preventing severe hyperbilirubinemia that is associated with neurotoxicity through phototherapy.

Table 50.1 Normal Red Blood Cell Indices During Gestation

Weeks of Gestation	Erythrocytes (×10^{12}/L)	Hemoglobin (g/dL)	Hematocrit (%)	Mean Corpuscular Volume (fL)
18–21	2.85±0.36	11.7±1.3	37.3±4.3	131.11±10.97
22–25	3.09±0.34	12.2±1.6	38.6±3.9	125.1±7.84
26–29	3.46±0.41	12.9±1.4	40.9±4.4	118.5±7.96
>36	4.7±0.4	16.5±1.5	51.0±4.5	108±5

Values represent means ±1 standard deviation.
From Dror Y, Chan A, Baker J, Avila M. Hematology. In: MacKonald M, Seshia ME, eds. *Avery's Neonatology: Pathophysiology and Management of the Newborn*. 7th ed. Philadelphia: Lippincott Williams & Wilkins; 2016 (pp. 872–1199, Table 43.1).

Table 50.2 Inheritance Pattern of the ABO Blood Group

		Maternal Allele		
		A	B	O
Paternal Allele	A	AA	AB	AO
	B	AB	BB	BO
	O	AO	BO	OO

- Severe cases may require exchange transfusion to control hyperbilirubinemia or packed red cell transfusion to treat anemia.

Rh Incompatibility and Alloimmune Hemolytic Disease of the Newborn

OVERVIEW

- Hemolytic disease of the newborn (HDN) is caused by the destruction of fetal/neonatal RBC by maternal IgG (immunoglobulin).
- HDN is classically caused by antibodies targeting the D antigen of the Rh locus.
- HDN can also be caused by antibodies that target the C and E antigens of the Rh locus, as well as antibodies to other RBC antigens, such as anti-Kell and anti-Duffy. Maternal sensitization to these antigens is not prevented by RhoGAM (anti-D) administration.
- ABO incompatibility is not a common cause of HDN. ABO incompatibility causes anemia and hyperbilirubinemia after birth but rarely causes significant fetal anemia.
- HDN is typically mild with the first pregnancy and becomes more clinically significant with each subsequent pregnancy.

SYMPTOMS AND DIAGNOSIS

- Pregnant women are screened for antibodies to fetal red cell antigens.
  - In women with high titers of anti-D or other antibodies targeting fetal RBC antigens, fetal anemia can be monitored noninvasively using MCA Doppler studies. Elevated MCA Dopplers suggest fetal anemia, which can be verified using percutaneous umbilical cord blood sampling (PUBS).
- Symptoms in affected fetuses can range from mild anemia to hydrops fetalis due to severe anemia and high output cardiac failure.
- Affected neonates can have significant jaundice, as well as ongoing hemolytic anemia, manifested by low hemoglobin and hematocrit, a high reticulocyte count, and a positive direct Coombs test.

PREVENTION AND TREATMENT

- RhoGAM (anti-D antibody) is given to Rh-negative mothers so that they clear Rh-positive fetal cells from their circulation before they generate anti-D antibodies.
- Severe fetal anemia is treated with in utero transfusion.
- The goal of neonatal therapy is to control hyperbilirubinemia with phototherapy or exchange transfusion, as appropriate. Anemia is treated with packed red blood cell transfusion, when necessary.
- Careful follow-up of the hematocrit after discharge is important. Infants with HDN can have an exaggerated physiologic nadir that may require packed red cell transfusion.

The Hemoglobinopathies

OVERVIEW

α-Thalassemia

- Humans have four copies of the α-globin gene, located on chromosome 16.
- Deletion of 1, 2, 3, or 4 α-globin genes results in a silent carrier state, α-thalassemia trait, Hb H (β4), and Hb Barts (γ4), respectively.
- α-Globin is the predominant α-type chain after the first trimester, therefore severe α-thalassemia (Hb H and Hb Barts disease) are often associated with severe fetal anemia that can result in hydrops fetalis and fetal demise.

β-Thalassemia

- Humans have two copies of the β-globin gene located on chromosome 11.
- The clinical phenotype of β-globin gene deletions is very heterogeneous and is strongly influenced by complex genetic interactions. There are four clinical classifications of β-thalassemia despite only having two β-globin genes: silent carrier, β-thalassemia trait, β-thalassemia intermedia, and β-thalassemia major.
- γ-Globin is the major β-type chain until after birth. The expression of γ-globin prevents infants with β-thalassemia from being symptomatic in the fetal and newborn period.

Sickle Cell Anemia and Other Sickle Cell Hemoglobinopathies

- Hb S results from point mutation at position 6 in the β-chain that substitutes valine for glutamic acid. Hb S is more common in patients of African and Mediterranean descent, and heterozygosity for Hb S is thought to confer resistance to malaria.
- Patients homozygous for Hb S have sickle cell anemia, characterized by sickling of red blood cells, moderate to severe anemia, painful crises, increased risk of stroke, and eventually end-organ damage to the kidneys and lungs.
- Patients with sickle cell trait (one copy of Hb S and one copy of Hb B) are generally asymptomatic but can have difficulty tolerating extreme exertion, high altitude, or significant dehydration.
- Inheritance of Hb SS with hereditary persistence of fetal hemoglobin results in milder disease phenotype. Conversely, coinheritance of Hb S with β-thalassemia can result in severe disease.
- Hb S is a variant of the β-type chain. Symptoms of sickle cell anemia therefore do not present in the newborn period due to high levels of γ-globin expression.

Hemoglobin Variants

- Over 500 other hemoglobin variants have been described. Hemoglobin variants can impact hemoglobin stability, solubility, iron oxidation, and oxygen affinity. The clinical presentation of the hemoglobin variant depends on the specific mutation and hemoglobin chain affected.
- In general, only mutations in the α-, $^{G}\gamma$- and $^{A}\gamma$- chains are symptomatic in the neonatal period.
- Anemia from mutations in either $^{G}\gamma$- or $^{A}\gamma$- resolves as hemoglobin switching occurs and the neonate begins to express significant amounts of β-globin.

DIAGNOSIS

- Diagnosis of hemoglobinopathies is generally made through hemoglobin electrophoresis.

SYMPTOMS AND TREATMENT

- Severe α-thalassemia (Hb H and Hb Barts disease) is associated with severe fetal anemia and hydrops fetalis. Survival of these infants generally depends on in utero and postnatal transfusions, with phototherapy and exchange transfusion used to control hyperbilirubinemia. α-thalassemia trait causes a mild anemia that is generally not symptomatic in the newborn period.
- The β-globinopathies, such as β-thalassemia and sickle cell anemia, are not symptomatic in the neonatal period due to the expression of fetal hemoglobin (Hb F; α2, γ2).
- Detection of a hemoglobinopathy, such as sickle cell anemia, by newborn screening requires referral to a pediatric hematologist for confirmation of the diagnosis and follow-up care.

Newborn Screening for Hemoglobinopathies

- All 50 states perform newborn screening for sickle cell anemia and other hemoglobinopathies, such as α- and β-thalassemia.
- The majority of newborn screening programs use a combination of isoelectric focusing and high-performance liquid chromatography for initial screening. Common patterns of hemoglobin expression detected by newborn screening are shown in Table 50.3. Abnormal test results are subjected to confirmatory testing, such as hemoglobin electrophoresis.
- Infants suspected to have a hemoglobinopathy based on newborn screening results should have testing repeated in 6 months under the supervision of a pediatric hematologist.
- Infants with sickle cell anemia are at risk of splenic dysfunction. Early identification of infants with sickle cell anemia allows for parent education, penicillin prophylaxis, and immunization against *Haemophilus influenzae* and *Streptococcus pneumoniae*. It also allows for earlier identification and treatment of life-threatening splenic sequestration syndrome.

Approach to the Anemic Infant

- Anemia is defined as a hemoglobin or hematocrit greater than two standard deviations below the mean for gestational age.
- The differential diagnosis for anemia presenting at birth is broad but can be divided into three main categories:
  - Blood loss (hemorrhage)
  - Destruction (hemolysis)
  - Hypoproduction
- An overview of the diagnostic approach to the anemic infant is shown in Fig. 50.3.

Blood Loss (Hemorrhage)

OVERVIEW

- Blood loss can be acute or chronic.
  - Chronic blood loss is generally better tolerated due to fetal compensation.
  - The hemoglobin and other red cell indices will be normal if sampled soon after an acute blood loss. Hemodilution will result in anemia by 3–4 hours after the event, with the true extent of the blood loss reflected in the hematocrit by 6–12 hours after the event.

Common Etiologies of Blood Loss

- Fetal: cephalohematoma, subgaleal hemorrhage, intraventricular hemorrhage, umbilical cord rupture, twin-twin transfusion syndrome.
- Maternal/placental: placenta previa, abruptio placentae, vasa previa, fetal placental hemorrhage, fetal maternal hemorrhage (demonstrated by Kleihauer-Betke

test, which is the presence of acid resistant fetal erythrocytes on maternal blood smear).

- Twin-to-twin transfusion syndrome: primarily affects monochorionic diamniotic gestations, and occurs due to an imbalance of blood flow through placental intravascular connections. The donor twin is at risk of anemia, hypovolemia, and oligohydramnios. The recipient twin is at risk of polycythemia, hyperviscosity, and polyhydramnios. Severely affected pregnancies may be treated by reduction amniocentesis or laser ablation of abnormal vascular connections. Both twins are at risk for adverse neurologic and cardiac outcomes.

DIAGNOSIS AND TREATMENT

- The reticulocyte count is critical for distinguishing between chronic and acute blood loss, with a normal reticulocyte count suggesting acute blood loss and an elevated reticulocyte suggesting chronic blood loss.
- Acute blood loss can be treated with packed red blood cell transfusion.
- Chronic blood loss may require partial exchange transfusion, to correct anemia without significantly increasing intravascular volume.

Table 50.3 Common Patterns of Hemoglobin Expression Identified on Newborn Screening

Hemoglobin Pattern	Interpretation
FA	Normal
A significantly greater than F	Transfusion prior to screening
FAS	Sickle cell trait
FSC	Sickle cell disease
FS	Sickle cell anemia or sickle-β0-thalessemia
FAB	2%–8% Hb Barts (γ4): α-thalassemia trait 25%–50% Hb Barts: Hb H disease

A, Adult hemoglobin; *B,* hemoglobin Barts; *C,* hemoglobin C; *F,* fetal hemoglobin; *S,* hemoglobin S.

Adapted from Diab Y and Luchtman-Jones. Hematologic and oncologic problems in the fetus and neonate. In: Fanaroff and Martin, eds. *Neonatal Perinatal Medicine*. Philadelphia: Elsevier Saunders; 2015 [pp. 1294–1393, Box 88.5].

Blood Destruction (Hemolysis): Immune Mediated

- Please see earlier section on hemolytic disease of the newborn (HDN).

Hemolysis Due to Intrinsic Red Cell Defects (Nonimmune Mediated Hemolysis)

RBC ENZYME DEFECTS

- Mature RBCs lack mitochondria and are therefore reliant on glycolysis (Embden-Meyerhof-Parnas pathway) and the hexose monophosphate shunt to generate energy (ATP) and essential cofactors and antioxidants, most notably NADPH. Mutations of the enzymes in these metabolic pathways leads to hemolysis due to energy failure and/or inability to tolerate oxidative stress.

Glucose-6-Phosphate Dehydrogenase Deficiency

- Glucose-6-phosphate dehydrogenase (G6PD) deficiency is the most commonly inherited enzyme disorder of red blood cells. G6PD supplies NADPH and reduced glutathione to the red cell via the hexose monophosphate shunt (also called the *pentose phosphate pathway;* Fig. 50.4).

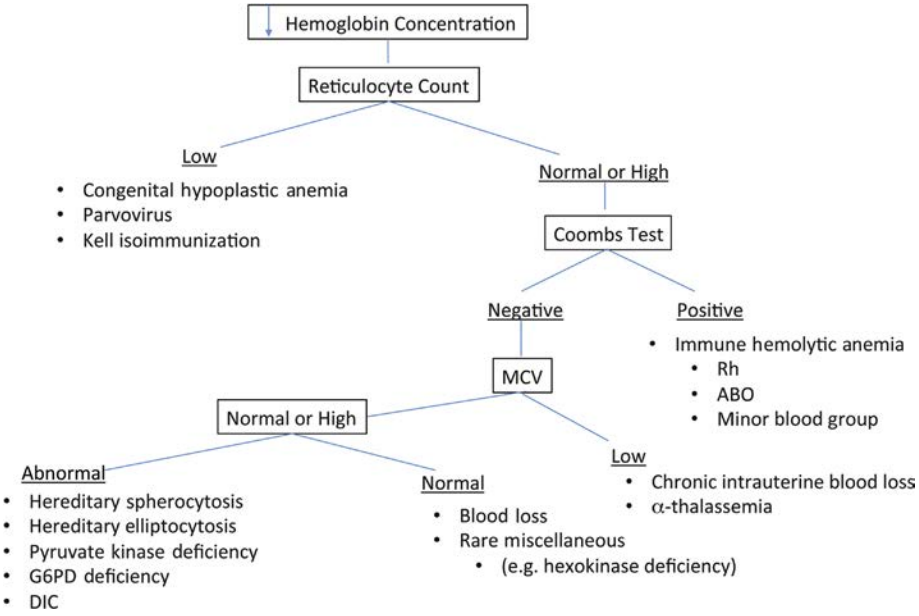

Fig. 50.3 Approach to the anemic infant. *DIC,* disseminated intravascular coagulation; *MCV,* mean corpuscular volume. (Adapted from Dror Y, Chan A, Baker J, Avila M. *Hematology in Avery's Neonatology: Pathophysiology and Management of the Newborn.* Philadelphia: Lippincott Williams & Wilkins; 2016 [pp. 872–1199, Fig. 43.12].)

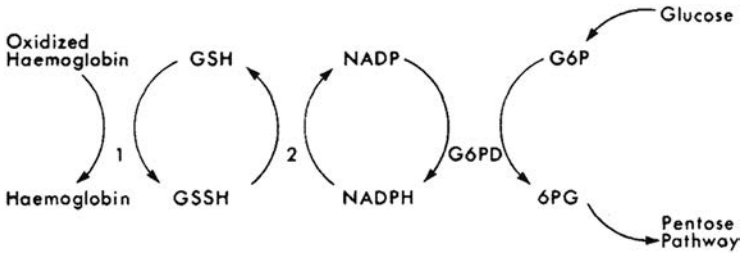

Fig. 50.4 Antioxidant defenses of the erythrocyte. *1,* Glutathione peroxidase; *2,* glutathione reductase; *G6PD,* glucose-6-phosphate dehydrogenase; *6PG,* 6-phosphogluconate; *G6P,* glucose-6-phosphate; *GSH,* reduced glutathione; *GSSH,* oxidized glutathione; *NADP,* nicotinamide adenine dinucleotide phosphate; *NADPH,* nicotinamide adenine dinucleotide phosphate, reduced. (From Dror Y, Chan A, Baker J, Avila M. Hematology. In: Avery, GB, ed. *Avery's Neonatology: Pathophysiology and Management of the Newborn.* 7th ed. Philadelphia: Lippincott Williams & Wilkins; 2016 [pp. 872–1199, Fig. 43.6].)

Deficiency of this enzyme leads to hemolysis when challenged with oxidative stress. Over 100 variants of the G6PD enzyme have been described.

- Although G6PD deficiency can occur in people of all genetic backgrounds, G6PD deficiency is most common in people of African and Mediterranean descent, suggesting a selective advantage against malaria. In the United States, approximately 10% of African-American males are affected.
- The G6PD variant common in African-American populations (the A- variant) results in a mild reduction in enzymatic activity and enzyme stability. This variant is frequently associated with neonatal jaundice and can predispose to methemoglobinemia.
- The G6PD variant common in Mediterranean, Ashkenazi Jewish, and Asian populations is more severe and can result in fatal hemolytic anemia in the face of oxidative challenge.
- G6PD is X-linked recessive, although heterozygous females can be symptomatic if there is imbalanced X-inactivation.
- G6PD deficiency can be difficult to diagnose during a hemolytic episode. Reticulocytes and young RBCs have the highest levels of G6PD. Older RBCs, with lower levels of G6PD, are generally lost first during a hemolytic crisis, artificially elevating G6PD levels.

Other Enzyme Defects

- Pyruvate kinase (PK) deficiency is the next most common enzyme deficiency but is much less prevalent than G6PD deficiency, occurring in ~1 in 20,000 individuals. PK is the second enzyme in the ATP-producing glycolytic pathway, and PK deficiency results in hemolysis from energy deficiency. PK is most frequently autosomal recessive, although other modes of inheritance have been reported.
- Defects in other enzymes involved in glycolysis, the hexose monophosphate shunt, or nucleotide metabolism are much less common but can result in hemolytic anemia.

MEMBRANE PROTEIN DEFECITS

- Cytoskeletal proteins interact with the lipid bilayer of the red blood cell and provide the support and stability necessary for the red blood cell to successfully traverse the microvasculature. Mutations in cytoskeletal proteins result in defects in red blood cell shape and/or deformability resulting in removal of red blood cells from circulation by the reticuloendothelial system.

Hereditary Spherocytosis

- Hereditary spherocytosis (HS) is most commonly due to autosomal dominant defects in ankyrin but can also be due to mutations in spectrin, band 3, and protein 4.2 (Fig. 50.5).
- HS is characterized by a hemolytic anemia that can range from mild to severe and is accompanied by spherocytes on peripheral blood smear and increased sensitivity of red cells to osmotic (hypotonic) lysis.
- Affected infants can have splenomegaly and prolonged hyperbilirubinemia.
- HS occurs most commonly in infants of northern European ancestry but can occur in all ethnic backgrounds.

Other RBC Membrane Protein Defects

- Hereditary elliptocytosis (HE) is due to autosomal dominant mutations in α- or β-spectrin and is characterized by elliptical-shaped red blood cells (ovalocytes) and a hemolytic anemia, which is generally milder than in HS. HE tends to occur in infants of African and Mediterranean ancestry.
- Hereditary pyropoikilocytosis (HPP) is caused by homozygous or compound heterozygous mutations of α- or β-spectrin.

Defects in Hemoglobin Production or Stability

- Defects in hemoglobin quantity or quality can result in hemolytic anemia. For details, please see section on thalassemias and hemoglobinopathies, earlier.

RBC Hypoproduction

OVERVIEW

- Hypoproduction refers to anemia due to low production of red blood cells and is typically characterized by a low reticulocyte count. Hypoproduction can be due to acquired disorders, most commonly parvovirus B19 infection, or it can be due to intrinsic bone marrow defects, such as Diamond-Blackfan anemia.

Parvovirus

- Parvovirus B19 binds to the P-antigen on the surface of red cell progenitors, disrupting erythroid maturation and resulting in a reticulocytopenic anemia.
- In utero infection with parvovirus can result in severe fetal anemia that may require in utero transfusions to prevent the development of hydrops fetalis.

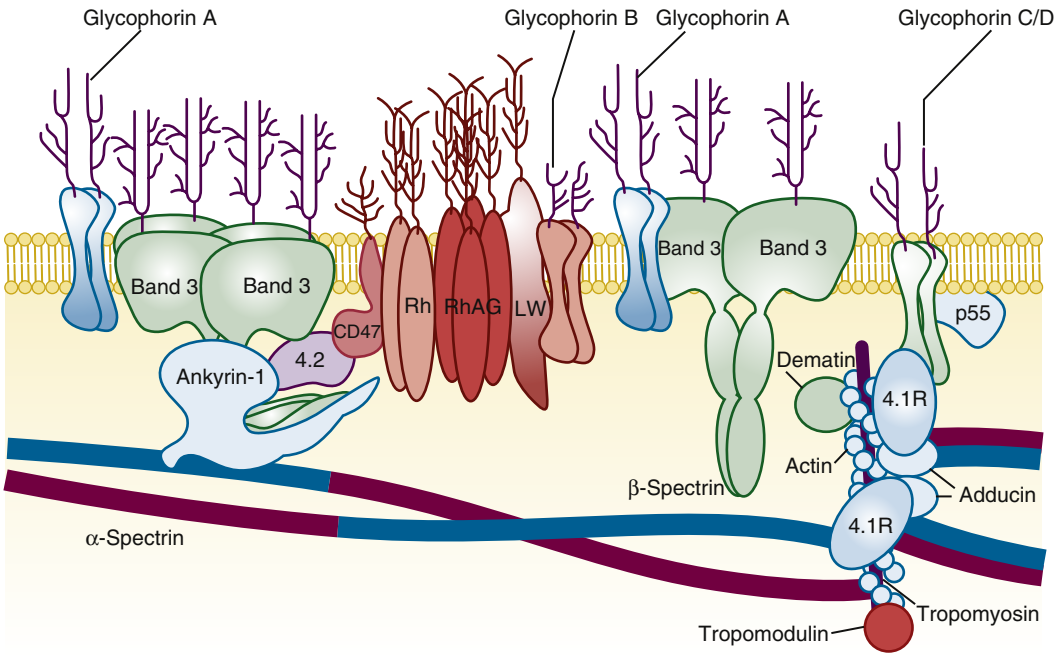

Fig. 50.5 A cross section of the erythrocyte membrane. (From Gallagher PG. Red blood cell Membrane disorders. In: Hoffman R, Benz E, Silberstein L, Heslop H, Weitz J, Anastasi J, Salama M, Abutalib S, eds. *Hematology: Basic Principles and Practice.* 7th ed. Elsevier; 2018 [pp. 626–647, Fig. 45.1].)

- Parvovirus can also lead to aplastic crisis in patients with hemoglobinopathies or other inherited red cell disorders.

HDN Due to Anti-Kell Antibodies

- Although frequently discussed in the context of hemolytic disease of the newborn, maternal antibodies to the Kell antigen present on the surface of fetal red blood cells can cause hypoproduction in addition to hemolysis. The Kell antigen is expressed at highest levels on the surface of red blood cell precursors, resulting in the preferential destruction of those cells and a reticulocytopenic anemia.

Congenital Bone Marrow Failure Syndromes

- Diamond-Blackfan anemia (DBA) is a rare, autosomal dominant bone marrow syndrome characterized by macrocytic anemia and reticulocytopenia that are frequently accompanied by congenital abnormalities including short stature, abnormal facies, abnormal thumbs, and other skeletal abnormalities.
  - Patients with DBA frequently have mutations in genes that encode ribosomal subunits, with RPS19 being the most commonly mutated gene in DBA.
- Fanconi anemia (FA) is a congenital bone marrow failure syndrome that can affect infants but is not typically diagnosed until late childhood.
  - FA can also be associated with thrombocytopenia and leukopenia. FA is due to a defect in DNA repair enzymes and is associated with an increased incidence of cancers later in life.
  - Diagnosis is typically made by DNA breakage analyses.
- Shwachman-Bodian-Diamond syndrome (SBDS) is a congenital bone marrow failure syndrome that is characterized by neutropenia, often accompanied by anemia and/or thrombocytopenia, exocrine pancreatic insufficiency, and skeletal abnormalities.
  - SDS is due to mutations in the SBDS gene on chromosome 7.
- Pearson syndrome is a rare mitochondrial disease characterized by anemia, exocrine pancreatic insufficiency, renal, and hepatic failure. Diagnosis is made by mitochondrial gene sequencing.

Iron Homeostasis

- The majority of the iron in the body (~75%) is bound to heme-containing proteins, including myoglobin and hemoglobin, with a small amount of iron contained in enzymes such as catalase or cytochromes. The remaining iron is contained in the storage proteins ferritin and hemosiderin.
- Hepcidin is a key hormone that regulates iron homeostasis. It inhibits intestinal iron absorption and release of iron from macrophages. Hepcidin is also an acute phase reactant and may contribute to anemia of chronic disease.
- Infants, especially preterm infants, require a higher percentage of daily iron intake than adults to meet the demands of growth.
- The majority of iron is transferred to the fetus during the third trimester. Maternal anemia, diabetes, or hypertension with growth restriction can result in suboptimal iron transfer and low iron stores in the fetus.

Iron Deficiency and Iron Deficiency Anemia

OVERVIEW

- Iron is an essential nutrient. Iron deficiency (ID) occurs when there is insufficient iron to maintain normal

physiologic functions. Iron deficiency may precede the development of iron deficiency anemia (IDA).

- Iron is essential for normal neurologic development and function. Both ID and IDA have been associated with adverse neurologic outcome in numerous studies, although causality has not been definitively proven. Some studies have suggested that iron supplementation can improve cognitive function in children with ID.

Diagnosis

- IDA results in an increased red blood cell distribution width (RDW) and a microcytic, hypochromic anemia. The red blood cells in IDA may have increased central pallor (hypochromia) and basophilic stippling.
- The most readily available measure of iron status is ferritin, with ferritin levels <12 diagnostic of iron deficiency. Ferritin is an acute phase reactant, and measurement of ferritin during illness or inflammation may result in a false negative result. Simultaneous measurement of C-reactive protein is often done to rule out elevation of ferritin due to inflammation.
- The reticulocyte Hb concentration and the serum transferrin receptor 1 are also recommended by the AAP to assess iron status. These tests are not affected by inflammation but are not widely available.
- Zinc protoporphyrin (ZPP) is formed when hemoglobin formation is disrupted by iron deficiency or lead toxicity. Elevated ZPP can therefore be an indirect indication of iron deficiency.

Prevention of Iron Deficiency Anemia

- Most full-term infants have sufficient iron stores for the first 4–6 months of life. Supplementation with 1 mg/kg of elemental iron is recommended beginning at 4 months of age and continued until iron-rich foods are added to the diet.
- Risk factors for IDA include severe maternal iron deficiency or diabetes, anemia at birth, frequent blood sampling or other ongoing blood loss, prematurity, and small for gestational age.
- Breast milk contains less iron than iron-supplemented formula, however the iron in breast milk is highly bioavailable. Full-term infants who receive greater than half their feeds from breast milk require iron supplementation of 1 mg/kg beginning at 4 months of age. Term infant formulas are supplemented with sufficient iron (10–12 mg/L), and additional iron supplementation is not required unless clinically indicated.
- Preterm infants are at higher risk of IDA due to lower iron stores and more rapid rates of growth, although it is important to note that preterm infants who have had multiple blood transfusions may be at risk for elevated iron levels. In general, preterm infants should receive supplementation of 2 mg/kg elemental iron beginning at 1 month of age.
- Cow's milk should not be introduced before 1 year of age due to increased risk of IDA.

Polycythemia

Overview

- Defined as a Hgb or Hct greater than two standard deviations above the mean. For a term infant, polycythemia is defined as an Hgb >22 g/dL or an Hct greater than 65%.
- Polycythemia most often results from in utero hypoxia. It has been associated with a number of conditions including: maternal hypertension, placental insufficiency, maternal use of vasoconstrictive drugs (such as tobacco or cocaine), maternal diabetes, genetic disorders (including trisomy 21 and Beckwith-Wiedemann syndrome), twin-twin transfusion syndrome, and delayed cord clamping.

SYMPTOMS AND TREATMENT

- Symptoms of polycythemia include jitteriness, hypoglycemia, and respiratory distress. Polycythemia has been associated with persistent pulmonary hypertension of the newborn, as well as renal vein and cerebral sinovenous thrombosis.
- The treatment for symptomatic polycythemia is partial exchange transfusion. Polycythemia has been associated with adverse neurologic outcome; however, treatment with partial exchange transfusion has not been shown to improve long-term neurologic outcomes.

Suggested Readings

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Questions

1. What is the primary site of erythropoietin production for the fetus?
   a. The kidney
   b. The liver
   c. The bone marrow
   d. The mother

2. Anemia of prematurity (AOP) is a multifactorial disease. Which of the following does NOT contribute to the development of AOP?
   a. Frequent blood sampling of premature neonates
   b. Suppression of erythropoiesis due to systemic illness
   c. Inability of EPO to stimulate erythropoiesis in premature infants
   d. Shorter life span of erythrocytes in preterm infants

3. ABO incompatibility is a common cause of neonatal hemolysis and jaundice. Which of the following statements about ABO incompatibility is true?
   a. The majority of pregnancies with ABO incompatibility will result in hemolysis and jaundice.
   b. ABO incompatibility worsens with each pregnancy.
   c. ABO incompatibility often results in fetal anemia that can lead to hydrops fetalis.
   d. Only infants with an A or B blood group whose mother has the O blood type are at risk of hemolysis due to ABO incapability.

4. What is the main hemoglobin produced by the fetus during the second trimester?
   a. Hb F [$\alpha 2\ \gamma 2$]
   b. Hb Gower 1 [$\zeta 2 \varepsilon 2$]
   c. Hb Gower 2 [$\alpha 2 \varepsilon 2$]
   d. Hb Portland [$\zeta 2 \gamma 2$])

5. Which of these diseases is symptomatic in the neonatal period?
   a. α-thalassemia major
   b. β-thalassemia
   c. Sickle cell anemia

6. Your patient, who has never been transfused, has a newborn screen which demonstrates the predominance of Hb F, with small amounts of Hb S and Hb A detected. What is the correct interpretation of the screening results?
   a. Sickle cell anemia
   b. Sickle cell trait
   c. Normal

7. The inheritance pattern of G-6-PD deficiency is:
   a. Autosomal dominant
   b. Autosomal recessive
   c. X-linked recessive
   d. X-linked dominant

8. When is the majority of iron transferred from the fetus to the mother?
   a First trimester
   b. Second trimester
   c. Third trimester

9. Iron supplementation should be considered for breastfed term infants at what age?
   a. 1 month
   b. 4 months
   c. 1 year
   d. Never, it is not necessary

10. What is NOT an appropriate clinical reason to consider a partial exchange transfusion (PET) for polycythemia?
    a. To prevent neurodevelopmental delays
    b. For an extremely elevated central hematocrit (>70)
    c. For an elevated central hematocrit (>65) with persistent symptoms of polycythemia such as jitteriness or hypoglycemia.

51 White Blood Cells

JEFFREY R. ANDOLINA

White blood cells (WBCs) are produced in the bone marrow and originally come from hematopoietic stem cells. Hematopoiesis can be summarized in Fig. 51.1. Hematopoietic stem cells first differentiate into a common lymphoid progenitor and a common myeloid progenitor. The lymphoid progenitor will develop into all lymphocytes, including B lymphocytes, T lymphocytes, and natural killer (NK) cells. Conversely, the common myeloid progenitor will develop into all other blood cells, including red blood cells (erythrocytes), platelets, and all other white blood cells, including granulocytes, monocytes, and macrophages. Granulocytes include neutrophils, eosinophils, and basophils. Neutrophil developmental progression is summarized in Fig. 51.2. The development of WBCs is determined by the programmed expression of cell surface molecules, interactions by cytokines, and location. WBCs develop and mature in multiple locations, including the bone marrow, the thymus and lymphoid system, and the peripheral tissues. For further details on the development, components, and normal and abnormal function of WBCs, please refer to the section on Immunology.

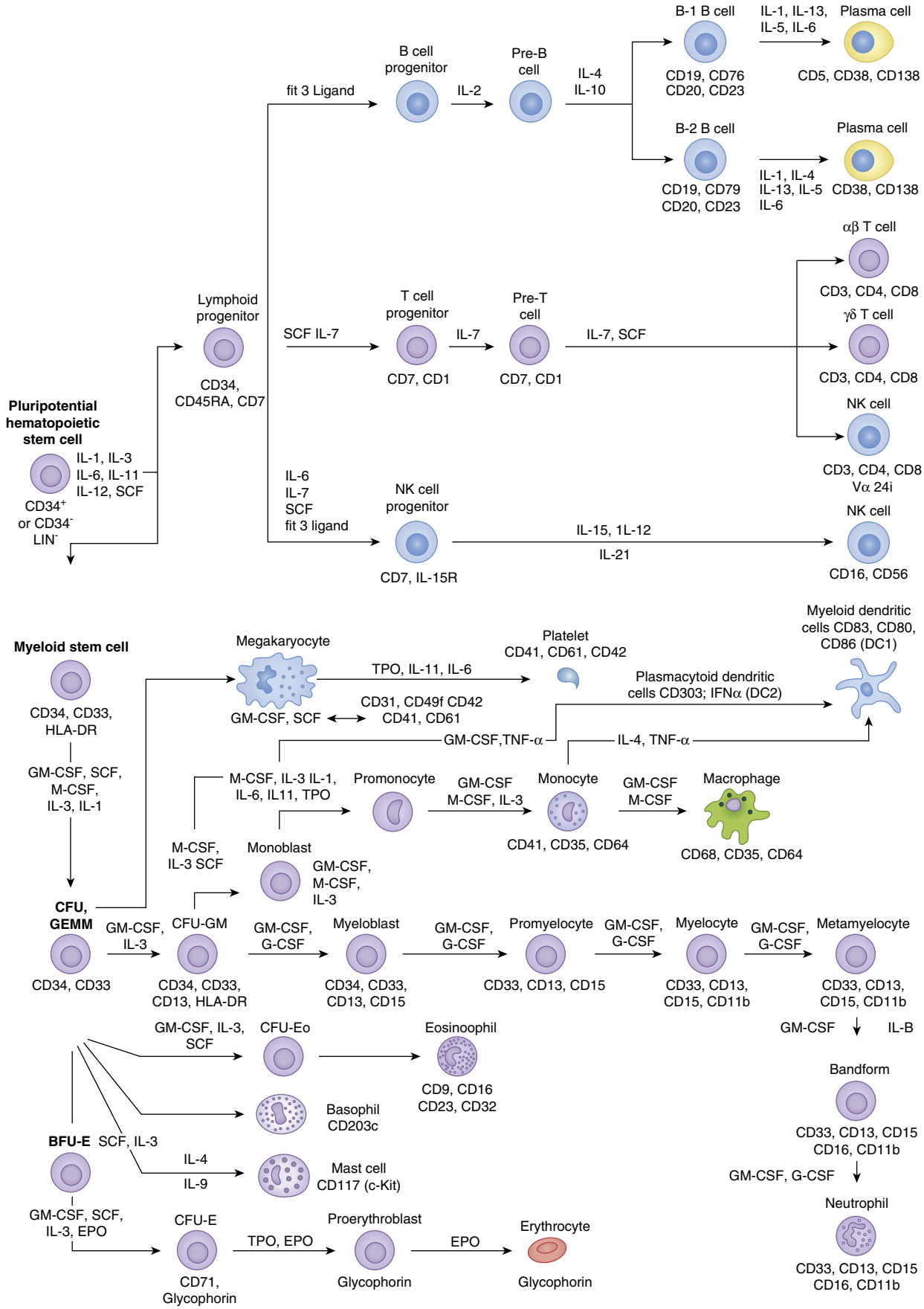

Fig. 51.1 Hematopoiesis. (From Lewis DE, Harriman GR, Blutt SE. Organization of the immune system. *Clinical Immunology.* Mosby; Published January 1, 2013. [pp. 16–34. Fig. 2.1].)

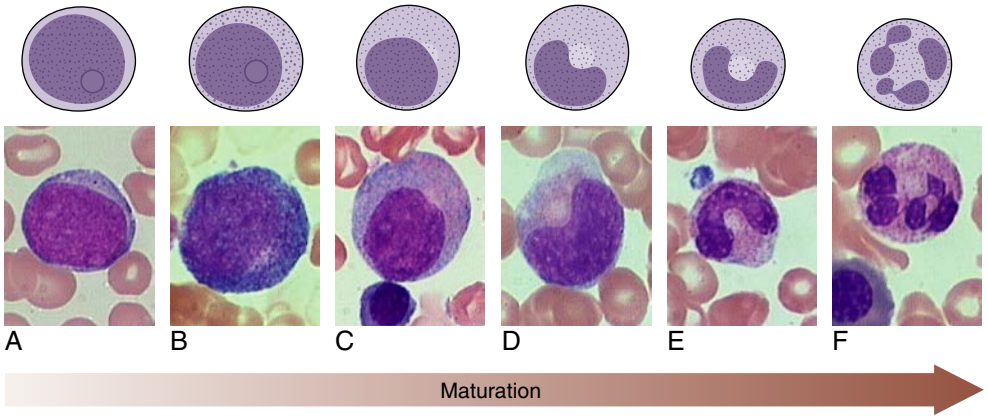

Fig. 51.2 Neutrophil maturation. (A) Myeloblast. (B) Promyelocyte. (C) Myelocyte. (D) Metamyelocyte. (E) B and (F) Neutrophil. (Adapted from University of Virginia website. https://www.med-ed.virginia.edu/courses/path/innes/nh/wcbmaturation.cfm)

52 Platelets and Coagulation

LAURIE STEINER

Platelet Production and Regulation of Platelet Levels

- Platelets are produced by specialized cells in bone marrow (called megakaryocytes) in response to hormone called thrombopoietin (TPO). Maturing megakaryocyte progenitors replicate DNA without dividing, causing them to become polypoid (contain > two copies of each chromosome), typically 8–18N. During this process, the cytoplasm of megakaryocyte progenitors matures and eventually produces platelets.
- The typical life span of a platelet in circulation is 7–10 days.
- The liver plays central role in platelet homeostasis. TPO is produced constitutively by the liver. Platelets express TPO receptor and serve as sink for circulating TPO. When platelet levels are low, circulating platelets do not adsorb TPO. TPO levels rise, stimulating platelet production.
- Neonates have higher numbers of circulating megakaryocyte progenitors than older children and adults, but those progenitors are smaller and have lower ploidy. Thrombocytopenic neonates tend to have lower TPO levels than thrombocytopenic children or adults.

Thrombocytopenia

OVERVIEW

- Thrombocytopenia generally defined as platelet count less than 150×10^9/L; some otherwise healthy preterm and term neonates can have platelet counts in the range of $100–150 \times 10^9$/L.
- Thrombocytopenia is very common in sick neonates, affecting approximately 30% of NICU patients. Severe thrombocytopenia, defined as a platelet count less than 50×10^9/L, is less common, but still affects roughly 5%–10% of NICU patients.
- Thrombocytopenia can be due to maternal, placental, or fetal etiologies (each are detailed below); however in many ELBW (Extremely Low Birthweight Infant) no etiology for thrombocytopenia is found, despite a thorough diagnostic evaluation.

SYMPTOMS AND TREATMENT

- Symptoms of thrombocytopenia include petechiae, bruising, and bleeding from sites such as the mucosa and heel sticks. Severe thrombocytopenia can also be associated with more internal bleeding such as intraventricular hemorrhage.
- Thrombocytopenia is treated by platelet transfusion.

Maternal Factors Associated With Neonatal Thrombocytopenia

- Neonatal thrombocytopenia can be associated with maternal illness including preeclampsia and HELP (hemolysis, elevated liver enzymes, low platelets) syndrome.
  - Thrombocytopenia associated with preeclampsia typically nadirs at 2–4 days of life and resolves by 7–10 days.
- Maternal medications including heparin, thiazide diuretics, quinine, digoxin, hydralazine, and antiepileptics have been associated with fetal thrombocytopenia.
- Maternal infections, both bacterial and viral, can result in fetal or neonatal thrombocytopenia.
  - TORCH infections, particularly CMV, are frequently associated with neonatal thrombocytopenia.
- Maternal antibodies to platelet antigens are relatively uncommon, but can result in severe thrombocytopenia. There are two main classes of maternal platelet antibodies:
  - Alloimmune thrombocytopenia.
  - Autoimmune thrombocytopenia.

Neonatal Alloimmune Thrombocytopenia

OVERVIEW

- Neonatal alloimmune thrombocytopenia (NAIT) occurs when fetal platelets express a human platelet antigen (HPA) inherited from the father that the mother lacks. There are 16 different HPAs, however HPA-1a accounts for ~three-quarters of all cases of NAIT. In NAIT, the mother's platelet count is typically normal.

SYMPTOMS

- NAIT can result in severe thrombocytopenia (platelet count <50,000) in the first 72 hours of life that gradually improves over the first month of life as antiplatelet IgG levels decline.
- NAIT is associated with spontaneous mucocutaneous bleeding. Approximately 10% of affected infants will have intracranial bleeding, which can occur before or after delivery.

TREATMENT

- Platelet transfusion is the mainstay of therapy for severe thrombocytopenia.

- Optimal treatment of severe thrombocytopenia due to NAIT is transfusion of HPA-1a negative platelets. Maternal platelets, washed to remove antibody, may be used but HPA-1a negative or washed maternal platelets are often not available.
- Random pooled donor platelets can be quickly acquired and will rapidly increase platelet count. The survival of the random donor platelets in circulation may be short but they are effective initial therapy, particularly in settings of severe thrombocytopenia or hemorrhage.

- IVIG is often effective as an adjunctive therapy and may reduce the number of platelet transfusions needed. Prednisone has been used in severe cases.
- Infants with NAIT and severe thrombocytopenia should have an ultrasound to screen for intracranial hemorrhage.
- The recurrence rate of NAIT is high (>75%). Women with known HPA antibodies may be treated with IVIG or glucocorticoids to decrease the risk of fetal/neonatal thrombocytopenia.

Neonatal Autoimmune Thrombocytopenia

OVERVIEW

- Neonatal autoimmune thrombocytopenia is caused by maternal antibodies that react with both maternal and fetal platelets. The mother is usually thrombocytopenic and often has an autoimmune disease such as ITP (immune thrombocytopenia purpura) or SLE (systemic lupus erythematosus).

SYMPTOMS AND TREATMENT

- The platelet count of affected infants reaches nadir at 2–5 days of life. The thrombocytopenia may persist for weeks to months while maternal IgG persists in the infant's circulation.
- Persistent thrombocytopenia (>4months) can be seen in breastfed infants due to anti-platelet IgA antibodies in the milk of affected mothers.
- IVIG is effective at increasing the platelet count and should be given to infants with severe thrombocytopenia.
- Platelet transfusion can be used to transiently increase the platelet count in the case of severe thrombocytopenia (<30,000) or bleeding.

Placental Factors Associated With Neonatal Thrombocytopenia

- Placental factors are a rare cause of fetal thrombocytopenia, however placental abruption, thrombi, and vascular anomalies have been associated with fetal thrombocytopenia.

Neonatal Disorders Causing Thrombocytopenia

- The differential diagnosis of neonatal disorders causing thrombocytopenia can generally be divided into two categories:
  - Consumption and sequestration
  - Hypoproduction
- The approach to the diagnosis of the thrombocytopenic infant is shown in Fig. 52.1.

PLATELETS CONSUMPTION AND SEQUESTRATION

- Platelet consumption is one of the most common causes of neonatal thrombocytopenia. Common causes of platelet consumption include DIC (disseminated intravascular coagulation) and NEC (necrotizing enterocolitis).
- Thrombosis is also a common cause of thrombocytopenia.
  - Consider a deep vein thrombosis (DVT) investigation for infants for whom thrombocytopenia cannot be explained by another cause, particularly for infants with central venous catheters.
- Infections, particularly fungal infections, have also been associated with thrombocytopenia.
  - Thrombocytopenia associated with infection is likely due to increased consumption (DIC), however damage to megakaryocytes may also play a role.
- Kasabach-Merritt phenomenon refers to thrombocytopenia and consumptive coagulopathy due to a vascular malformation, usually either a tufted angioma or a kaposiform hemangioendothelioma.
  - In Kasabach-Merritt, platelets are both sequestered in the vascular lesion and destroyed by the consumptive coagulopathy.
- Platelets may also be sequestered in an enlarged spleen.
  - Hypersplenism can be associated with hemolytic anemia, viral infections, and portal vein thrombosis.

HYPOPRODUCTION

- Perinatal hypoxic insult has been associated with mild thrombocytopenia that is attributed to decreased platelet production and does not usually require treatment.
- Preeclampsia, placental insufficiency, and infections (particularly TORCH infections), can also be associated with neonatal thrombocytopenia due to decreased production.

Genetic Causes of Platelet Hypoproduction

- Chromosomal abnormalities, including trisomy 13, 18, and 21 and Turner syndrome, are associated with both fetal and neonatal thrombocytopenia.
- Thrombocytopenia-absent radius (TAR) syndrome is an autosomal recessive syndrome characterized by severe thrombocytopenia and bilateral absent radii.
  - Thumbs are present in TAR, helping to distinguish it from Fanconi anemia.
  - Thrombocytopenia in TAR is due to a maturation defect in megakaryocyte progenitors, and generally improves after the first year.
  - Infants with TAR are at high risk of intracranial hemorrhage due to severe thrombocytopenia.
- Fanconi Anemia can be associated with thrombocytopenia, but it does not often present with thrombocytopenia in the neonatal period.
- Congenital amegakaryocytic thrombocytopenia results in severe thrombocytopenia due to mutations in the

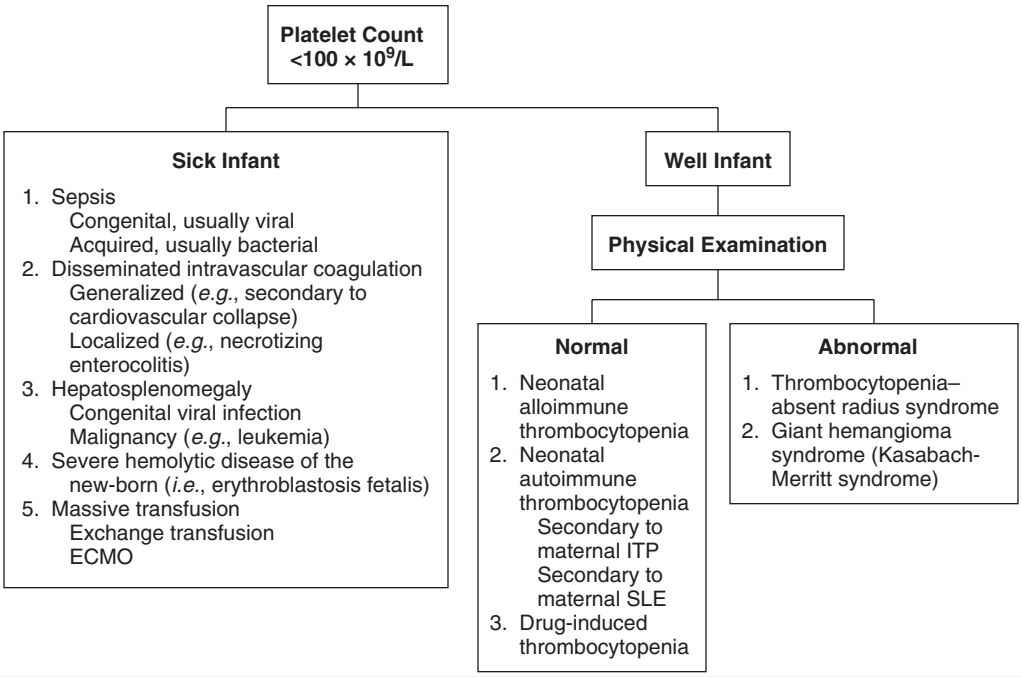

Fig. 52.1 Approach to the diagnosis of the thrombocytopenic newborn. *ECMO,* Extracorporeal membrane oxygenation; *ITP,* immune thrombocytopenic purpura; *SLE,* systemic lupus erythematosus. (Modified from Young G. Hemostatic disorders of the newborn. In: Gleason C, Devaskar S, eds. *Avery's Neonatology: Pathophysiology and Management of the Newborn.* 7th ed. Lippincott, Williams, and Williams; 2016; 902 Fig 43.17.

TPO receptor gene, which results in near absence of megakaryocytes in the bone marrow. Treatment is hematopoietic cell transplant.
- Wiskott-Aldrich syndrome is an autosomal recessive disorder characterized by thrombocytopenia with small platelets, eczema, and immunodeficiency.
- Bernard-Soulier syndrome is an autosomal recessive syndrome characterized by mild thrombocytopenia with large platelets with impaired function.
- May-Hegglin anomaly is an autosomal recessive condition characterized by mild to moderate thrombocytopenia with large platelets and often leukocyte inclusion bodies.

THROMBOCYTOSIS

- Thrombocytosis is generally defined as a platelet count > 450,000/μL; normative data based on chronological and gestational age is available. Thrombocytosis can be primary or secondary.
  - Primary thrombocytosis is rare and is due to mutations in the JAK2 protein.
  - Secondary, or reactive, thrombocytosis is much more common and can be associated with conditions including infection, inflammation, anemia, vitamin E deficiency, and iron deficiency.
- Thrombocytosis is generally well tolerated in neonates and does not necessitate specific treatment to lower platelet levels.

The Coagulation System

- Coagulation factors are synthesized by the fetus and do not cross the placenta.
- There are well-described gestational-age-dependent differences in the quantity and function of hemostasis proteins.
- Comparison of neonatal and adult levels of coagulation factors is shown in Table 52.1.
- Bleeding disorders can present with purpura, petechiae, ecchymosis, and mucosal bleeding, or as prolonged bleeding from heel stick or circumcision.
  - Bleeding in an otherwise well term infant suggests an inherited bleeding disorder or immune-mediated thrombocytopenia.
  - Bleeding in an ill neonate more likely due to an acquired hemostatic disorder.

Inherited Coagulation Disorders

HEMOPHILIA

Overview

- Hemophilia is the most common inherited bleeding disorder to present in the neonatal period. Hemophilia is due to deficiency of factor VIII (hemophilia A) or factor IX (hemophilia B, also known as Christmas disease).
  - Both forms of hemophilia are X-linked recessive, however 30%–50% of mutations in factor VIII are due to de novo mutations.

SYMPTOMS, DIAGNOSIS, AND TREATMENT

- Patients with hemophilia will have a prolonged aPTT (activated Partial Thromboplastin Time) on routine coagulation testing. Definitive diagnosis requires measurement of factor levels.
  - Hemophilia A can be diagnosed at birth. Mild cases of hemophilia B can be difficult to diagnose in neonates, as factor IX levels are lower in neonates than older children and adults.

Table 52.1 Differences in Coagulation Tests and Blood Factor Levels in Neonates Compared to Adults

Component	Neonatal Versus Adult Level	
Primary hemostasis	↔	Platelet count
	↑	vWF
Coagulation factors	↓	FII, FVII, FIX, FX
	↓	FXI, FXII
	↓ to ↔	FV, FXIII
	↔	Fibrinogen
	↑	FVIII
Anticoagulant factors	↓	TFPI, AT, PC, PS
	↑	α_2 M
Fibrinolysis	↓	Plasminogen
	↔ to ↑	PAI

α_2 M, α_2-Macroglobulin; *AT,* antithrombin; *F,* factor; *PAI,* plasminogen activator inhibitor; *PC,* protein C; *PS,* protein S; *TFPI,* tissue factor pathway inhibitor; *vWF,* von Willebrand factor.

(Hoffman R, Benz E, Silberstein L, Heslop H, Weitz J, Anastasi J, Salama M, Abutalib S. Elsevier. 2018. Adapted from Chapter 150. Disorders of Coagulation in the Neonate.)

- Approximately one-third of infants with hemophilia will have clinically significant bleeding in the neonatal period and are at high risk for intracranial hemorrhage. Screening of affected infants for intracranial hemorrhage is recommended.
- Treatment of hemophilia is factor replacement.

VON WILLEBRAND DISEASE

Overview

- von Willebrand disease (VWD) is most common inherited bleeding disorder, diagnosis rarely made in newborn period because von Willebrand factor (VWF) levels are increased in the neonatal period (see Table 52.1).
  - VWD is generally inherited in an autosomal dominant manner, although recessive inheritance has been described for some subtypes.
  - Type 3 VWD is the rarest subtype, but is the most likely subtype to present in the neonatal period and can be difficult to distinguish from severe hemophilia A.

TREATMENT

- Moderate to severe bleeding in neonatal period treated using plasma-derived VWF-containing factor VIII concentrate. DDAVP (desmopressin) sometimes used in older children to increase VWF levels, but is contraindicated in neonates due to risk of hyponatremia.

Acquired Coagulation Disorders

VITAMIN K DEFICIENCY BLEEDING

Overview

- Vitamin K is an essential cofactor required for the carboxylation of factors II, VII, IX, and X.
- Neonates are at high risk for vitamin K deficiency bleeding (VKDB) because they have poor vitamin K stores at birth and the bacteria that produce vitamin K have not yet colonized the intestinal track.

SYMPTOMS

- Early VKDB: presents in first 24 hours of life, usually associated with maternal medications such as warfarin, isoniazid, or antiepileptics. Early VKDB can result in skin and scalp hemorrhage, as well as severe intracranial, intra abdominal, and intrathoracic hemorrhage.
- Classic VKDB: Presents from dol 2–7. It occurs more commonly in breastfed infants, although many cases are idiopathic. Classic VKDB generally presents as bruising and bleeding from the umbilical cord.
- Late VKDB: Occurs after two weeks of age and is frequently associated with intracranial hemorrhage. Infants at risk for late VKDB include exclusively breastfed babies who did not receive the vitamin K shot, infants with cholestatic liver dysfunction, and infants with chronic intestinal malabsorption.

DIAGNOSIS AND TREATMENT

- Prolongation of the PT (Prothrombin Time) is the earliest laboratory evidence of vitamin K deficiency. If the deficiency is not corrected, the aPTT eventually becomes prolonged.
- A single intramuscular injection of vitamin K after birth is sufficient to prevent bleeding from vitamin K deficiency and is the standard of care in the United States. Oral vitamin K is not as efficacious as the IM preparation. Breastmilk is not a good source of vitamin K, and infants who are exclusively breastfed but do not receive IM vitamin K are at risk for VKDB.

DISSEMINATED INTRAVASCULAR COAGULATION (DIC)

Overview

- DIC is characterized by bleeding and microvascular thrombosis due to secondary activation of the coagulation cascade from tissue damage due to an underlying disease process.
- Neonates are more susceptible to DIC than older children and adults due to lower levels of antithrombin and protein C (see Table 52.1).
- DIC has been associated with numerous disease processes. Sepsis, NEC, and perinatal asphyxia are commonly associated with DIC in neonates.

SYMPTOMS, DIAGNOSIS, AND TREATMENT

- DIC results in the consumption of both platelets and coagulation factors. Although no single laboratory test is diagnostic for DIC, laboratory findings consistent with DIC include thrombocytopenia, prolonged PT and aPTT, positive D-dimers, fibrin degradation products, and low fibrinogen. When interpreting these laboratory values, it is important to use gestational age appropriate normative values.
- Successful treatment of DIC is dependent on identifying and treating the underlying cause. Supportive treatment includes transfusion of platelets, FFP, and cryoprecipitate. In patients with severe thrombosis, such as

arterial or venous thromboembolism or purpura fulminans, cautious use of unfractionated heparin may be considered.

Neonatal Deep Vein Thrombosis (DVT)

OVERVIEW

- The majority of cases of DVT in neonates are associated with central line use.
- Symptoms of DVT depend on its location and can include catheter dysfunction, limb or face swelling, effusion, and SVC (superior vena cava) syndrome.
- Persistent thrombocytopenia without another etiology is suggestive of DVT.

DIAGNOSIS AND TREATMENT

- DVT is typically diagnosed using Doppler ultrasonography.
- Treatment of DVT is complex; many cases can be managed with supportive care. Clots that are large, occlusive, or show evidence of extension may require anticoagulation therapy with low molecular weight heparin (LMWH), generally for 6–12 weeks.

Neonatal Renal Vein Thrombosis

OVERVIEW

- Renal vein thrombosis (RVT): most common non-catheter-related thrombotic event in neonates.
- Risk factors include gestational diabetes, prematurity, perinatal asphyxia, and congenital heart disease.

SYMPTOMS AND DIAGNOSIS

- The classic triad for diagnosis of RVT is thrombocytopenia, hematuria (macro- or microscopic), and a palpable flank mass. Acute renal injury and hypertension are also common. Definitive diagnosis is made by Doppler ultrasonography.

TREATMENT

- Treatment includes serial monitoring for extension of thrombosis. Anticoagulation is indicated for bilateral RVT or unilateral RVT that extends into the IVC (inferior vena cava).

Neonatal Arterial Thrombosis

OVERVIEW

- Arterial thrombosis is a rare, potentially life-threatening event that is most often associated with umbilical artery catheters.

SYMPTOMS, DIAGNOSIS, AND TREATMENT

- Affected infants may be asymptomatic or can have diminished pulses, catheter dysfunction, hypertension, renal dysfunction, and/or mesenteric ischemia.
- Diagnosis is made by Doppler ultrasound.
- Treatment includes removal of line and anticoagulation therapy. For cases resulting in severe limb or organ ischemia, consider thrombolytic therapy or thrombectomy.

Neonatal Purpura Fulminans

OVERVIEW

- Neonatal purpura fulminans (PF) is a coagulation disorder characterized by cutaneous purpuric lesions and DIC.
- PF is due to inherited or acquired deficiency of protein C or protein S. Acquired PF is more common than inherited forms, is often secondary to sepsis, and has an association with GBS (group B strep) infection.
- PF can be associated with severe complications including cerebral thrombosis, renal vein thrombosis, vitreous hemorrhage retinal detachment, and necrosis resulting in loss of limb.

DIAGNOSIS AND TREATMENT

- Diagnosis is largely clinical. Infants with PF have a characteristic rash that begins as dark red lesions that progressively become dark purple or black and indurated. The lesions occur most commonly at sites of trauma, such as IV sticks.
- Inherited forms of PF are diagnosed by a combination of undetectable levels of protein C or protein S and genetic studies of either the parents or the affected child.
- Treatment for PF includes replacement of proteins C and S with fresh frozen plasma or with protein C concentrate for patients with protein C deficiency.
- Infants with PF due to inherited deficiencies in protein C or S require anticoagulation.
- For acquired PF cases, it is imperative to treat the underlying cause.

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Questions

1. Neonatal thrombocytopenia associated with pre-eclampsia typically
   a. Requires platelet transfusion
   b. Lasts 2–4 months
   c. Reaches a nadir within 2–4 days
   d. Is often associated with significant bleeding

2. Which of the following are true about neonatal alloimmune thrombocytopenia (NAIT)?
   a. It is associated with maternal thrombocytopenia.
   b. It is due to maternal antibodies against fetal platelet antigens.
   c. It does not cause severe thrombocytopenia.
   d. Random donor platelets are not an effective treatment.

3. Neonatal autoimmune thrombocytopenia is
   a. Associated with maternal thrombocytopenia
   b. Due to maternal antibodies against the fetal platelet antigen HPA1a
   c. Not associated with severe thrombocytopenia
   d. Not effectively treated with random donor platelets

4. DIC is more common in neonates than older children and adults because
   a. Neonates have lower von Willebrand levels than adults
   b. Coagulation factors pass from the mother to the fetus
   c. Neonates have lower platelet levels than adults
   d. Neonates have lower levels of antithrombin and protein C

5. Early onset vitamin K deficient bleeding (VKDB) is associated with
   a. Oral vitamin K
   b. Breastfeeding
   c. Maternal medications
   d. Malabsorption

6. Late onset vitamin K deficient bleeding (VKDB) is associated with
   a. Intracranial hemorrhage
   b. Mucosal bleeding
   c. Umbilical cord bleeding
   d. Excessive bleeding from circumcision

7. The classic triad of renal vein thrombosis is:
   a. thrombocytopenia, hematuria, and a palpable flank mass
   b. thrombocytopenia, high blood pressure, and hematuria
   c. high blood pressure, hematuria, and a palpable flank mass
   d. hematuria, anemia, and thrombocytopenia

8. Unexplained thrombocytopenia in an infant with a central line should prompt an evaluation for
   a. Fanconi anemia
   b. DVT
   c. Wiskott-Aldrich syndrome
   d. NAIT

9. Infants with thrombocytopenia absent radii (TAR)
   a. Often have anemia and immune deficiency
   b. Have improvement in platelet levels over the first year of life
   c. Lack thumbs
   d. Have mild thrombocytopenia

10. Neonatal purpura fulminans (PF) is due to all of the following except:
    a. inherited deficiency of protein C
    b. inherited deficiency of protein S
    c. group B streptococcus-associated sepsis
    d. central line placement

53 Transfusion Therapy in Neonates

JEFFREY R. ANDOLINA

Transfusions of blood products are common in neonates. The majority of extremely-low-birth-weight neonates will require at least one transfusion. It is critical to understand indications for transfusions, including symptoms and abnormal laboratory values that would trigger intervention. Evidence-based data on transfusion indications are relatively scarce, so expert consensus often drives institutional protocols. While transfusions are generally considered safe, there are risks and complications that can be caused by transfusion.

Transfusion Therapy in Neonates

BASIC INFORMATION

- Blood donors are the sole source of transfusion products.
- Whole blood is processed and divided into multiple separate blood products.
  - Packed red blood cells
  - Platelets
  - Fresh frozen plasma (FFP)
  - Cryoprecipitate
  - Granulocytes (used only very rarely)
- Complications may occur with any of the above blood products.
  - Critically ill neonates are thought to be more likely to develop complications.

Packed Red Blood Cells

BASIC INFORMATION

- Packed red blood cells (PRBC) are commonly called "blood" transfusions.
- PRBC are stored refrigerated, with an anticoagulant/preservative such as CPD/CPDA-1 (citrate-phosphate-dextrose/citrate-phosphate-dextrose-adenine).
- Donor PRBC must be compatible with the patient by ABO group (O, A, B, or AB) as well as Rh type (positive or negative).
  - Type and screen will determine the patient's ABO and Rh type.
  - Type and cross or crossmatch consists of actual mixing of a tiny amount of donor and recipient PRBC.
  - In emergent situations, O negative PRBC will always be compatible.
- PRBC are most commonly given as "simple" transfusions.
  - PRBC are dosed by volume, typically 15 mL/kg of PRBC given over 4 hours.
- Alternatively, in rare instances, exchange transfusions can be performed, in which partial or complete volume of the patient's blood is removed at the same time that the transfused blood is given. Sometimes a double volume exchange transfusion is performed as part of management for hyperbilirubinemia to avoid bilirubin encephalopathy.
  - In addition to exchange transfusion, ECMO (extracorporeal membrane oxygenation) is another setting in which large volume PRBC is used.
- In most institutions, neonates receive fresh PRBC, meaning the most recently donated packed red blood cell units.
  - Often this means the blood was collected from the donor less than ~14 days.
  - Data showing efficacy of this approach is controversial.
- For neonates, PRBC units are leukocyte-reduced to reduce the risk of infection and reactions.
- For neonates, PRBC units are often irradiated, in addition to leukocyte-reduced, to reduce the risk of transfusion-associated graft versus host disease.
  - If not irradiated, some centers may use CMV-negative PRBC.
- Blood relatives are very strongly discouraged for neonatal patients, as blood from a relative holds no advantages and has multiple additional risks.
  - Neonates can make an immune response to similar antigens in blood products.
  - Higher risks of transfusion-associated graft versus host disease.
    - Irradiation of blood products will completely remove the risk of transfusion-associated graft versus host disease.

CLINICAL INDICATIONS FOR PACKED RED BLOOD CELLS (PRBC)

- There is no exact laboratory value that would trigger a PRBC transfusion, as the decision to transfuse should most often be based on the clinical status and symptoms of the patient.
- However, studies have generally shown that a lower hemoglobin trigger (7.0 g/dL) was as safe and effective as a higher or more conservative value (8.0 or 9.0 g/dL). A large randomized trial in pediatric intensive care units showed that hemoglobin trigger of 7.0 g/dL (in comparison to 9.5 g/dL) is safe, without increased adverse events (Lacroix et al., 2007).
  - Transfusing PRBC for hemoglobin <7.0 g/dL would be reasonable.
  - For patients who have additional complications or surgeries, a higher threshold may be required.

- Symptoms and clinical indications that would trigger need for PRBC include:
  - Acute blood loss.
  - Anemia with anticipated blood loss during surgery.
  - Significant/unexplained tachycardia or tachypnea.
  - Significant/unexplained apnea or bradycardia.
  - Hemodynamic instability.

Platelets

BASIC INFORMATION

- Platelets may be collected by two methods from blood donors.
  - Derived from whole blood units, called random donor platelets.
  - Collected through apheresis from donor, called apheresis donor platelets.
  - Many centers prefer apheresis donor platelets, if available.
- Collected platelets are stored in plasma, at room temperature, and under agitation, and thus only have a storage half-life of a few days.
- Platelets have to be ABO compatible between donor and patient.
- Platelets are dosed by volume; typically 10 mL/kg of platelets are given over 1 hour.

CLINICAL INDICATIONS FOR PLATELETS

- Decision to transfuse should take into account etiology of thrombocytopenia, clinical status, and symptoms of the patient.
- Active bleeding should trigger consideration of platelet transfusion if thrombocytopenic.
- Generally, neonates kept at a higher platelet threshold than are older children or adults.
  - This is due to increased risk of major bleeding (e.g., intraventricular hemorrhage [IVH]) in very young and premature infants, particularly within first week of life.
- Historically, neonates have often been transfused with platelets to maintain a platelet count >50,000/μL.
  - In stable neonates, many centers are now lowering that transfusion cutoff to 20,000–30,000/μL.
- Antibody-mediated thrombocytopenia is very common in neonates:
  - NAIT (neonatal alloimmune thrombocytopenia) and maternal ITP (immune thrombocytopenic purpura) are both common causes of thrombocytopenia in this age group.
  - Platelet transfusions are used for these conditions; however, often the increase in platelet count is small or short-lived.
  - IVIG (intravenous immunoglobulin) 1 gram/kg for 1–3 days is a safe and effective therapy for antibody-mediated thrombocytopenia.
  - Steroids are no longer recommended given increased infectious risks.
  - For patients with severe NAIT, washed maternal platelets are considered the gold standard, if available.
- Thrombocytopenia may also be from decreased production or due to consumption from infection or disseminated intravascular coagulation (DIC).
- Patients may require a higher platelet threshold (e.g., >50,000–100,000/μL) if undergoing major surgery or ECMO.

Fresh Frozen Plasma (FFP)

BASIC INFORMATION

- FFP is the liquid component of blood and consists of all of the clotting factors, including fibrinogen.
- Transfused FFP also should be ABO compatible between donor and patient.

CLINICAL INDICATIONS FOR FRESH FROZEN PLASMA

- The decision to transfuse FFP should take into account clinical status, symptoms.
- FFP is also dosed by volume, typically 10 mL/kg.
- FFP is typically given to critically ill infants who have persistent bleeding secondary to DIC.
  - Patients with continued bleeding and oozing despite PRBC and platelets may benefit from FFP infusion.
- There are no documented laboratory thresholds for FFP infusion; vary by the risk or degree of bleeding, gestational age, and clinical status.
  - Most patients who receive FFP will have markedly abnormal coagulation studies (which vary with the gestational age of the neonate), with a very high prothrombin time (PT)/international normalized ratio (INR) and aPTT (activated partial thromboplastin time).

Rare Blood Products

BASIC INFORMATION

- Cryoprecipitate consists of fibrinogen and only a few of the clotting factors.
- Cryoprecipitate is generally considered to be the blood product richest in fibrinogen.
  - Neonates with persistent, refractory hypofibrinogenemia may benefit from cryoprecipitate.

COMPLICATIONS FROM TRANSFUSIONS

- The majority of neonates do well with transfusions.
- Although relatively uncommon, multiple risks and complications exist with the transfusion of any blood product.
- Hemolytic transfusion reaction:
  - Hemolytic transfusion reactions occur when patients receive ABO-incompatible blood; most commonly, this occurs when patients with type O blood receive an incorrect A, B, or AB type blood.
  - This is rare, and when it occurs, is typically due to clerical error.
  - Massive hemolysis occurs, and symptoms include fever, hypotension, and hematuria.
  - This is prevented by transfusing only ABO compatible blood products and using a type and cross (crossmatch) with every PRBC transfusion.

- Patients may also have a nonhemolytic transfusion reaction, which is thought to be antibody-mediated.
- Infectious transmission from blood products:
  - Despite significant donor screening and testing, infection transmission through blood products may rarely occur.
  - Historically, hepatitis B and C and human immunodeficiency virus (HIV) were most common and most concerning.
    - Current risks of hepatitis or HIV transmission are now less than 1 in 500,000 (hepatitis) and less than 1 in 1 million (HIV).
    - Still, these tiny risks should be discussed with family prior to transfusion.
  - CMV transmission, which is rare, is a concern in neonatal period.
    - Irradiation or CMV-negative blood products should eradicate risk of CMV transmission.
  - Other very rare infectious transmission remains theoretically possible.
  - Infections are prevented mainly by leukocyte depletion, which is done for all PRBC products in neonates.
  - Overall, blood products in the United States are extraordinarily safe, with absolute risk of infectious transmission <1 in 100,000.
  - Very rarely, there can be bacterial contamination of a blood product, which can cause sepsis and may also present as new fever during or soon after transfusion.
- Transfusion related acute lung injury (TRALI):
  - TRALI is now the most common cause of morbidity from transfusions.
  - TRALI is more common when high numbers of transfused blood products are given quickly.
  - Likely underrecognized and underreported in neonates.
  - Symptoms of TRALI include the following:
    - Acute onset of symptoms, typically within 6 hours of transfusion.
    - Respiratory distress/ shortness of breath.
    - Hypoxia.
    - Pulmonary infiltrates/edema on chest x-ray.
    - Not due to a cardiac etiology.
  - Pathophysiology thought to be due to antibody mediated recipient neutrophil activation.
  - Management of TRALI consists of discontinuing blood product (if still infusing) and good supportive care and respiratory support.
- Transfusion associated cardiac overload (TACO):
  - TACO may also cause significant morbidity after transfusions.
  - TACO more common when high numbers of blood products given quickly.
  - Likely underrecognized and underreported in neonates.
  - Symptoms of TACO include the following:
    - Acute onset of symptoms, typically during transfusion.
    - Respiratory distress/shortness of breath.
    - Hypertension.
    - Edema and fluid overload.
    - Excessively positive fluid balance.
  - Pathophysiology thought to be due to fluid overload.
  - Management of TACO consists of diuretics, slowing down of blood transfusions (if able), and good supportive care and respiratory support.

Suggested Readings

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Questions

1. A 7-day-old ex-28-week premature neonate has multiple medical problems and is found to be severely anemic, with hemoglobin of 6 g/dL. There is no evidence of hemolysis and the reticulocyte count is 1%. Your team plans a packed red blood cell transfusion for this patient. Which of the following red blood cell processing interventions by the blood bank would NOT be required for this patient?
   a. Type and cross to ensure ABO compatible blood
   b. Leukocyte-depleted PRBC to prevent viral infection transmission
   c. Irradiation to prevent CMV transmission
   d. Washing of the PRBC to prevent allergic reaction

2. A 4-day-old neonate with immunodeficiency has had significant blood loss after a major surgery. She now requires multiple transfusions of packed red blood cells. Her blood type is O positive. She has multiple family members offering to personally donate blood to her. Which of the following would be the most preferred donor?
   a. Random donor, blood type O positive
   b. Random donor, blood type A positive
   c. Patient's uncle, blood type O positive
   d. Patient's mother, blood type O positive

3. A 4-week-old neonate remains critically ill with multiple medical problems currently on oxygen by nasal cannula. After finishing a platelet transfusion, he suddenly develops multiple new symptoms, including hypoxia and increasing oxygen requirement, and low-grade fever. Chest x-ray shows new, widespread pulmonary edema. Cardiac silhouette is normal in size. What is the most likely etiology of this patient's reaction?
   a. Hemolytic transfusion reaction from ABO incompatible platelets
   b. CMV transmission from the platelet transfusion
   c. Transfusion related acute lung injury (TRALI)
   d. Transfusion associated circulatory overload (TACO)
   e. Sepsis from contaminated platelets

54 Solid Tumors and Leukemias

JEFFREY R. ANDOLINA

Cancer in neonates and young infants is quite rare. The most common malignancies in neonates include teratomas and neuroblastoma, though many others can occur. Diagnosis is often made on prenatal ultrasound, though providers must have a high index of suspicion given varying presenting symptoms and signs. It is presumed most malignancies in this age group have a genetic basis, with causative events occurring in utero. Germline mutations and cancer predisposition genes and syndromes are also seen in this age group. Diagnosis is often confirmed by biopsy, and treatments include surgery as well as systemic chemotherapy. Although neonates are a vulnerable population and suffer significant toxicity with therapies, the majority of patients can be successfully treated. See Table 54.1 for a summary of common neonatal tumors.

Congenital Leukemia

BASIC INFORMATION

- Congenital leukemia is very rare and typically originates in utero.
- Acute myeloid leukemia (AML) is the most common congenital leukemia.
- Acute lymphoblastic leukemia (ALL) is the second most common.
  - Rarely, juvenile myelomonocytic leukemia (JMML) may occur.
- Down syndrome major risk factor, causing increased incidence of both AML and ALL.
- Transient abnormal myelopoiesis (TAM), formerly called transient myeloproliferative disorder (TMD), form of transient leukemia only seen in neonates with Down syndrome.
  - Occurs in about 10% of neonates with Down syndrome.
  - Occurs in the first week of life, presents with leukemia cells in the blood and may have other symptoms of leukemia.
  - Observation is recommended as >80% of neonates with TAM will show spontaneous regression.
  - If a neonate with Down syndrome has TAM, that child will carry a 25% absolute risk of the development of AML by 4 years of age.

CLINICAL PRESENTATION

- Physical signs and symptoms
  - Hepatosplenomegaly is very common.
  - Skin nodules (consisting of leukemia cells, called leukemia cutis) are present in 60%, and this is unique in this age group.
  - Respiratory distress may occur from leukemia involvement in the lungs.
  - Central nervous systems (CNS) symptoms from stroke or bleed also possible.
  - Classic symptoms of leukemia including fevers, petechiae, bruising, and lethargy.

DIAGNOSIS AND EVALUATION

- Laboratory evaluation including complete blood count (CBC) reveals the diagnosis.
  - Leukemia is characterized by elevated WBC count, blasts in the periphery, anemia, and thrombocytopenia.
  - Peripheral blood smear evaluation and consult to pediatric hematology/oncology.
  - Comprehensive chemistries, phosphorus, uric acid, and lactate dehydrogenase (LDH) should be obtained.
- Neonates typically have very high WBC counts and very often have hyperleukocytosis (WBC $>100 \times 10^9$ cells/L).
  - Leukemias tend to be very aggressive and rapidly growing.
- Diagnosis is confirmed by bone marrow aspiration.
  - Flow cytometry will classify the acute leukemia and cell of origin.
  - Cytogenetics will evaluate for any translocations or chromosomal abnormalities in the leukemia population.
- Infant ALL and AML often characterized by an MLL (mixed lineage leukemia) genetic translocation; the MLL gene is on chromosome 11q23 and has multiple binding partners.

TREATMENT AND PROGNOSIS

- Congenital leukemia is very difficult to treat and generally carries a poor prognosis, with cure rates in range of 20%.
- Chemotherapy may be given for therapy, and treatment regimens are very intense for the aggressive acute leukemias seen in this age group.
  - Neonates suffer much more toxicity from chemotherapy than do older children.
  - Lumbar puncture (LP) with intrathecal chemotherapy (for treatment and prophylaxis) is used as well.
  - Radiation is generally omitted given the severe late effects of this agent.

Table 54.1 Common Neonatal Tumors

Tumor	Benign or Malignant	Clinical Features	Lab and Imaging Characteristics	Treatment and Outcome
Congenital leukemia; AML > ALL	Malignant	Skin nodules; hepatosplenomegaly; bruising/bleeding	Elevated WBC count, anemia, thrombocytopenia; bone marrow and lumbar puncture	Chemotherapy; very poor prognosis
Transient abnormal myelopoiesis (TAM)	Malignant but transient	Symptoms similar to leukemia; only seen in Down syndrome	Elevated WBC count	Observation; most resolve with time; 25% future risk of AML
Langerhans cell histiocytosis (LCH)	Clonal; ± malignant	Scaly, eczematous rash; lytic bone lesions; multisystem involvement possible	Biopsy confirms histiocyte proliferation; cells stain positive for CD1a and CD207	Single-system disease excellent prognosis; multisystem disease requires chemotherapy
Teratoma	90% benign; 10% malignant	Large midline mass, typically in sacrococcygeal region	AFP and beta-hCG	Surgical resection; excellent outcomes
Hemangiomas	Benign	Varied and dependent upon size and location; associations with syndromes and internal hemangiomas	If large size (>5 cm) or large number (>5), perform additional imaging	Natural history is proliferation in infancy followed by regression; propranolol is first-line treatment
Neuroblastoma	Malignant	Adrenal mass; hepatomegaly; blue skin nodules; stage IV-S (M-S) common in neonates	Biopsy required; urine HVA/VMA; MIBG scan	Observation; prognosis is excellent in neonates; spontaneous resolution
Cardiac rhabdomyomas	Benign	Cardiac mass(es); strong association with tuberous sclerosis (TS)	Surgical resection if unstable; brain MRI and genetic testing for TS	Observation if able; regression; long-term care with TS
Wilms tumor	Malignant	Renal mass	Resection/nephrectomy	Excellent prognosis

AFP, Alpha-fetoprotein; *ALL,* acute lymphoblastic leukemia; *AML,* acute myeloid leukemia; *beta-hCG,* beta-human chorionic gonadotropin; *HVA,* homovanillic acid; *MIBG,* metaiodobenzylguanidine; *MRI,* magnetic resonance imaging; *VMA,* vanillylmandelic acid; *WBC,* white blood cell.

Langerhans Cell Histiocytosis

BASIC INFORMATION

- Langerhans cell histiocytosis (LCH) is the preferred term for a group of disorders that includes histiocytosis X, eosinophilic granuloma, and other terms.
- LCH is a clonal disorder that results in proliferation of histiocytes.
- Classic pathology includes the "tennis-racket" shaped organelles called Birbeck granules.
  - Cells stain positive for CD1a and/or CD207 (Langerin).
- LCH presentation is varied and can be a single-system or multisystem disorder.
  - Bone and skin are the most commonly affected organs.
  - Less commonly affected organs: liver, spleen, lungs, bone marrow, and CNS.
  - Neonates and infants more likely to have multisystem disease than older children.

CLINICAL PRESENTATION

- Physical signs and symptoms
  - Skin involvement and cutaneous lesions are very common presentations of LCH in neonates.
  - Rash is typically dry and scaly and not responsive to topical therapies.
    - Appearance similar to severe "cradle cap."
    - May also appear eczematous or include colored papules.
  - Additional signs can occur with other organ involvement, including bruising, hepatosplenomegaly, and respiratory distress.

DIAGNOSIS AND EVALUATION

- Diagnosis is confirmed by biopsy of affected organ; biopsy is required.
  - Any severe, scaly rash not responding to topical therapy requires a skin biopsy.
  - LCH confirmed by CD1a or CD207 (Langerin) positivity.
  - BRAF mutations may be seen in LCH, and BRAF inhibitors are a possible targeted therapy in refractory cases.
- Laboratory evaluation may reveal abnormalities depending on the organs affected.
  - CBC should be performed and may reveal cytopenias if bone marrow is affected.
  - Chemistries, liver function tests, and coagulation studies with fibrinogen also recommended and may be abnormal if liver involvement.
  - Erythrocyte sedimentation rate (ESR), lactate dehydrogenase (LDH), and uric acid should also be performed.
  - Urinalysis for specific gravity and osmolality is recommended, as diabetes insipidus (DI) is a possible complication of CNS-LCH.
  - Bone marrow aspiration and biopsy considered if abnormalities on CBC.
  - Single-system LCH may have normal laboratory findings.

- Imaging is required to evaluate for bone and additional organ involvement.
  - Skeletal survey (x-ray of all bones) is required to evaluate for bone lesions.
    - LCH of bone typically presents as lytic lesions, associated granulomas may also occur.
  - Abdominal ultrasound to evaluate for liver and spleen involvement.
  - CNS imaging (magnetic resonance imaging [MRI] brain) if there are symptoms or signs of CNS involvement.
    - Additional imaging related to signs and symptoms (e.g., PET scan).

TREATMENT AND PROGNOSIS

- The management of LCH varied and dependent upon disease location and disease spread.
- Single-system LCH in skin or bone may be managed with observation alone or surgical resection alone.
  - LCH remains poorly understood, and mild cases may not need systemic therapies.
- Multisystem LCH (or multifocal bone LCH) will require systemic therapies.
- Systemic treatments consist of chemotherapy.
  - Steroids (prednisone) and vinblastine remain the mainstay of therapy.
  - Refractory patients may require more intensive chemotherapeutic agents.
  - BRAF inhibitor targeted therapy may also be considered.
- Prognosis is excellent for single-system LCH.
- Multisystem LCH in the infant age group carries a more guarded prognosis and requires intensive chemotherapy for optimal management.
- Diabetes insipidus (DI) may occur at presentation or as a late effect after LCH involving the CNS or "CNS-risk" bones.

Neonatal Teratoma

BASIC INFORMATION

- Teratomas are the most common tumor seen in neonates.
- The vast majority (90%) of teratomas are benign, though about 10% will be malignant (and have the capacity to metastasize) in the neonatal age range.
- Teratomas arise from primitive germ cells.
  - Mature teratomas are benign.
  - "Immature" teratomas may have malignant features.
  - A small percent of mature teratomas undergo malignant transformation over time.
- Malignant germ cell tumors may have elements of yolk sac tumor and/or choriocarcinoma.
  - These tumors secrete alpha-fetoprotein (AFP) and beta-human chorionic gonadotropin (beta-hCG).
- In neonates, teratomas occur in the midline.
- Most common location is sacrococcygeal region, less common location is mediastinum.
  - Sacrococcygeal teratomas are more common in girls.

CLINICAL PRESENTATION

- The majority of teratomas are now diagnosed before birth on prenatal ultrasound.
  - Large sacrococcygeal tumors are an indication for cesarean section.

Physical Signs and Symptoms

- Physical exam reveals a mass or extruding tumor in the genitourinary or anal region.
- Sacrococcygeal teratomas present as a mass between the anus and coccyx.
  - Tumors will often have external extension and can be very large.
  - Teratomas may be very vascular, and significant bleeding can occur.
  - Significant neurologic symptoms are uncommon.
- Respiratory distress from teratoma as mediastinal mass a less common presentation.

DIAGNOSIS AND EVALUATION

- Diagnosis is confirmed by pathology.
- Laboratory evaluation should include tumor markers, which are alpha-fetoprotein (AFP) and beta-human chorionic gonadotropin (beta-hCG).
  - LDH is also obtained.
  - CBC would be considered if concern for anemia from bleeding.
- Mature teratomas do NOT produce any AFP or beta-hCG.
- However, teratomas with immature or germ cell components will typically produce AFP ± beta-hCG.
- If teratoma produces these tumor markers, they can be helpful in monitoring for recurrence.
- Newborns have an average AFP level of 41,000 ng/mL, which decreases to the normal older child and normal adult range of 0–7 ng/mL by about 1 year of age.
- Imaging is extremely important to assess extent of tumor and for surgical planning.
- Ultrasound of the abdomen and pelvis is often done first line.
- MRI to determine extent of mass and involvement in surrounding structures.
  - Computed tomography (CT) may also be used though is less desired due to large amount of radiation exposure.
- If pathology shows completely mature (benign) teratoma, no additional imaging needed.
- If malignant elements are identified on pathology, imaging of the chest recommended to assess for metastases.

TREATMENT AND PROGNOSIS

- Surgical resection is the mainstay of therapy.
  - The majority of teratomas are able to be fully resected.
  - Achieving negative margins can be difficult/impossible in the sacrococcygeal region. Coccyx is always surgically removed.
  - For the rare patient with metastatic disease, chemotherapy may be considered.
- Prognosis is excellent for teratomas in the neonatal period.

- Mature (benign) teratomas do not recur approximately 90% of the time.
  - If recurs, will only be local, typically treated with repeat resection.
- Immature or malignant teratomas are also treated with surgery.
- These patients must be followed more closely, as there is a higher chance of recurrence.
- Surveillance imaging (ultrasound versus MRI) and tumor marker (AFP ± beta-hCG) screening is recommended for approximately 5 years.

Hemangiomas

BASIC INFORMATION

- Infantile hemangiomas are the most common vascular tumor in children, affecting approximately 4%–5% of infants.
- Hemangiomas are benign.
- They typically occur on the skin, though can occur anywhere, including mucous membranes, airway, and internal organs.
- Hemangiomas have a classic natural history.
  - They are typically small/subtle at birth.
  - They proliferate over the first year of life.
  - After about the age of 12 months, they slowly involute over the next few years.
- Hemangiomas are associated with numerous syndromes.
  - PHACES syndrome (posterior fossa malformations, hemangioma, arterial/aortic abnormalities, cardiac defects, eye abnormalities, sternal cleft/supraumbilical raphe syndrome).
- Numerous other vascular malformations may occur in neonates and infants, including malformations of capillaries, veins, arteriovenous (AVM), and lymphatics.
  - Kaposi hemangioendothelioma.

CLINICAL PRESENTATION

- Physical signs and symptoms:
  - Hemangiomas may occur on any region of the outer skin or internal organ.
  - Thorough skin exam required.
  - Hemangiomas are typically red or pink and may be palpable.
    - Physical appearance is variable and heterogeneous.
    - Internal hemangiomas may be detected based on symptoms.
  - Hemangiomas may be very faint, small, or undetectable at birth (as this is often prior to the proliferative phase).

DIAGNOSIS AND EVALUATION

- Hemangiomas are typically diagnosed on clinical ground alone.
  - Biopsy typically not required.
- Laboratory evaluation may be limited.
  - CBC required to evaluate for thrombocytopenia or anemia.
  - Coagulation studies are typically performed to evaluate for disseminated intravascular coagulation (DIC).
- Kasabach-Merritt syndrome: very large hemangiomas may cause hematologic abnormalities, including thrombocytopenia and DIC.
- Imaging is not required for small and superficial hemangiomas.
- Very large or atypical lesions require imaging to evaluate for internal hemangiomas.
- MRI is typically the imaging modality of choice for internal hemangiomas.
  - Ultrasounds can also be considered.
  - Liver is a relatively common site for hemangiomas in infants.
- Single hemangiomas >5 cm on the face or back require imaging to exclude syndromes.
- Cutaneous hemangiomas greater than 5 cm require imaging to assess for visceral involvement.

TREATMENT AND PROGNOSIS

- Observation is the treatment of choice, as the vast majority of hemangiomas will regress spontaneously and will not require system treatment.
- Generally, surgery is avoided whenever possible given that the surgical scar is typically significant and often worse than the hemangioma itself.
  - Biopsies are also often avoided given the bleeding risk with hemangiomas.
- Medical management is often required for very large hemangiomas or for those in critical areas (airway, brain).
- Corticosteroids no longer commonly used due to side effects.
- Generally, a multidisciplinary approach is required for difficult hemangiomas, including dermatology, neonatology, interventional radiology, and pediatric hematology.
- Propranolol has developed into the first-line treatment for hemangiomas.
  - Intralesional steroids, vincristine, laser therapy, and embolization procedures have also been used.
- Sirolimus (also known as rapamycin) is an mTOR inhibitor that has shown excellent response rates in massive hemangiomas and other vascular anomalies.

Neuroblastoma

BASIC INFORMATION

- Congenital neuroblastoma is the most common malignancy of the newborn, and second most common tumor (second to teratoma, which is typically benign).
- Neuroblastoma arises from neural crest cells, and the most common site of primary tumor is the adrenal gland.
- Neuroblastoma is known for very unusual and unpredictable behavior, including spontaneous regression as well as rapid proliferation.
- Congenital and neonatal neuroblastoma is a very different disease than that of toddlers and older children.
  - Biologically, neonatal neuroblastoma is very likely to spontaneously regress or to differentiate into a benign tumor.

- Incidence of neuroblastoma may be increased with additional surveillance (prenatal ultrasounds or urine screening).
- It is assumed that the actual number of neuroblastomas is much higher than the number diagnosed, as many newborns have neuroblastomas that spontaneously regress and are never detected.

CLINICAL PRESENTATION

- Many neuroblastomas are now diagnosed by prenatal ultrasound.
- Adrenal mass, or mass along sympathetic chain (may be in neck, chest, abdomen, or pelvis).
- Physical signs and symptoms are related to site of primary tumor and any metastases.
  - Abdominal/retroperitoneal mass may or may not be palpable.
  - Hepatomegaly may indicate metastases to the liver.
  - Blue nodular lesions may reflect skin involvement of neuroblastoma.
  - Respiratory distress may result from a chest mass.
  - Additional masses in the chest, abdomen, pelvis, bones, or bone marrow may also be identified.
  - Neuroblastoma often has metastases at diagnosis.

DIAGNOSIS AND EVALUATION

- Tumor biopsy remains the gold standard to diagnose neuroblastoma.
  - Adrenal lesions that may be neuroblastoma typically require biopsy or resection.
- Tumor pathology is critical for staging and risk group determination for neonatal neuroblastoma.
  - Most neonates will have "favorable" histology.
  - Most neonates will not have the unfavorable N-MYC amplification.
- A complete laboratory evaluation is required for neuroblastoma.
  - CBC, chemistries, liver function tests, coagulation tests, LDH, ESR, uric acid.
- Urine catecholamines can aid in the diagnosis.
  - Neuroblastoma produces urine homovanillic acid (HVA) and vanillylmandelic acid (VMA).
  - Urine HVA and VMA may or may not be elevated in neonatal neuroblastoma.
- Imaging is required in the work-up of neuroblastoma.
  - CT or MRI of neck, chest, abdomen, and pelvis is required.
  - MIBG (metaiodobenzylguanidine) scan is a nuclear medicine scan specific to neuroblastoma that is required to evaluate for metastases.
- Neuroblastoma is staged based on extent of disease spread I through IV, with stage I localized to the structure of origin and stage IV with distant metastases.
- There is a special stage for neuroblastoma called IV-S (or M-S) that is specific to infants.
  - Stage IV-S (M-S) includes patients age <12 months, with metastatic disease to the liver, bone marrow, or skin.
  - The "S" stands for special and is associated with spontaneous regression.
  - The vast majority of stage IV-S patients do not require any therapy and can be observed; the tumor regresses over the coming months.
  - These patients still require close observation.
  - If patients become symptomatic (e.g., respiratory distress from hepatomegaly from liver involvement of neuroblastoma), they may also require chemotherapy.

TREATMENT AND PROGNOSIS

- Treatment of neonatal neuroblastoma dependent on disease stage, resulting risk group.
- Neonatal age itself is a very favorable prognostic factor, and the majority of newborns can be observed and do not require treatment.
  - Stage IV-S patients are typically observed (as noted earlier).
- For the unusual neonate with high stage or high-risk disease, intensive systemic therapies are required to cure neuroblastoma.
  - Surgical resection of primary tumor.
  - Very intensive chemotherapy.
  - Additional therapies include radiation therapy and antibody therapy.
- Overall, the prognosis of neonates with neuroblastoma is excellent, with the vast majority being cured of their disease.

Rhabdomyomas

BASIC INFORMATION

- Rhabdomyomas are benign tumors typically located in the heart.
- They arise from striated muscle and are typically cardiac in origin.
  - Rhabdomyomas are a separate entity from rhabdomyosarcomas (a malignant tumor occurring in children).
- Rhabdomyomas arise in utero.
- Most commonly involve the myocardium of the ventricles or interventricular septum; can occasionally involve the atria.

CLINICAL PRESENTATION

- Rhabdomyomas may present with multiple cardiac symptoms.
- Symptoms may occur in utero or in the newborn period.
- Symptoms may include hydrops fetalis, fetal arrhythmias, respiratory distress, heart failure, or sudden death.
- Many rhabdomyomas occur as multiple; typically small, rarely can be very large.
  - The natural course of rhabdomyomas is spontaneous regression over time.
- Rhabdomyomas are very strongly associated with tuberous sclerosis (TS).
  - Approximately 80% of patients with rhabdomyomas will have TS.
  - Conversely, approximately 50% of TS patients will have rhabdomyomas.

- Tuberous sclerosis (TS) is an autosomal dominant genetic disorder causing numerous benign tumors in multiple organ systems, most notably in the brain.
  - Benign tumors, or "tubers," may grow in the brain and cause numerous problems including seizures.
  - TS also predisposes patient to numerous other tumors in the kidneys, liver, lungs, eyes, and skin, including astrocytoma, carcinomas.

DIAGNOSIS AND EVALUATION

- Many rhabdomyomas are diagnosed on prenatal ultrasound or fetal echocardiography.
- Echocardiogram or MRI will often confirm the suspected rhabdomyomas.
  - Electrocardiogram (EKG) required to evaluate for arrhythmias.
- Biopsy is typically not done; surgery is reserved for very large rhabdomyomas in patients who require immediate intervention.
- If rhabdomyomas are suspected, full evaluation for TS is critical.
  - Including MRI of the brain.
  - Consider genetic testing for TS of patient and parents.

TREATMENT AND PROGNOSIS

- Most rhabdomyomas are small and may not require any intervention.
  - Spontaneous regression over time is expected.
- Large rhabdomyomas or those causing significant symptoms may require cardiac surgery, though this is generally reserved for those infants with life-threatening tumors.
- Everolimus, an mTOR inhibitor, shown to have initial activity in cardiac rhabdomyomas.
- For those patients identified to have TS, lifelong multidisciplinary subspecialty care and screening for additional tumors is required.

Wilms Tumor

BASIC INFORMATION

- Renal tumors are relatively uncommon in neonates.
- Congenital mesoblastic nephroma is benign, most common kidney tumor in neonates.
- Wilms tumor is malignant and is the second most common primary kidney tumor in neonates (though the most common kidney tumor in children overall).
  - Wilms tumor is also known as nephroblastoma.
  - Wilms tumor is associated with numerous syndromes including Beckwith-Wiedemann syndrome.
  - Low propensity to metastasize.

CLINICAL PRESENTATION

- Wilms tumor may present as an abdominal or flank mass on physical exam.
- May also cause hematuria or hypertension.

DIAGNOSIS AND EVALUATION

- The majority of Wilms tumors in neonates are diagnosed by prenatal ultrasound.
- Laboratory evaluation may be normal, though should include CBC, chemistries with BUN and creatinine, liver function tests, and coagulation studies.
- Urinalysis should be performed to evaluate for hematuria.
- Imaging is required for the diagnosis of kidney tumors.
  - Ultrasound often done first, important to evaluate for local vascular spread.
  - CT scan of the abdomen/pelvis is most commonly used to evaluate kidney tumors; MRI is an acceptable alternative in neonates.
- Diagnosis is confirmed on pathology after nephrectomy.
- Wilms tumor pathology is "triphasic," includes blastemal, stromal, tubular components.
  - Anaplasia is a sign of a more aggressive tumor.
- Wilms tumor, like all renal tumors, is staged I though V, with stage I being localized in an intact renal capsules, stage IV having distant metastasis, and stage V being bilateral.

TREATMENT AND PROGNOSIS

- Kidney tumors managed with immediate nephrectomy, even in neonatal period.
- Pediatric surgery consultation and surgical resection/nephrectomy is typically curative.
- Metastases are rare.
- Low-stage Wilms tumor patients may be treated with surgery alone.
- Higher-stage Wilms tumor patients may require adjuvant chemotherapy or radiation.
- Prognosis is excellent, and cure rates exceed 90% for all groups.

Suggested Readings

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Questions

1. A 1-day-old neonate in the newborn nursery develops respiratory distress. On exam, he is noted to have significant increased work of breathing, as well as hepatosplenomegaly. Skin exam is notable for both significant bruising as well as numerous erythematous nodules. What is the most likely diagnosis?
   a. Acute myeloid leukemia
   b. Leukemoid reaction
   c. Neuroblastoma
   d. Cardiac rhabdomyomas
   e. Langerhans cell histiocytosis (LCH)

2. A 4-day-old neonate is suspected to have Down syndrome. Vital signs are stable and she has no concerning symptoms or physical abnormalities other than stigmata of trisomy 21. Screening complete blood count (CBC) shows that the patient has a white blood cell count of 60×10^9 cells/L and the white blood cell differential consists of 65% myeloblasts. She also has mild anemia and moderate thrombocytopenia. Which of the following is the most likely diagnosis?
   a. Acute myeloid leukemia (AML)
   b. Acute lymphoblastic leukemia (ALL)
   c. Leukemoid reaction
   d. Transient abnormal myelopoiesis (TAM)
   e. Neuroblastoma

3. For the neonate described in the previous question, short-term and long-term management would consist of which of the following?
   a. Observation and no long-term follow up
   b. Observation followed by screening history, physical, and laboratory tests every 3 months for at least 4 years
   c. Chemotherapy for AML followed by screening history, physical, and laboratory tests every 3 months for at least 4 years
   d. Chemotherapy for AML followed by bone marrow transplant

4. A 2-month-old infant presents with persistent eczematous rash over his scalp and behind his ears. Eventually, skin biopsy is performed and shows abnormal histiocyte proliferation, with immunostains positive for CD1a and CD207. The pathologist strongly suspects Langerhans cell histiocytosis. What would your next step be in the management of this patient?
   a. CT scan of the chest, abdomen, and pelvis to evaluate for additional tumors
   b. Bone marrow aspiration and biopsy
   c. Skeletal survey
   d. Repeat skin biopsy to confirm the diagnosis
   e. BRAF genetic testing

5. On prenatal ultrasound, a newborn was identified to have a large mass extruding from her body near her anus. The mass is quite large though there is no bleeding. The newborn is born via cesarean section and is stable at birth. You suspect a sacrococcygeal teratoma and consult the pediatric surgery team. What would your recommendations be for laboratory work-up?
   a. No laboratory tests are required for this patient
   b. Alpha-fetoprotein (AFP) and beta-human chorionic gonadotropin (beta-hCG); though these tests are actually normal in the majority of teratomas
   c. Alpha-fetoprotein (AFP) and beta-human chorionic gonadotropin (beta-hCG); the majority of teratomas will produce AFP and thus AFP will be elevated
   d. Alpha-fetoprotein (AFP) and beta-human chorionic gonadotropin (beta-hCG); the majority of teratomas will produce beta-hCG and thus beta-hCG will be elevated

6. A 2-week-old neonate is found to have a large (5 cm) raised erythematous lesion over her right forehead, which seems consistent with a hemangioma. Which would be the most appropriate next step in her evaluation?
   a. Complete skin exam by dermatology
   b. Ultrasound of the abdomen looking for internal hemangiomas
   c. MRI of brain
   d. Laboratory evaluation looking for thrombocytopenia and DIC

7. The 2-week-old neonate in the prior question is also found to have a large hemangioma that is compressing her airway. Surgical management and embolization are not thought to be feasible for her. Which would be the first-line medical management for her hemangioma?
   a. Prednisone
   b. Propranolol
   c. Vincristine
   d. Sirolimus

8. A newborn was identified to have what appears to be a mass in his right adrenal gland on prenatal ultrasound. Further imaging on the child shows a massively enlarged right adrenal gland, with lesions in the liver. Exam reveals hepatomegaly as well as blue nodular lesions on his skin. You suspect congenital neuroblastoma. Your next step in management would be:
   a. Pediatric surgery consultation for adrenal resection or biopsy.
   b. Observation alone as you are confident that the diagnosis is neuroblastoma, and that it should regress with time.
   c. MIBG (metaiodobenzylguanidine) scan.
   d. Induction multi-agent chemotherapy.
   e. Chemotherapy followed by tandem autologous stem cell transplant.

9. A 1-week-old female is found to have multiple, small lesions in her heart, which seem to be in the lining of the ventricles as confirmed on echocardiography and MRI. She is stable and does not require immediate surgery. You suspect that she has cardiac rhabdomyomas. Which

of the following conditions is very closely associated with rhabdomyomas and must be tested for immediately?
a. Sturge-Weber syndrome
b. Beckwith-Wiedemann syndrome
c. Down syndrome
d. Rhabdomyosarcoma
e. Tuberous sclerosis

10. A 1-day-old neonate is found to have a palpable abdominal mass. Further imaging confirms a large retroperitoneal mass arising from the middle of the left kidney. The mass is relatively large though the kidney capsule appears intact on CT scan. The child is otherwise healthy and has no symptoms. Which of the following would be the next step in management?
a. Pediatric surgery consultation for immediate nephrectomy
b. Genetic testing for familial cancer syndromes
c. MIBG (metaiodobenzylguanidine) scan and urine HVA/VMA
d. 24-hour urine collection for evaluation of hematuria
e. Full body MRI to evaluate for metastases

SECTION 15

Neurology

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55 Neurologic Evaluation

NIRANJANA NATARAJAN

The examination of the preterm or neonate varies based on gestational age. However, neurologic examination of the neonate should include evaluation of mental status, cranial nerves, motor strength and tone, response to sensory stimulation, and primitive reflexes. These aspects evolve during development and are often state dependent in a neonate.

Physical Examination

- Head circumference, with assessment of fontanelle.
- Level of alertness: response to touch, ability to spontaneously open eyes to exam.
- Cranial nerve exam: use of brainstem reflexes to aid assessment.
- Primitive reflexes.
- Motor examination: degree of spontaneous movement, presence or absence of patterned movements, tone by gestational age. Tone develops caudal to rostral, with increasing flexor tone with maturation.
- Deep tendon reflexes.

Mental Status

Mental status in the neonate may often be determined first by observation, followed by attempts to interact with the neonate. This portion of the exam is "state dependent"; neonates are optimally examined in the time when they are awake and in a calm state. Neonates examined immediately after or during a feed may be sleepy, thus limiting examination. Key observations help determine the neonate's mental status:

- Does the neonate arouse easily with unswaddling or light touch?
- If crying with examination, does he or she soothe easily by containment or pacifier (if appropriate for postmenstrual age [PMA])?
- Can the neonate stay awake for the exam, or is stimulation required to maintain an awake state?

Encephalopathy

Altered mentation is referred to as *encephalopathy*. The modified Sarnat scale has helped categorize the varying degrees of encephalopathy into mild, moderate, and severe, which incorporate motor posture and tone, as well as primitive reflexes. As discussed elsewhere in this section, the differential of neonatal encephalopathy is broad, with hypoxic-ischemic encephalopathy as the most frequent cause.

- Mild encephalopathy: hyperalert or irritable neonates. Tone is frequently increased, with a hyperactive Moro response. Sympathetic tone predominates.
- Moderate encephalopathy: lethargic, with decreased spontaneous movements. Tone is typically decreased with weak or incomplete primitive reflexes. Parasympathetic tone predominates.
- Severe encephalopathy: stuporous appearance or no responsiveness. There is no spontaneous activity seen, and tone is flaccid with absent primitive reflexes.

Cranial Nerves

Similar to the adult coma patient, the use of brainstem reflexes aids in the neurologic assessment of the neonate.

- Optical blink reflex (dazzle reflex): CN II (optic) and CN VII (facial). By 26 weeks' PMA, neonates consistently blink to light stimulus. By 32 weeks, blink will remain as long as light remains present.
- Pupillary response: CN II and CN III. Pupillary reaction to light begins at 30 weeks' PMA; consistent reaction present by 32 to 35 weeks' PMA.
- Visual tracking and optokinetic reflex: by term, a neonate should be able to visually fixate on a face and briefly track it at a distance of approximately 1 foot. By 34 weeks' PMA, he or she can follow a bright red object. Optokinetic nystagmus to a rotating drum is present by 36 weeks, and consistent by term.
- Oculomotor functions, controlled by CN III (oculomotor), CN IV (trochlear), and CN VI (abducens), can be evaluated by oculocephalic reflex by 25 weeks' gestation. Eye position at rest (such as dysconjugate gaze) should be evaluated.
- Facial strength can be evaluated with observation: a neonate with hypotonic facies, as noted by "carp" appearance with mouth open, or decreased nasolabial folds, may suggest a neuromuscular disorder. Neonates with asymmetric facies present only when crying should be closely evaluated for hypoplasia of the depressor anguli oris muscle, which can occur in isolation, but also can be associated with renal or cardiac defects; this is not a disorder of the facial nerve or central nervous system.
- Gag reflex: CN IX (glossopharyngeal) and CN X (vagus).

Primitive Reflexes

- Moro response: obtained by sudden dropping of neonate's head in comparison to the torso. This is best elicited by holding the neonate in an upright sitting position with one hand holding the trunk, with second hand prepared to catch the neonate's head behind it. The neonate is dropped, and the falling head captured by the examiner. The hands should open and the arms first abduct then flex.

  - Present by 28 weeks.
  - Well formed by 37 weeks.
  - Disappears by 6 months.
  - Asymmetric Moro reflex raises suspicion of a brachial plexus injury. Asymmetry is rarely, if ever, secondary to focal brain injury.
- Palmar response: elicited by placing a finger or object in the palm. Normal response is complete hand closure.
  - Present by 28 weeks and strong by 32 weeks
  - Disappears by 2 months of age when voluntary grasp arises
  - Asymmetric absence of palmar response is worrisome for peripheral injury
  - Persistent fisting with thumb tucked interiorly is suggestive of cerebral injury
- Tonic neck reflex: flexion of arm contralateral to head movement.
  - Present by 35 weeks
  - Strongest near 44 weeks
  - Disappears by 6 months of age
  - Obligatory tonic neck reflex is concerning for a focal cerebral injury
- Rooting reflex of turning toward a stimulus when touched near the lips starts near 28 weeks and serves to help a neonate find the breast for nursing.

Motor Tone and Strength

Strength in the neonate can be determined by observation, assessing for frequency of spontaneous movements.

Tone develops caudal to rostral, with increasing flexor tone to the extremities with increasing maturity to term gestation.

- Tone can be estimated on examination by observing posture. Frog legging is indicative of hypotonia, while persistent leg extension can indicate high tone in the term neonate.
- Degree of head lag, ventral suspension, scarf sign, shoulder slip-through, popliteal angle, ankle flexion can help determine tone.
- Assessments such as the Dubowitz neurologic exam or the Ballard exam can help assess tone for gestational age.

Deep Tendon Reflexes

- Easiest to elicit in the pectoralis, biceps, brachioradialis, patella, and achilles.
- Maintain head in midline, as positioning may alter examination.
- Between 4–6 beats of clonus is normal in neonates.
- Extensor response on plantar stimulation (Babinski) is normal.
- Abnormal responses include asymmetry with head midline, unilateral sustained clonus, unilateral extensor plantar response, or obligate extensor plantar response.

Abnormalities Suggesting Increased Intracranial Pressure

When examining neonates with risk or presence of hydrocephalus, certain findings may clue the clinician to increasing intracranial pressure:

- splaying of sutures
- bulging fontanelle
- skew deviation of eyes in primary gaze
- tight popliteal angle
- increased or unexplained apnea and bradycardia events

Suggested Readings

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56 Development of the Nervous System

LAURA PRICE

Table 56.1 summarizes central nervous system developmental stages, timing of development, and anomalies associated with maldevelopment at each stage of development.

Myelomeningocele: Neural Tube Defect Resulting in Exposed Meninges and Spinal Cord

- Etiology: disorder of primary neurulation at 3–4 weeks, gestation
- Epidemiology: 0.2 per 1000 US births
- Ultrasound diagnosis:
  - Direct visualization of spinal lesion
  - "Lemon sign"—concave shape of frontal calvarium
  - "Banana sign"—posterior convexity of cerebellum (in Chiari II malformation)

MATERNAL RISK FACTORS

- Previously affected neonate from same partner (highest risk)
- Low folic acid intake, B_{12} deficiency
- Use of valproate, carbamazepine, alcohol, and/or isotretinoin
- Obesity, pregestational diabetes
- Hyperthermia

PREVENTION

- Pregestation initiation of folic acid: 400 micrograms daily
- If mother had prior child with myelomeningocele: 4000 micrograms daily

MANAGEMENT

- Prenatal surgery: in select centers in select patients
- Benefits of prenatal repair
  - Decreased need for CSF shunt
  - Improved function and ambulation
- Risks of surgery
  - Rupture of membranes (ROM), abruption, prematurity, requires cesarean-section (C-section) delivery

Delivery

- Observational studies of C-section versus vaginal show overall equivocal outcomes
- Route of delivery per obstetric indications or if significant hydrocephalus

Initial Postnatal Management

- Keep saline-soaked sterile gauze over lesion
- Avoid direct pressure on lesion by placing side-lying or prone
- Antibiotic for meningitis is prophylaxis prerepair
- Routine postnatal repair <72 hours of age

ASSOCIATED FINDINGS

- Chiari II (majority of cases)
- Hydrocephalus (80%–90% of cases)
- Agenesis of the corpus callosum
- Diffuse microstructural anomalies/hypoplasia of cranial nerve nuclei

LONG-TERM OUTCOMES

- Bowel and bladder dysfunction in virtually all children
- 30%–50% will develop latex allergy, keep on latex precautions
- Secondary renal injury due to obstructive hydronephrosis and recurrent urinary tract infection (UTI)
- Majority with normal IQ, many with learning disabilities

Encephalocele: Extracranial Meninges ± Brain Parenchyma

- Etiology: abnormal closure of the anterior neural tube

INITIAL MANAGEMENT

- If open: antibiotic prophylaxis and repair <24 hours of age
- If closed and stable airway: delayed repair depending on anatomy

ASSOCIATED FINDINGS

- Hydrocephalus requiring shunt in minority of cases

LONG-TERM OUTCOMES

- Rostral encephaloceles: better prognosis
- Occipital lesions: more commonly hydrocephalus and seizures

Table 56.1 CNS Developmental Stages and Associated Anomalies

Aspect/Stage of Development	Timing of Development	Associated Abnormalities
Primary neurulation (neural tube formation)	3–4 weeks	▪ Encephalocele ▪ Myelomeningocele ▪ Anencephaly ▪ Myeloschisis ▪ Craniorachischisis
Secondary neurulation (canalization)	4–7 weeks	▪ Tethered cord ▪ Meningocele ▪ Spinal cysts ▪ Teratoma ▪ Lipoma
Prosencephalic development	2–3 months	▪ Holoprosencephaly ▪ Septo-optic dysplasia ▪ Agenesis of corpus callosum ▪ Agenesis of septum pellucidum
Neuronal/glial proliferation	2–4 months	▪ Micrencephaly ▪ Macrencephaly ▪ Holoprosencephalies

Neuronal migration	3–5 months	▪ Schizencephaly
		▪ Lissencephaly
		  ▪ (e.g., Miller-Dieker)
		  ▪ (e.g., Walker-Warburg)
		▪ Polymicrogyria (e.g., Zellweger)
		▪ Pachygyria
		▪ Heterotopia

Neuronal organization	3 months–2+ years	▪ Fetal alcohol syndrome ▪ Aneuploidy (e.g., trisomies 13, 18, 21)
Myelination	Term–years	▪ Malnutrition ▪ White matter hypoplasia

Hydrocephalus: Excess CNS Fluid Volume

- Etiology: in neonates, hydrocephalus is generally a result of abnormal CSF circulation or absorption
- Aqueductal stenosis (X-linked with adducted thumbs, or nonfamilial)
- Intraventricular hemorrhage
- Chiari type II malformation (in setting of myelomeningocele)
- Dandy-Walker malformation (posterior fossa cysts)
- Intrauterine infection (toxoplasmosis [toxo]/cytomegalovirus [CMV])
- Tumors
- Ex vacuo: developmental anomalies and ischemic volume loss

SYMPTOMS

- Apnea/bradycardia episodes
- Lethargy
- Restricted upgaze/abnormal ocular movement

TREATMENT

Most Common

- Early shunt placement in anatomic/congenital obstruction
  - Ventriculoperitoneal shunt
  - Ventriculoatrial if abdominal scarring/infection
  - Ventriculo-subgaleal shunt (VSG)
- Serial lumbar puncture (LP) in communicating hydrocephalus, though may become ineffective as this often evolves to obstructive hydrocephalus

Other Potential Treatments

- Ventricular access device (VAD): same outcome/complications as VSG
- Endoscopic third ventriculostomy (ETV) has controversial neonatal efficacy
- Acetazolamide and furosemide are both shown to worsen outcomes

Prognosis is best predicted by two variables:

1. Cerebral mantle thickness prior to shunting
2. Etiology of the hydrocephalus:
   a. better in communicating hydrocephalus and myelomeningocele
   b. poorer in aqueductal stenosis and Dandy-Walker malformation

Microcephaly: Occipitofrontal Circumference More Than Two Standard Deviations (SD) Below the Mean

CAUSES INCLUDE

- Microcephaly vera: genetic (typically autosomal recessive) or environmental
- Early developmental malformations include:
  - Anencephaly, holoprosencephaly
  - Schizencephaly, lissencephaly, and polymicrogyria
  - Septo-optic dysplasia
- Aneuploidies
  - Trisomies 13, 18, and 21
- Syndrome-associated examples
  - Smith-Lemli-Opitz syndrome
  - Williams syndrome
  - Cornelia de Lange syndrome
  - Prader-Willi syndrome
- Developmental disruptions
  - Infections: toxoplasmosis, rubella, CMV, herpes simplex virus (HSV), Coxsackie viruses
  - Maternal: diabetes mellitus (DM), uremia, phenylketonuria (PKU), hyperthermia, radiation, cocaine, ethanol (ETOH), phenytoin
  - Vascular events, stroke, hypoxic-ischemic encephalopathy (HIE), intraventricular hemorrhage (IVH) injury, periventricular leukomalacia (PVL)
  - Neurodegenerative and metabolic disorders
- Multisuture craniosynostosis

Macrocephaly: Occipitofrontal Circumference More Than Two SD Above the Mean

CAUSES INCLUDE

- Isolated and familial macrocephaly
- Hydrocephalus disorders
- Growth/overgrowth syndromes
  - Achondroplasia
  - Beckwith-Wiedemann syndrome
  - Sotos syndrome
  - Simpson-Golabi-Behmel syndrome
- Chromosomal disorders
  - Fragile X syndrome
  - Klinefelter syndrome
- Neurocutaneous disorders
  - Neurofibromatosis type I
  - Tuberous sclerosis
  - Sturge-Weber syndrome
- Degenerative and metabolic disorders (Tay-Sachs disease with neonatal macrocephaly)
- Mass effect: tumors, vascular anomalies, hematomas, effusions

Neonatal Neurotransmitter Effects

- Excitatory amino acids such as *glutamate* dominate in fetal/early neonatal life
  - Topiramate, a glutamate receptor blocker, is a promising neonatal antiseizure drug
- *Adenosine* is elevated in fetal CNS; it suppresses fetal respiration and decreases O_2 consumption
  - Theophylline and caffeine are adenosine agonists, reducing neonatal apnea
- *GABA (gamma-aminobutyric acid)*: receptor activation opens chloride channels
  - Excitatory in fetus due to high chloride content in nerve cells, which leads to depolarization
  - GABA transitions to inhibitory when neurons go from high to low chloride content
  - Phenobarbital and benzodiazepines are GABAergic:
    - Inhibitory in adults
    - Often excitatory in fetal or early neonatal neurons

Table 56.2 summarizes various factors that can affect cerebral blood flow in neonates.

Table 56.2 Moderators of Cerebral Blood Flow

Increase in This Factor	Effect on Cerebral Blood Flow	Mechanism/Notes
Dopamine	Increases	▪ MAP increase in pressure-passive perfusion ▪ β-adrenergic receptor activation
Indomethacin	Decreases	▪ Prostaglandin inhibition
Ibuprofen	No effect	▪ No significant CNS prostaglandin inhibition
Methylxanthine (aminophylline, caffeine)	Decreases	▪ Antagonist to adenosine
Arterial blood pressure	Increases	▪ When pressure-passive perfusion
Venous blood pressure	Decreases	▪ Sudden/significant increase in RA pressure ▪ Germinal matrix bleed→venous congestion
⇑ $PaCO_2$	Increases	▪ Hypercarbia: ⇑ perivascular H+
⇓ $PaCO_2$	Decreases	▪ Hypocarbia: ⇓ perivascular H+
⇑ Pao_2	Decreases	▪ Hyperoxia: increased Ca+ vasoconstriction
⇓ Pao_2	Increases	▪ Hypoxia: ⇑ H+, K+, adenosine, +prostaglandin
Hgb	Decreases	▪ Increases CaO_2 (until significant polycythemia)

Cerebral blood flow is regulated by changes in vascular resistance (primarily arteriolar diameter) affected by local chemical factors. The chemical factors resulting in vasodilation include: H+, K+, adenosine, prostaglandins, nitric oxide, and osmolarity. Ca+ increase results in vasoconstriction.

*CaO_2; CNS,*central nervous system; *Hbb*, hemoglobin: *MAP*, mean arterial pressure; *$PaCO_2$*, arterial partial pressure of CO_2 (carbon dioxide); *Pao_2*, arterial partial pressure of oxygen; *RA*, right atrial.

Suggested Readings

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Shankaran S. Complications of neonatal intracranial hemorrhage. *NeoReviews*. 2000;21(3):e44–e47.

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Question

1. You are called to consult with a 25-year-old mother whose first child is wheelchair-bound due to a lumbar myelomeningocele. Her pregnancy history is significant for tobacco smoking and occasional cocaine use. She is now at 8 weeks' gestation, started taking a prenatal vitamin this week, stopped her acne medication this week, and is taking an antiemetic as needed. She is very worried about the risk of this baby being born with a myelomeningocele. Which of the following is true in regard to the recurrence risk?
   a. She is reducing the risk of recurrence by starting a prenatal vitamin with folic acid in the first trimester.
   b. Her cocaine use increases the risk of recurrence in this pregnancy.
   c. Smoking cessation prior to pregnancy greatly reduces the incidence of myelomeningocele.
   d. The recurrence risk is greater if this baby has the same father as her first child.
   e. Acne medications do not affect the rate of myelomeningocele.

57 Neonatal Encephalopathy

JENNIFER BURNSED

Neonatal encephalopathy (NE) is defined as an alteration in consciousness or neurologic exam in a neonate. The possible etiologies of NE are broad (Box 57.1) but it is most commonly caused by hypoxic-ischemic encephalopathy (HIE).

Hypoxic Ischemic Encephalopathy

BASIC INFORMATION

- Most common cause of neonatal encephalopathy
- Pathophysiology: mismatch between cerebral blood flow and oxidative metabolism resulting in injury and encephalopathy
  - Phases of injury
    - Decreased cerebral ATP and membrane depolarization
    - Increased excitotoxic neurotransmitter release and neuron damage
    - Reperfusion
    - Irreversible cell death
- Risk factors are listed in Table 57.1

DIAGNOSIS AND EVALUATION

- Clinical presentation
  - Depends on duration, timing, and severity of event or insult and may evolve over hours to days
  - Clinical staging based on Sarnat criteria listed in Table 57.2.

Box 57.1 Causes of Neonatal Encephalopathy

Hypoxic ischemic encephalopathy
Perinatal stroke
Kernicterus
Metabolic derangements (inborn errors of metabolism, hypoglycemia)
Intracranial hemorrhage
Sinovenous thrombosis
Infection
Maternal toxins

- Evaluation
  - History
    - Evidence of intrauterine distress (abnormal fetal heart tracing, meconium-stained amniotic fluid, acidosis on umbilical cord gas)
    - Difficult resuscitation (required assisted ventilation, chest compressions, medications)
    - Low Apgar scores (<7) at 5 or more minutes
  - Neurologic exam
    - Altered level of consciousness, hypotonia, jitteriness, apnea, abnormal cry, and/or seizures
    - Exam evolves with time
    - Seizures often seen in first 6–12 hours, usually onset within first 24 hours
    - See Table 57.2 for Sarnat criteria and exam findings
  - Electroencephalogram (EEG)
    - Monitor for seizures using electroencephalogram (EEG) or amplitude-integrated EEG (aEEG)
    - Electrographic seizures without clinical correlate are common (especially after administration of antiepileptic medication)
    - EEG background useful for determining severity and evolution of encephalopathy and outcome
  - Neuroimaging
    - Computed tomography scan (CT) not recommended for diagnosis or prognosis, MRI is gold standard
    - Ultrasound may be helpful to visualize cerebral edema and severe injury but not an ideal modality
    - Magnetic resonance imaging (MRI) is sensitive for diagnosis and prognosis
      - Abnormal signal in posterior limb of internal capsule associated with poor motor outcome
      - Helpful in predicting outcome at 18 months
    - Patterns of injury
      - Global: usually occurs in context of severe/prolonged insult
      - Basal ganglia/thalamus injury pattern: often seen with acute event
      - Watershed/white matter injury pattern: prolonged/partial injury, in arterial watershed zones

Table 57.1 Risk Factors for Neonatal Encephalopathy

Preconception	Antepartum	Intrapartum
Fertility treatments	Multiple gestation	Induction of labor
Insulin-dependent diabetes mellitus	Placental abruption	Maternal fever
Thyroid disease	Intrauterine growth restriction	Emergency cesarean section
Advanced maternal age	Severe preeclampsia	Instrumented delivery
Nulliparity	Antepartum hemorrhage	Cord prolapse
	Postterm gestation	Malpresentation
		Lack of trained personnel

Table 57.2 Clinical Staging of Hypoxic-Ischemic Encephalopathy (Sarnat Criteria)

Finding	Stage 1	Stage 2	Stage 3
Level of consciousness	Alert	Lethargic	Comatose
Muscle tone	Normal	Hypotonic	Flaccid
Tendon reflexes	Normal/increased	Increased	Depressed/absent
Myoclonus	Present	Present	Absent
Complex reflexes			
Sucking	Active	Weak	Absent
Moro	Exaggerated	Incomplete	Absent
Grasp	Normal/exaggerated	Exaggerated	Absent
Oculocephalic ("doll's eyes")	Normal	Overreactive	Reduced/absent

TREATMENT

- Supportive care
  - ABCs (airway, breathing, circulation)
  - Monitor for and treat seizures appropriately (aEEG or EEG monitoring, antiepileptic medications)
  - Treat/support other end-organ dysfunction (myocardial dysfunction, pulmonary hypertension, hepatic dysfunction, renal injury, coagulopathy)
  - No consensus regarding treatment of cerebral edema (use of steroids, hyperventilation, furosemide, and mannitol have not been shown to be helpful and may be harmful)
  - Maintain normoglycemia, normotension, and normal blood gases
  - Avoid hyperthermia, which has been linked to worse outcomes
- Therapeutic hypothermia
  - Routine care for moderate to severe HIE, whole body and selective head cooling are equally effective
  - Initiate in the first 6 hours of age, as soon as possible (earlier onset associated with improved outcomes)
  - Multimechanistic (decreases cerebral metabolic rate, decreases cerebral edema, antiinflammatory, decreases free radical production)
  - Improved 18–21-month neurodevelopmental outcomes with the number needed to treat ~7
- Outcomes
  - Variable, depends on severity of insult and pattern of injury
  - Delayed return of spontaneous respirations, need for chest compressions, seizures, and base deficit >–16 are associated with poor outcome
  - *Mild encephalopathy* usually has normal outcome; patients with *severe encephalopathy* are at high risk of severe impairments (spastic quadriplegia, epilepsy, cortical visual impairment) or death; *moderate encephalopathy* outcomes are highly variable
  - Injury to deep gray matter or posterior limb of internal capsule is often associated with worse outcomes (particularly motor)

Metabolic Encephalopathies

BASIC INFORMATION

- Causes
  - Severe hypoglycemia
  - Kernicterus
  - Inborn errors of metabolism

Table 57.3 Classic Magnetic Resonance Imaging Findings in Metabolic Disorders

Disorder	Magnetic Resonance Imaging Findings
Nonketotic hyperglycinemia	Early delayed myelination, agenesis of corpus callosum, atrophic basal ganglia, progressive cerebral atrophy
Molybdenum cofactor deficiency/sulfite oxidase deficiency	Edema in white matter and caudate, cystic changes, cortical/white matter/basal ganglia injury consistent with asphyxia
Pyridoxine-dependent seizures	Cerebellar hypoplasia, generalized atrophy, thin corpus callosum
Zellweger syndrome	Subependymal cysts, profound hypomyelination, cortical malformations
Pyruvate dehydrogenase deficiency	Delayed myelination, agenesis of corpus callosum, atrophy
Maple syrup urine disease	Delayed myelination, generalized edema
Urea cycle disorders	Resemble asphyxia: gray/white matter edema (subacute), cortical/white matter injury (chronic)

  - Organic acidurias, urea cycle defects, amino acidopathies, peroxisomal disorders, mitochondrial disorders, glycogen storage disorders

CLINICAL PRESENTATION

- Seizures, encephalopathy, vomiting, abnormal tone
- May mimic HIE or infection but history often doesn't support an acute event or infectious risk factors
- Depending on the disorder, patient may have asymptomatic period at birth then present with encephalopathy in the coming hours to days as toxic metabolites accumulate
- May have metabolic acidosis, hyperammonemia
- MRI may reveal pattern of injury inconsistent with HIE

DIAGNOSIS AND EVALUATION

- Blood gas, electrolytes, creatinine, BUN, liver function tests, ammonia, lactate, plasma amino acids, urine organic acids, CSF studies (lactate, pyruvate)
- MRI –(see Table 57.3 for characteristic patterns of injury) (table adapted from Ibrahim, et al. 2014)

TREATMENT

- Nil per os (NPO)
- IV dextrose containing fluids, no protein initially

- Avoid catabolic state
- Genetic/metabolic consultation
- More focused treatment depends on specific disorder (may need emergent dialysis, IV alternative waste therapy, such as sodium benzoate or sodium phenylacetate)

Suggested Reading

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Question

1. You are admitting a newborn with suspected hypoxic-ischemic encephalopathy (HIE). Based on the physical exam you are attempting to stage the infant based on Sarnat staging. On exam, you note that the infant is lethargic, floppy, exhibits an exaggerated grasp reflex, and a weak suck reflex. How would this infant be classified?
   a. Mild HIE
   b. Moderate HIE
   c. Severe HIE
   d. Normal infant
   e. None of the above

58 Intracranial Hemorrhage and Vascular Injury

SONIA LOMELI BONIFACIO

Subdural Hemorrhage

BASIC INFORMATION

- Subdural hemorrhage occurs between the dura mater and the arachnoid tissue that surrounds the brain. The dura mater contains blood vessels (bridging veins) and the major venous sinuses.
- Risk factors include macrosomia, use of forceps, cephalopelvic disproportion, and shoulder dystocia.
- It is the most common intracranial hemorrhage in term newborns.
- Incidence is 2.9/100,000 live births, doubles with vacuum or forceps use, and is 10 times higher if both vacuum and forceps are used.
- Compression or stretching forces can lead to tearing of the falx cerebri or the cerebellar tentorium (both extensions of the dura mater), leading to hemorrhage.
- Injury of the superficial veins leads to hemorrhage over the surface of the brain.
- Injury of the straight sinus or vein of Galen leads to hemorrhage at the base of the brain into the posterior fossa.

CLINICAL PRESENTATION

- Should be suspected when there is a history of a traumatic or difficult delivery and neonate has neurologic signs such as unequal pupils, eye deviation, or hemiparesis.
- Neonates may present with pallor, irritability, lethargy, and/or decreased Moro reflex.
- Exam may show a bulging anterior fontanelle.
- Posterior fossa bleeds may present differently with apnea and bradycardia, encephalopathy (altered mental status), seizures, or opisthotonos.
- U/S is not a good test for diagnosis; magnetic resonance imaging (MRI) should be performed if subdural hemorrhage is suspected.

TREATMENT

- If asymptomatic, no treatment is needed.
- If symptomatic, neurosurgical consultation and evacuation of posterior fossa bleed may be needed.
- Monitor for seizures, signs of neurologic deterioration, and signs of increasing intracranial pressure.

Subarachnoid Hemorrhage

BASIC INFORMATION

- Subarachnoid hemorrhage is bleeding that occurs under the arachnoid layer.
- Due to bleeding of bridging veins in subarachnoid space.
- The second most common intracranial hemorrhage in term neonates.

CLINICAL PRESENTATION

- Neonates are usually asymptomatic.
- May present at 24–48 hours after birth with apnea and seizures.
- Diagnosed by computed tomography (CT) or MRI.
- Usually self-resolves but if it progresses to herniation then patient needs neurosurgical consultation.

Epidural Hematoma

BASIC INFORMATION

- Caused by injury to the middle meningeal artery and thus usually associated with an overlying skull fracture.
- Rare; associated with instrumented deliveries.
- Bleeding between the dura and the skull.

CLINICAL PRESENTATION

- May present with hypotonia, seizures, bulging fontanelle, encephalopathy.
- Diagnose with CT or MRI.

TREATMENT

- Usually close observation.
- Monitor for signs of herniation; if present, consult neurosurgery.

Intraventricular Hemorrhage (IVH)

BASIC INFORMATION

- IVH most commonly occurs in premature neonates with the highest incidence in those born at <29 weeks' gestation.

- Incidence has decreased over the last two decades but still occurs in about 20% of the highest risk patients.
- 50%–75% of survivors with IVH develop cerebral palsy, cognitive impairments, or hydrocephalus.
- There are two commonly referred to grading systems: Papile and Volpe. Grade IV IVH, which previously was described as an extension of a hemorrhage into the parenchyma, is now referred to as a periventricular hemorrhagic infarction (PVHI) and is thought to represent a venous infarction.
- Pathogenesis is multifactorial and related to the fragile subependymal germinal matrix (site of origin of IVH), pressure passive state due to poor autoregulation, lack of supporting basement membrane of the germinal matrix, fluctuations in cerebral blood flow, increased cerebral venous pressure, endothelial injury, and possible disturbances in coagulation.
- Can be seen in term infants in association with sinovenous thrombosis.

CLINICAL PRESENTATION

- Presents between days 3–4 of life and usually by 1 week after birth.
- Presentation depends on severity of hemorrhage; grades I–II may be clinically silent, grade III and PVHI may present with sudden deterioration, tachycardia, hypotension, a decreasing hematocrit, and a full fontanelle.
- A low-grade hemorrhage can extend to a higher grade hemorrhage over the course of several days.
- Diagnosis is made by head U/S.
- Screening U/S should be done on neonates born at <32 weeks or at <1500 grams. Scans done on the fourth day will detect 90% of bleeds.

TREATMENT

- The best treatment for IVH is the prevention of preterm births. Administration of antenatal steroids and magnesium sulfate also reduces the incidence of IVH. Postnatal interventions include delayed cord clamping and use of care bundles in the first 72 hours after—gentle ventilation, minimal handling, midline head positioning, and maintenance of normal carbon dioxide levels.
- Treatment is supportive care and maintenance of homeostasis to avoid secondary brain injury. Blood pressure should be kept in the normal range for gestational age, and volume resuscitation should be slow to avoid rapid changes in cerebral blood flow.
- Larger grade hemorrhages need to be monitored for development of obstructive hydrocephalus by closely following head circumference and serial U/S to monitor for ventricular dilation.
- Serial lumbar punctures are done in some centers to avoid placing reservoirs or drains.
- Ventriculoperitoneal (VP) shunts may be needed but carry significant risk of infection and malfunction.

Intraparenchymal Cysts, Echodensities, Periventricular Leukomalacia

BASIC INFORMATION

- Periventricular white matter is an area vulnerable to injury in preterm neonates.
- Echodensities in the periventricular white matter are common and can be transient, prolonged, or progress to cyst formation. The reported prevalence of these echodensities ranges from 18%–40% and is dependent on gestational age (GA) at birth. Outcome of echodensities that resolve is thought to be favorable. The impact of echodensities that persist on neurodevelopment is unknown.
- Intraparenchymal cysts are thought to be due to hypoxia-ischemia and/or inflammatory insults. In preterm neonates they typically appear in the periventricular region.
- Periventricular leukomalacia (PVL) refers to white matter injury, characterized by focal cystic necrotic lesions in the area around the ventricles. PVL and periventricular white matter injury (PWMI) are thought to be due to hypoxia-ischemia, inflammation, infection, and abnormal oligodendrocyte maturation.

CLINICAL PRESENTATION

- WMI identified by U/S is clinically silent in the neonatal period.
- Neurologic exam at discharge and evaluation of generalized movements may identify subtle abnormalities in neonates with significant PVL or WMI.
- PVL and more diffuse PWMI increase the risk for development of cerebral palsy, specifically spastic diplegia (tightness and stiffness affecting lower extremities more than upper extremities).
- Diagnosis is by cranial U/S at 30 days or at term-corrected gestational age.

TREATMENT

- There are no treatments available.

Cerebellar Hemorrhage

BASIC INFORMATION

- Cerebellar hemorrhages are increasingly recognized in premature neonates due to improved U/S imaging techniques and increased use of MRI.
- They can be isolated or seen in conjunction with IVH or white matter injury (WMI).
- They may occur in 2–5% of low-birth-weight babies (based on postmortem studies).
- Pathogenesis is likely multifactorial and similar to IVH.

- Risk factors include being very low birth weight, needing resuscitation at birth, low Apgar score, hemodynamic instability, Persistent Ductus Arteriosus (PDA), and prolonged mechanical ventilation.
- They can be small or large; smaller hemorrhages are harder to visualize on U/S.

CLINICAL PRESENTATION

- They are clinically silent in the neonatal period.
- There are several studies demonstrating an association with increased neonatal morbidity and mortality as well as cognitive, motor, and behavioral abnormalities.

TREATMENT

- There are no treatments for cerebellar hemorrhages.
- Supportive care.

Prenatal Vascular Injury

BASIC INFORMATION

- Neurologic vascular injury prior to birth can result in significant disruption of normal brain development dependent on the gestational age at which the insult occurs.
- Pathogenesis includes emboli, hemorrhage, vasoconstriction, and disseminated intravascular coagulation (DIC).
- Risk factors include demise of a co-twin, infection with cytomegalovirus (CMV), maternal diabetes, cocaine exposure, fetal vascular changes post maternal abdominal trauma, and certain hereditary conditions.

CLINICAL PRESENTATION

- Depending on the age and mechanism, this may be identified prior to birth with routine U/S surveillance of pregnancy.
- Fetuses may be identified as microcephalic.
- Destruction of brain tissue and resultant encephalomalacia or intracranial hemorrhage may be identified.
- Schizencephaly (fluid-filled cavity in the fetal brain), also known as porencephaly or brain cleft, may also result from antenatal vascular injury (usually diagnosed after 28 weeks).
- Prenatal MRI may be obtained to identify the pathophysiology and extent of injury.
- At birth, symptoms depend on extent of brain injury and proximity of injury to birth.
- There may be abnormal tone (low or high) and possibly contractures, poor feeding, and abnormal mental status.
- Risk for abnormal motor and cognitive development and seizures.

TREATMENT

- No known treatment.
- Supportive care.

Perinatal Cerebral Infarction

BASIC INFORMATION

- Cerebral infarction (stroke) refers to a heterogeneous group of conditions in which there is a focal disruption of cerebral blood flow secondary to arterial or cerebral venous thrombosis or embolization, occurring between 20 weeks of fetal life through the 28th postnatal day and confirmed by neuroimaging or neuropathology studies.
- Perinatal cerebral infarction occurs between 28 weeks and 7 days after birth; neonatal occurs between 0–28 days of life; and presumed perinatal presents at >28 days of age, usually with handedness.
- Can be either ischemic or hemorrhagic.
- Stroke is as common in newborns as it is in adults and occurs in between 1/2300 and 1/4000 births.
- Arterial ischemic stroke: tends to be left-sided in distribution of the Middle Cerebral Artery (MCA) and have a slight male predominance.
- Cerebral sinovenous thrombosis—tends to involve the large sinuses/veins (superior sagittal sinus) that may be traumatized during delivery. Presents differently than arterial ischemic/hemorrhagic infarction.
- Etiology is thought to be multifactorial with complex interplay of neonatal, maternal, genetic, and delivery factors.

CLINICAL PRESENTATION

- Most arterial ischemic/hemorrhagic strokes present usually by 24 hours after birth with clinical seizures (focal motor or apnea without bradycardia) in an otherwise well-appearing infant.
- Some may also have mild encephalopathy and mild hypotonia but it is rare to have focal motor deficits or asymmetry on exam.
- Seizures tend to be repetitive and increase in frequency in the first hours after onset.
- Clinical presentation of cerebral sinovenous thrombosis (CSVT) differs from an arterial stroke. CSVT tends to present after several days of age in the setting of dehydration or sepsis, and patients tend to be more encephalopathic than those with focal arterial stroke.
- Presumed perinatal arterial ischemic strokes tend to present with signs of early handedness at 3–11 months of age, seizures at 5–14 months of age, or with an abnormal gait at 12–21 months of age.

TREATMENT

- Currently there are no treatments for stroke.
- Supportive care (hydration and avoidance of hyperthermia) with monitoring for and treatment of seizures likely impacts severity of brain injury. Hypothermia has not been trialed for stroke. Erythropoietin is effective in animal models but not yet tested in human randomized controlled trials (RCTs). Anticoagulation has been used in treatment of CSVT but is not considered standard of care.
- All infants should be referred to occupational therapy postdischarge; high-risk infant follow-up programs and child neurology follow-up recommended.

- Epilepsy in early childhood may occur in up to two-thirds of patients.
- Outcome is dependent on size and location; 40% will be normal, 57% will have cognitive or motor impairments, 3% may die. Very low risk of recurrence.

Suggested Readings

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Questions

1. The appropriate time frame at which periventricular leukomalacia (cystic PVL) can first be identified is:
   a. just after birth (first 24 hours)
   b. after 4 weeks of life
   c. at 7 days after birth
   d. after discharge home

2. Which neonate is at greatest risk of developing a significant intracranial hemorrhage?
   a. Term infant after a vacuum assisted delivery
   b. A 32-week infant born after induction for maternal preeclampsia
   c. A 26-week infant born after placental abruption who requires intubation and chest compressions at the time of birth

59 Neonatal Neurology: Cranial and Neurologic Trauma

SONIA LOMELI BONIFACIO

Caput Succedaneum

BASIC INFORMATION

- Etiology
  - Caput succedaneum represents swelling of the scalp secondary to pressure of the scalp and fetal head against the uterine and vaginal walls or cervix during labor and delivery. This pressure results in accumulation of blood and serum in the tissue *above the periosteum* but *below the skin* resulting in swelling of the scalp.
  - Due to its location above the periosteum, caput can cross suture lines.

CLINICAL PRESENTATION

- Swelling of the scalp observed after birth.
- There can be abrasions of the skin overlying the area of caput that can develop a secondary infection.
- Natural history and complications.
  - Benign with infrequent complications.
  - Caput resolves within several days to a week after birth.
  - If the caput enlarges after birth or is very large at birth and a vacuum was used, consider an iatrogenic encephalocele. Imaging should be performed if there are neurologic deficits or hemodynamic instability.

Cephalohematomas

BASIC INFORMATION

- Represent a collection of blood *underneath the periosteum.*
- Can occur in instrumented or noninstrumented deliveries and are common.

CLINICAL PRESENTATION

- Characterized by a swelling or mass on the cranium that does NOT cross suture lines, and thus they are usually unilateral. See Figure 59.1.
- They are most prominent on the third day after birth.
- They can form palpable nodules that resolve over the course of several months.
- Natural history and complications.
  - Monitor for development of hyperbilirubinemia.
  - Involute over the course of several weeks.
  - Rare complications include secondary infections of the cephalohematoma and osteomyelitis of the underlying skull.

Subgaleal Hemorrhages

BASIC INFORMATION

- Subgaleal hemorrhages represent bleeding (rupture of the emissary veins) that occurs in the large potential space beneath the epicranial aponeurosis and above the periosteum.
- These hemorrhages can be large and have devastating consequences with potential loss of 40% or more of the newborn's blood volume (125 mL assuming a weight of 3.5 kg and blood volume of 90 mL/kg).
- Bleeding is circumferential and thus extends down toward the orbits, along the temporal and occipital regions, and to the nape of the neck.
- In large bleeds the ears may appear to be protruding.
- Each 1-cm increase in occipital frontal circumference (OFC) represents 30–40 mL of bleeding into the space
- The incidence is 4/10,000 noninstrumented deliveries and 64/10,000 vacuum-assisted deliveries.

CLINICAL PRESENTATION

- Boggy fluctuant cranium with distention that crosses suture lines. See Figure 59.1.
- Can extend down toward nape of neck, and ears may appear protuberant.
- Large subgaleal hemorrhages can result in hemorrhagic shock.
- Mortality rates are high (14%) due to shock and coagulopathy (due to consumption of clotting factors).
- Signs and symptoms include tachycardia, pallor and poor perfusion, a decreasing hematocrit, and increasing head circumference.

TREATMENT

- Frequent repeated assessment and measurement of head circumference (OFC), vital signs, and hematocrit are required.
- Highest risk period for extension of bleeding is in the first 24–48 hours after birth.

- Consider admission to the intensive care unit and placement of umbilical lines for volume resuscitation, blood transfusion, and monitoring of blood pressure.
- Appropriate and timely volume resuscitation with normal saline, transfusion of packed red blood cells (PRBCs), and replacement of clotting factors (FFP) and platelets as indicated by laboratory studies.
- Hemodynamic support as indicated by monitoring of blood pressure.
- Magnetic resonance imaging (MRI) can be performed to confirm the location of hemorrhage and to rule out secondary hypoxic-ischemic injury in the setting of significant hemorrhage and shock.
- Follow for hyperbilirubinemia.

Skull Fractures

BASIC INFORMATION

- Skull fractures can occur during unassisted and assisted deliveries and tend to occur in the frontal and parietal regions.
- In unassisted deliveries, fractures can be due to compression of the skull against the pelvic bones.
- In assisted deliveries compression by forceps can result in a fracture.
- Fractures can be depressed or linear.
- Linear fractures by definition are nondepressed and usually do not require intervention. However, they can be associated with an intracranial injury, although the incidence is rare.
- Depressed skull fractures are associated with prolonged second stage labor and instrumented deliveries, and they tend to occur over the parietal region.
- There may be intracranial bleeding associated with a depressed skull fracture, especially after forceps use.

CLINICAL PRESENTATION AND MANAGEMENT

- Linear skull fractures may not be detected at birth. If they are detected and there are no additional neurologic signs or symptoms, follow-up x-rays can be performed to document healing and to rule out the development of a leptomeningeal cyst.
- Small, <1-cm depressed skull fractures can be managed with close observation.
- Larger fractures (>1 cm) should be followed closely for the development of neurologic sequelae such as subdural bleeding and seizures, should receive adequate imaging in the form of computed tomography (CT) and possibly MRI, and should receive a neurosurgical consultation within 12 to 24 hours of birth. Treatment to be determined by neurosurgery.

Spinal Cord Injuries

BASIC INFORMATION

- Spinal cord injuries tend to occur in full-term infants in deliveries that are complicated by shoulder dystocia and require assistance such as forceps or vacuum application, as well as in vaginal breech deliveries.
- They are rare and occur in 0.14/10,000 live births.
- High cervical spine injuries are associated with rotation and longitudinal traction of the head and neck during delivery.
- Fetuses with hypotonia may have an increased risk of spinal cord injury due to decreased muscle tone that allows the spine to be stretched and flexed more than the cord can accommodate.
- Injuries can range from a spinal epidural hematoma to full transection.
- The spinal cord can also be injured secondary to hemorrhagic compression or ischemia due to spinal stroke, and injury has been seen in the setting of umbilical arterial catheters or extravasation of parenteral fluids from a central venous catheter.
- Presentation and prognosis are dependent on the extent of injury to the cord and the level of the cord at which the injury occurs.
- Transection of the spinal cord represents the worst injury and results in complete paralysis below the level at which the transection occurs.
- High cervical or brainstem lesions carry a very high mortality rate due to compromise of the respiratory system.
- Lower cervical lesions still carry significant morbidity and mortality.

CLINICAL PRESENTATION

- At birth patients can present with significant respiratory depression, hypotonia, and paraparesis.
- There can be urinary retention and abdominal distention.

TREATMENT

- The airway should be secured with intubation, and the head and neck should be immobilized.
- X-rays may show abnormalities of the spine.
- MRI can be used to visualize the spinal cord.
- Neurosurgical consult should be provided.
- Reports of use of therapeutic hypothermia in rare cases.

Brachial Plexus Injury

BASIC INFORMATION

- Brachial plexus injuries occur due to lateral traction of the fetal head and are often associated with macrosomic infants, prolonged labors, and reduction of shoulder dystocia.
- Injury is due to compression of the nerve within the nerve sheath from hemorrhage or edema.
- Severe cases may involve avulsion of the nerve from the cord.
- Injury can involve C5, C6, and sometimes C7 and occasionally can include from C5 through T1. It is usually unilateral.
- The clinical manifestations are related to the nerve roots that are involved.

CLINICAL PRESENTATION

- When C5/C6 (Erb-Duchenne palsy) are involved, the arm is held in adduction and is internally rotated with extension and pronation of the forearm.
- If C7 is also involved, the wrist is held in a flexed position due to weakness of the extensor muscles (Waiter's tip deformity).
- On physical exam there will be an asymmetric Moro reflex, absent on the affected side, and biceps reflex will be weak or absent.
- Klumpke paralysis involves the lower part of the brachial plexus (C8–T1). Neonates will have weakness of the flexor muscles of the wrist and intrinsic muscles of the hand. Grasp reflex will be absent. There may be loss of sensation. Klumpke is the least frequently observed of the brachial plexus injuries.
- If the cervical sympathetic nerves are involved there may be unilateral miosis (Horner syndrome).
- Complete brachial plexus injury = complete paralysis of the arm.

TREATMENT

- Supportive and physical therapy to prevent contractures.
- Position arm in a natural position.
- Recovery dependent on severity.
- Mild injuries improve over a course of 1–2 weeks.
- Complete brachial plexus injury and Klumpke carry a poorer prognosis.

Facial Nerve Injury

BASIC INFORMATION

- Most common cranial nerve injury due to birth trauma.
- Most common site is at exit of nerve from stylomastoid foramen resulting in a lower motor neuron lesion.
- Due to compression of nerve against maternal sacrum.

CLINICAL PRESENTATION

- Unable to close eye, loss of normal nasolabial fold, asymmetric crying facies; forehead is spared as it is innervated by opposite nerve.

TREATMENT

- None as it usually self resolves after 1 week.
- May need moisturizing eye drops.

Phrenic Nerve Injury

BASIC INFORMATION

- Phrenic nerve injury is associated with brachial plexus injuries and results in paralysis or poor movement of the diaphragm on the affected side.
- Extreme traction of the neck and shoulders during delivery may transect and or injure the phrenic nerve and brachial plexus.
- Risk factors include macrosomia and use of forceps.
- Neonates with congenital heart disease who have surgery in the newborn period are also at risk of phrenic nerve injury.
- The diagnosis should also be considered in patients who have had surgery involving the chest or neck and cannot be weaned off mechanical ventilation.

CLINICAL PRESENTATION

- Neonates present with respiratory distress and tachypnea and may have cyanosis.
- Physical exam may identify reduced rib cage movement on the side of the injury and exaggerated movement on the unaffected side.
- There may be paradoxical movement of the diaphragm.
- Chest x-ray will demonstrate an elevated hemidiaphragm.
- Echocardiogram or fluoroscopy can be used at the bedside to evaluate diaphragmatic movement.

Laryngeal Nerve Injury

BASIC INFORMATION

- Laryngeal nerve injury can result in vocal cord paralysis.

CLINICAL PRESENTATION

- Patients may present with stridor, respiratory distress, a hoarse, faint, or absent cry, and feeding difficulties including dysphagia and aspiration.
- Neonates are diagnosed by direct laryngoscopy.
- Treatment is dependent on severity.

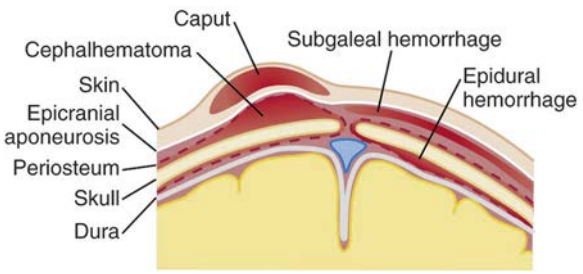

Fig. 59.1 Sites of extracranial (and extradural) hemorrhages in the newborn. Schematic diagram of important tissue planes from skin to dura. (From Kleigman, et al. *Nelson Textbook of Pediatrics.* 19th ed. Philadelphia: Elsevier; 2011 [pp. 565–e93–5, Fig. 93.1].)

Suggested Readings

Akangire G, Carter G. Birth injuries in neonates. *Pediatrics in Review*. 2016;37:451.

Brand MC. Part 1: recognizing neonatal spinal cord injury. *Advances in Neonatal Care*. 2006;(1):15–24.

MacKinnon JA, Perlman M, Kirpalani H, et al. Spinal cord injury at birth: diagnostic and prognostic data in twenty-two patients. *J Pediatr*. 1993;122:431–437.

Menticoglou SM, Perlman M, Manning FA. High cervical spinal cord injury in neonates delivered with forceps: report of 15 cases. *Obstet Gynecol*. 1995;86(Pt 1):589–594.

Questions

1. A newborn presents to the ER after a home water birth and unknown breech presentation with subsequent head and left arm entrapment for 10 minutes. The infant was limp and had no respiratory effort and required resuscitation after birth. Significant traction and torsion were required to deliver the arm and head. The neonate is encephalopathic with some response to stimulation, few spontaneous movements, and poor tone. Given the history, in addition to HIE, which of the following birth injuries would be most likely to be identified in this patient?
   a. Cephalohematoma
   b. Skull fracture
   c. Brachial plexus injury
   d. High cervical spine injury

2a. You are called to the *well-baby nursery* to evaluate a 2-hour-old term infant who was born after a prolonged second stage of labor and required forceps followed by vacuum application times three. The nursing staff is concerned that the baby appears pale and the head feels boggy. You assess the infant and agree that the baby is pale and poorly perfused with a fluctuant-feeling scalp that is diffuse around the head. You are most concerned about which of the following conditions identified in Fig. 59.1?
   a. Caput
   b. Cephalohematoma
   c. Subgaleal hemorrhage
   d. Extradural hemorrhage

2b. You are informed that the head circumference has increased by 2 cm over 1 hour. How much blood could this represent?
   a. 100 cc
   b. 20 cc
   c. 40 cc
   d. 80 cc

2c. What is the next step in management of this patient?
   a. Continued monitoring of infant in mother's room with vital sign checks every 4 hours
   b. Close observation in well-baby nursery environment
   c. No follow up needed
   d. Admission to NICU with placement of umbilical lines, volume resuscitation, and blood transfusion

60 Neonatal Seizures

JENNIFER BURNSED

BASIC INFORMATION

- The neonatal period is one of the most common times for seizures to occur during one's lifetime
- Premature infants are more likely than term infants to have seizures
- Causes are diverse and broad (Table 60.1)
- Most common cause is hypoxic ischemic encephalopathy (HIE)
- Clinical versus electrographic
  - Clinical seizures can be difficult to diagnose (behaviors may actually be normal or state-specific behaviors or nonepileptic abnormal behaviors in a sick neonate) and should be confirmed with electroencephalogram (EEG)
  - Electrographic seizures (seizures on EEG without obvious behavioral manifestations) are common in the encephalopathic neonate
  - Electroclinical disassociation: surface electrodes used for monitoring are unable to pick up activity of "deep" neurons that may be producing clinical events (may be caused by antiepileptic medications or use of neuromuscular blockade)
- Clinical seizure classes
  - Subtle seizures
    - May be referred to as "motor automatisms" or "buccolingual movements"
    - Most commonly observed type
    - Example: repetitive tongue or lip movements, eye movements, "bicycling" of legs, autonomic changes (blood pressure, heart rate, desaturations, apnea)
  - Clonic seizures
    - Rhythmic rapid flexion followed by slow extension
  - Tonic seizures
    - Sustained flexion or extension of the limbs, trunk, or neck
    - EEG correlation is important, as up to 30% of these movements are nonepileptic; either "brainstem release" or tonic posturing
  - Myoclonic seizures
    - Rapid, isolated jerking movements that are generalized, multifocal, or focal
    - Different from clonic seizures because they lack the slow return phase
    - Benign sleep myoclonus of newborn—movements stop when infant aroused to waking state
    - EEG correlation is important in work-up

CLINICAL PRESENTATION

- Presentation depends on seizure type (Table 60.2)
- Nonepileptic behaviors may be mistaken for seizures; generally, seizure activity should be confirmed by EEG
  - Examples: jitteriness, benign sleep myoclonus, neonatal dyskinesia
  - Signs the behavior may be nonepileptic—provoked by sensory stimulation, able to be stopped with touch/restraint, no autonomic changes, no gaze abnormalities
- Neonatal epilepsy syndromes
  - Benign familial neonatal seizures ("third day fits"):
    - Classically begin on day 3 of age
    - Most often resolve in first months of life
    - Potassium channel mutation
  - Benign idiopathic neonatal seizures ("fifth day fits"):
    - Classically begin on day 5 of age
    - Clonic seizures ± apnea
    - Often resolves in first weeks to months of life
- Physical exam may give clues helpful for diagnosis
  - Encephalopathy (hypoxia-ischemia, inborn error of metabolism, infection)
  - Congenital anomalies
    - Facial port-wine stain in V1/V2 distribution: Sturge-Weber Syndrome
    - Cardiac rhabdomyomas ± hypopigmented skin lesions: tuberous sclerosis
    - Congenital deafness + cardiac arrhythmias: ion channel mutation (such as Jervell and Lange-Nielsen Syndromes)

DIAGNOSIS/EVALUATION

- History
  - Birth history to assess for possibility of hypoxic-ischemic encephalopathy
  - Prenatal concern for structural brain abnormality
  - Maternal factors that may lead to electrolyte or metabolic abnormalities (hypoglycemia or hypocalcemia in the infant of a diabetic mother)
  - Maternal drug use or intoxication
  - Family history of seizures/epilepsy or neurologic problems
  - Timing of seizure presentation
    - Fetal (may be observed as frequent "hiccups" by mother): nonketotic hyperglycinemia (classically)
    - <24 hours of age: HIE, infection (meningitis/sepsis), pyridoxine dependent seizures, maternal drug administration, intracranial hemorrhage or injury ante- or peripartum (subarachnoid hemorrhage, intraventricular hemorrhage), hypoglycemia
    - 24–72 hours: infection, neonatal abstinence syndrome/withdrawal, neurocutaneous syndrome, inborn error of metabolism (particularly urea cycle defects), cerebral infarction, cerebral hemorrhage

Table 60.1 Differential Diagnosis of Neonatal Seizures

Electrolyte abnormalities
- Hypoglycemia
- Hypocalcemia
- Hypomagnesemia
- Hypernatremia
- Hyponatremia
- Hypomagnesemia

Metabolic
- Nonketotic hyperglycinemia
- Ketotic hyperglycinemia
- Galactosemia
- Glycogen storage disease
- Urea cycle defects
- Neonatal adrenoleukodystrophy
- Zellweger syndrome

Infectious
- Bacterial meningitis
- Viral encephalitis
- Congenital infection (HSV, CMV, toxoplasmosis)
- Brain abscess

Injury/Cerebrovascular
- Hypoxia-ischemia
- Intraventricular hemorrhage
- Subarachnoid hemorrhage
- Epidural/subdural hematoma
- Cerebral infarct
- Ischemic or hemorrhagic lesions
- Cortical vein thrombosis

Structural/anatomic abnormality
- Cerebral dysgenesis

Genetic
- Autosomal dominant neonatal seizures
- Benign familial seizures
- Neurocutaneous syndromes

Medication/toxin
- Prenatal exposures/withdrawal
- Local anesthetics
- Prescribed medications (isoniazid)

CMV, cytomegalovirus; HSV, herpes simplex virus.
Modified from Gleason C. *Avery's Diseases of the Newborn*. 10th ed. Table 65.2.

Table 60.2 Classification and Clinical Characteristics of Neonatal Seizures

Seizure Class	Characterization
Focal clonic	▪ Repetitive, rhythmic contractions of muscle groups (limbs, face, trunk) ▪ Unifocal or multifocal ▪ May be synchronous or asynchronous in muscle groups on one side of body ▪ May be simultaneous but asynchronous on both sides of body ▪ Cannot be suppressed by restraint ▪ Epileptic
Focal tonic	▪ Sustained posturing of single limbs ▪ Sustained asymmetric trunk posturing ▪ Sustained eye deviation ▪ Cannot be provoked with stimulation or suppressed by restraint ▪ Epileptic
Generalized tonic	▪ Sustained symmetric posturing of limbs, trunk, neck ▪ May be extensor, flexor, or mixed ▪ May be provoked or intensified by stimulation ▪ May be suppressed by restrained or repositioning ▪ Nonepileptic
Myoclonic	▪ Random, single rapid contractions of muscle groups of limbs, face, trunk ▪ Not repetitive or may recur at slow rate ▪ Generalized, focal, or fragmented ▪ May be provoked with stimulation ▪ Epileptic or nonepileptic
Spasms	▪ May be flexor, extensor, or mixed ▪ May occur in clusters ▪ Cannot be provoked or suppressed ▪ Epileptic

Adapted from Gleason C. *Avery's Diseases of the Newborn*. 10th ed. Table 65.1.

  - 72 hours–1 week: familial seizures, cerebral dysgenesis, kernicterus, inborn errors of metabolism (methylmalonic aciduria, propionic acidemia, urea cycle defects), cerebral hemorrhage or infarct
  - 1 week–1 month: cerebral dysgenesis, Herpes simplex virus (HSV) encephalitis, inborn errors of metabolism, tuberous sclerosis
- Laboratory evaluation
  - Blood gas and electrolytes
    - Acidosis may be associated with hypoxic-ischemic encephalopathy or inborn errors of metabolism
    - Hypoglycemia, hyponatremia, hypernatremia, or hypocalcemia as primary cause of seizure
  - Metabolic studies
    - Lactate and pyruvate levels, plasma amino acids, urine organic acids, ammonia
  - Genetic studies if concern for benign familial neonatal seizures/channel gene mutations
  - Cerebrospinal fluid analysis
    - Cell count, culture, Gram stain, glucose, and protein to assess for infection
    - HSV Polymerase chain reaction (PCR) if concern for HSV infection
    - Lactate, pyruvate, and amino acids for metabolic work-up
- Electroencephalography
  - Synchronized video monitoring ideal to correlate behavior
  - Prolonged monitoring is ideal in order to record events concerning for seizures, as well as baseline background of EEG
  - May help identify "seizure focus" based on EEG channels/location with abnormalities
  - Identification of interictal electroencephalographic abnormalities may help with prognosis and outcome
- Imaging
  - Magnetic resonance imaging (MRI) is ideal modality
    - Anatomic abnormality, intracranial hemorrhage (intraventricular, subarachnoid, subdural), venous infarction, perinatal ischemic stroke, hypoxic-ischemic injury
  - Head ultrasound may be useful for some diagnoses if unable to obtain MRI

TREATMENT

- Depends on etiology
  - Antiepileptic drugs (AEDs) may not be necessary in infants with reversible/treatable metabolic or electrolyte derangements (such as hypoglycemia, hypocalcemia, pyridoxine deficiency) or neonatal abstinence syndrome/withdrawal
- Antiepileptic drugs
  - Most commonly used medication is phenobarbital (benzodiazepines, levetiracetam, phenytoin, and valproic acid are also used)
  - Medication choice and length of treatment are dependent on center/clinician—mixed efficacy and safety data in neonates

Suggested Reading

Natarajan N, Ionita C. Neonatal seizures. In: Gleason C, ed. *Avery's Diseases of the Newborn*. 10th ed. Philadelphia: Elsevier Saunders; 2018:961–970.

Questions

1. A term infant is born after an uncomplicated pregnancy and delivery. When the infant is 3 hours old he begins to exhibit lethargy, poor feeding, and movements concerning for seizure. Upon admission to the neonatal intensive care unit he requires intubation for apnea. Frequent seizures are confirmed on electroencephalography (EEG). The infant continues to have seizures despite treatment with three different antiepileptic medications. After administration of another substance, the infant's seizures cease. What is the most likely diagnosis?
   a. Maple syrup urine disease
   b. Hypoxic-ischemic encephalopathy
   c. Pyridoxine-dependent seizures
   d. Subdural hematoma
   e. Kernicterus

61 Central Nervous System Infections

RONNIE GUILLET

Bacterial Meningitis

BASIC INFORMATION

- Overview
  - The incidence of neonatal meningitis is approximately 0.3/1000 live births, with a mortality rate of 10%–15% in term infants and approximately twice that in preterm infants.
  - Bacterial meningitis is more common in the first postnatal month than at any other age. *Early onset* meningitis is that which occurs in the first week (usually first 72 hours), is vertically transmitted, and is associated with complications of labor and delivery; *late onset* meningitis is due to community or nosocomial transmission.
  - There is a poor correlation between blood and CSF (cerebrospinal fluid) cultures. Meningitis occurs in 23% of neonates with sepsis; 20% of neonates with GBS (Group B streptococcus) meningitis have negative blood cultures.
- Pathogens
  - GBS remains the most common in term infants; early onset decreased with GBS screening protocols; no change in frequency of late onset GBS meningitis.
  - Other organisms include gram-negative *Enteric bacilli* (30%–40% of cases) and *Listeria* spp.
    - 50% of gram negatives are *Escherichia coli* (most with K1 polysaccharide capsular antigen): the most common pathogen in preterm infants.
    - Also, *Klebsiella*, *Enterobacter*, *Citrobacter*, *Serratia.*
  - Nosocomial pathogens include *Staphylococcus*, *Candida*, *Pseudomonas.*

CLINICAL MANIFESTATIONS

- Similar to sepsis: temperature instability (60%), irritability, lethargy, decreased tone, seizures, poor feeding, respiratory distress, apnea, diarrhea, full (but not bulging) fontanel.
- Outcomes/prognosis:
  - Mortality has decreased to 10%–20%, though higher in preterm infants.
  - Neurologic sequelae: developmental delay, seizures, hydrocephaly, subdural effusions, ventriculitis, brain abscess (especially *Citrobacter* spp.), cerebral palsy, blindness, hearing loss.
  - Morbidity is correlated with initial severity; predictors of severity include prolonged seizures, coma, need for inotropes, decreased WBC count.
    - 21%–38% of survivors with mild deficits.
    - 24%–29% of survivors with severe deficits.

DIAGNOSIS AND EVALUATION

- Blood culture, CBC (Complete blood count) with differential, urine culture (if newborn at least a week old).
- Lumbar puncture (preferably before initiation of antibiotics).
- CSF interpretation should be based on gestational age, chronologic, age and birth weight (Table 61.1).

Table 61.1 CSF (Cerebrospinal fluid) Reference Ranges

TERM INFANTS[a]				
Postnatal age		Median WBC/mm^3 (IQR)	Median Protein mg/dL (IQR)	Median Glucose mg/dL (IQR)
≤7 days		3 (1–6)	78 (60–100)	50 (44–56)
8 days–6 months		2 (1–4)	57 (42–77)	52 (45–64)
PRETERM INFANTS (<37 WEEKS' GESTATIONAL AGE)[a]				
≤7 days		3 (1–7)	116 (93–138)	53 (43–65)
8 days–6 months		3 (1–4)	93 (69–122)	47 (40–58)
VERY LOW BIRTH WEIGHT INFANTS (24–33 WEEKS' GESTATIONAL AGE)[b]				
BW ≤1000 grams	≤7 days	3 (1–8)	162 (115–222)	70 (41–89)
BW 1001–1500 g	8–28 days	4 (0–14)	159 (95–370)	68 (33–217)
	≤7 days	4 (1–10)	136 (85–176)	74 (50–96)
	8–28 days	7 (0–44)	137 (54–227)	59 (39–109)

BW, Body weight; *IQR*, Interquartile range; *WBC*, white blood cell.
[a]Srinivasan L et al. Cerebrospinal fluid reference ranges in term and preterm infants in the neonatal intensive care unit. *J. Pediatr.* 2012;161(4):729–734.
[b]Rodriguez AF et al. Cerebrospinal fluid values in the very low birthweight infant. *J. Pediatr*. 1990;116(6):971–974.

Table 61.2 Treatment Regimens for Bacterial Meningitis

Organism	Initial Treatment	Subsequent Treatment	Duration	Additional Comments
GBS	Ampicillin + aminoglycoside	Ampicillin or penicillin alone	14 days	Consider repeat LP at end of treatment
Gram-negative	Cefotaxime + aminoglycoside	Cefotaxime alone after negative cultures	21 days	Consider 14 days from negative culture
Citrobacter *Enterobacter* *Serratia* *Pseudomonas*	Fourth generation cephalosporin (cefepime) or carbapenem (meropenem) + aminoglycoside		21 days	Meropenem may be toxic at lower gestational ages and may result in seizures Consider repeat lumbar puncture before stopping antibiotics
Coagulase negative staph	Vancomycin		14–21 days after negative culture	Remove foreign body if possible
Listeria *Enterococcus*	Ampicillin + aminoglycoside	Ampicillin alone	14 days from negative culture	

GBS, Group B Streptococcus; *LP,* lumbar puncture.

- Similar cell counts regardless of gestational age, but counts drop more slowly in preterm infants than in term infants; cell counts decrease with increasing chronologic age.
- 1%–10% of infants with meningitis have normal CSF cell counts.
- 20% of Gram stains are "no organisms seen."
- In *Listeria* meningitis there is a predominance of mononuclear cells.
- CSF protein and glucose concentrations are highly variable.

- Lumbar puncture should be repeated in 24–48 hours if results are not definitive in a symptomatic infant; should be repeated in 2–3 days after start of treatment to assess for sterilization of CSF.

TREATMENT

- Initial therapy: ampicillin and an aminoglycoside; add cefotaxime if a gram-negative is suspected; adjust when organism is identified (Table 61.2).
- Neuroimaging may be considered to exclude parameningeal foci and/or abscess.
- There is no evidence that steroids improve outcome (except in tuberculosis meningitis).

Other Pathogens

HERPES SIMPLEX

- Higher risk of perinatal transmission during initial maternal episode (57% vs. 2%).
- Three categories of disease.
  - Skin, eyes, mouth (SEM): 45%.
  - Disseminated: 25%.
  - Central nervous system (CNS): 30%.
- Presentation of CNS herpes simplex: nonspecific signs and symptoms + bulging fontanelle, generalized or focal seizures; approximately 16–17 days after birth, compared to symptoms presenting on average 9–11 days after birth for other two categories.
- Treatment: markedly reduces mortality (50% to 15% or less) and morbidity.
  - Acyclovir 60 mg/kg/day, in three divided doses for at least 21 days.
  - Suppressive therapy for 6 months.

CANDIDA

- Risk of invasive disease is inversely related to birth weight, as is mortality.
- At least 15% of infants with invasive disease have CNS involvement.
  - Because CSF parameters, cultures, and imaging are unreliable, infants with invasive disease should be presumed to have CNS involvement and be treated accordingly.
- Invasion of CNS results in meningoencephalitis, cerebral abscesses, and ventriculitis with obstructive hydrocephaly.
- Choice of therapeutic agent is guided by presence or absence of renal involvement; continued for at least 21 days.
  - Use antifungal dosing adequate to treat hematogenous meningoencephalitis.
    - AmB-d (amphotericin B-d) 1–1.5 mg/kg/day
    - Fluconazole 12 mg/kg/day; consider loading dose of 25 mg/kg
    - Micafungin 10 mg/kg/day

Suggested Readings

James SH, Kimberlin DW. Neonatal herpes simplex virus infection: epidemiology and treatment. *Clin Perinatol.* 2015;42:47–59.
Kelly MS, Benjamin Jr DK, Smith PB. The epidemiology and diagnosis of invasive candidiasis among premature infants. *Clin Perinatol.* 2015;42:105–117.
Ku LC, Boggess KA, Cohen-Wolkowiez M. Bacterial meningitis in infants. *Clin Perinatol.* 2015;42:29–45.
Remington and Klein. *Infectious Diseases of the Fetus and Newborn Infant.* 8th ed. 2016. Philadelphia, PA; Elsevier.
Wade KC, Monk HM. New antifungal and antiviral dosing. *Clin Perinatol.* 2015;42:177–194.

Question

1. Which is the most common pathogen isolated in meningitis in very low birth weight infants?
   a. Group B *Streptococcus* (GBS)
   b. *Escherichia coli*
   c. *Candida* spp.
   d. *Staphylococcus epidermidis*

62 Neonatal Abstinence Syndromes

LAURA PRICE

Abstinence Syndromes After Opiate, Benzodiazepine, Barbiturate, and Cocaine Exposure

The Modified Finnegan scoring system is the American Academy of Pediatrics (AAP) recommended opiate abstinence scoring system. It is utilized for the evaluation of infants withdrawing from opiates and is not diagnostic of opiate withdrawal. It is often difficult to predict the course of abstinence syndromes in neonates, further complicated by the frequency of polysubstance or polypharmacy exposure. See Table 62.1 for details of each exposure.

ALCOHOL

Fetal Effects

- Increased risk of spontaneous abortion, abruption, breech, poor growth/SGA (symmetric), microcephaly
- Known teratogen associated with anomalies in all organs, including:
  - Central nervous system (CNS) anomalies, neural tube defects
  - Ofacial clefts, skeletal anomalies
  - Cardiac defects (ventricular septal defect (VSD), arterial septal defect (ASD), transposition, tetralogy of Fallot (TOF), great vessel anomalies)
  - Renal agenesis or dysplasia
  - Hypoplastic nails, abnormal fingerprint, hockey stick palmar creases
  - Abnormal hair whorls

Neonatal Effects

- Dose-dependent spectrum from "alcohol effects" to fetal alcohol syndrome (FAS)

Fetal Alcohol Syndrome (FAS)

- Severe disorder affecting growth, IQ, behavior, and appearance
  - Smooth philtrum
  - Thin upper lip vermillion border
  - Short palpebral fissures

Withdrawal

- Rarely recognized and likely underreported
- Symptoms: irritability, tremors, seizures, and opisthotonos
- Long-term effects: attention deficit hyperactivity disorder (ADHD), IQ reduction, and behavioral changes

Treatment

- Environmental support: frequent feeds, holding, decreased stimulation

SELECTIVE SEROTONIN REUPTAKE INHIBITORS

Fetal Effects

- Selective serotonin reuptake inhibitors (SSRIs) readily cross the placenta and fetal blood-brain barrier
- Affect fetal 5-hydroxytryptamine (5-HT) levels
- Associated with increased rates of congenital anomalies (very low absolute numbers):
  - Cardiac defects (right-sided outflow tract defects) (paroxetine: avoid during first trimester)
  - Potential: anencephaly (paroxetine), craniosynostosis, Arnold-Chiari I (controversial)
- Absolute risks of SSRIs are low and should not prevent necessary maternal treatment

Neonatal Effects

- Persistent pulmonary hypertension (PPHN) initially thought to be associated with SSRI use, subsequent data are contradictory
- Neonatal symptoms may be due to toxicity and/or withdrawal
- Timing: present in the first day and resolve by days 2–6
- Toxicity/withdrawal symptoms:
  Tachypnea, irritability, tremors/jittery, temperature instability, poor feeding, seizures
- No reduction in neonatal symptoms with maternal SSRI discontinuation 2 weeks prior to birth
- Breastfeeding preferred (sertraline with lowest concentrations in breast milk)

Treatment

- Environmental supports: frequent feeds, holding, breastfeeding, limiting stimulation
- Pharmacologic therapy
  - Not usually indicated
  - In extreme cases consider phenobarbital or benzodiazepine

Table 62.1 Neonatal Abstinence Syndromes

Exposure	Fetal Effects	Withdrawal	Treatment
Opiates	▪ Placental transfer increases with advancing GA ▪ Methadone crosses placenta more readily than buprenorphine ▪ Fetal dependence increases with methadone ▪ Decreased fetal growth ▪ Increased fetal distress	▪ Timing: peaks 3–4 days after methadone/buprenorphine ▪ CNS: hyperactivity, hypertonia, irritability, tremor, myoclonic jerks, sneezing, fever, and seizure ▪ Respiratory: tachypnea ▪ GI: hyperphagia, increased/poor suck, emesis, diarrhea, weight loss ▪ Vasomotor: nasal congestion, flushing, sweating, mottling ▪ Cutaneous: chin/knee excoriation, facial scratches, diaper dermatitis	▪ Environmental: maximal rooming-in, swaddling, holding, decreased stimulation ▪ Breastfeeding (minimal transfer methadone or buprenorphine) ▪ Morphine PO Q 3–4 hours or ▪ Methadone Q 12–24 hours ▪ ± Phenobarbital adjuvant ▪ Buprenorphine, clonidine therapy being studied
Benzodiazepines	▪ Placental transfer ▪ Significant chronic exposure results in fetal dependence ▪ Acute late third-trimester diazepam treatment results in "floppy infant syndrome" at birth	▪ Timing: at or after the end of the first week of life and may be prolonged ▪ Symptoms: hypertonia, tremors, irritability, sucking, emesis, diarrhea, and seizures ▪ Seizures are more common than in opiate withdrawal	▪ Environmental support ▪ Low-dose phenobarbital
Barbiturates	▪ Placental transfer ▪ Chronic maternal use results in fetal dependence	▪ Timing: later, median 6 days ▪ Symptoms: Hypertonia, hyperactivity, irritable, myoclonic jerks, emesis, diarrhea, and seizures	▪ Environmental support ▪ Low-dose phenobarbital
Cocaine (amphetamines similar effects, limited data)	▪ Placental transfer ▪ Growth restriction ▪ Microcephaly ▪ Fetal stroke ▪ Möbius syndrome ▪ Gastroschisis, NEC ▪ Fetal distress, demise ▪ Prematurity ▪ Abruption	▪ Timing: shortly after birth ▪ Neonatal symptoms thought to be from toxicity, *not* withdrawal ▪ Symptoms: hypertonia, irritability, tremors, tachycardia, arrhythmia, and seizure	▪ Environmental support ▪ Phenobarbital for seizure

CNS, Central nervous system; *GA,* gestational age; *GI,* gastrointestinal tract; *NEC,* necrotizing enterocolitis; *PO,* per os-orally.

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Question

1. You are called to see an 18-hour-old term neonate for tremors, emesis, diarrhea, crying, and 12% weight loss. The maternal history is significant for maternal opiate dependence on buprenorphine 16 mg daily. Social history reveals cigarette smoking ½ pack per day (½ ppd). Prenatal course was otherwise uncomplicated with normal anatomic scan. Urine toxicology screens during pregnancy and on admission were all negative. Labor and delivery were unremarkable. Which of the following statements about this neonate is true?
   a. If the mother was treated with methadone instead of buprenorphine, the baby would likely have less significant withdrawal.
   b. The mother should be counseled against breastfeeding, given her dose of buprenorphine.
   c. Modified Finnegan abstinence scoring should be initiated to confirm the diagnosis of NAS.
   d. This patient will likely require increased caloric density and volume of feeds.
   e. The mother was noncompliant with her buprenorphine therapy before delivery.

63 Neurology: Hypotonia and Other Aspects

NIRANJANA NATARAJAN

Hypotonia and Weakness

BASIC INFORMATION

- Hypotonia can be secondary to specific genetic causes or secondary to disorders affecting the central or peripheral nervous system. Key features on the history and examination may help distinguish these causes, along with further diagnostic evaluation.
- Syndromic or genetic disorders can also cause neonatal hypotonia.
- Central nervous system (CNS) causes include brain malformations; peripheral nervous system causes include disorders of the motor neuron, neuromuscular junction, and primary muscle diseases, such as muscular dystrophies and myopathies.

CLINICAL FINDINGS AND HISTORY

- Clinical manifestations of neuromuscular disorders include:
  - Facial hypotonia, with open-mouth appearance (so-called cupid's bow or carp appearance)
  - Decreased spontaneous movement and decreased tone for gestational age
  - Respiratory failure, with or without a bell-shaped chest, without respiratory disease
  - Muscle contractures
- Evaluation of deep tendon reflexes can help the clinician distinguish central causes from peripheral causes of weakness. The presence of increased reflexes localizes to the CNS, whereas the absence of reflexes raises concern for a motor neuron or muscle process.
- Evaluation for signs of neonatal encephalopathy or presence of seizures may suggest a CNS abnormality. Note that neuromuscular conditions may also predispose the neonate to difficulty in the birthing process, and thus hypoxic-ischemic encephalopathy may coexist.
- The presence of dysmorphic features, cardiac disease, or other multiorgan involvement can indicate various genetic causes of hypotonia or inborn errors of metabolism to clinician.
- Pregnancy history should include questions regarding fetal movement, history of prior pregnancy losses, and family history of neurologic disorders.
- Examination of the mother, including assessment of facial weakness and myotonia, may indicate specific causes of neonatal hypotonia and weakness to the clinician.

DIFFERENTIAL DIAGNOSIS

- Congenital muscular dystrophies present with significant hypotonia and weakness, along with significant elevation of creatine phosphokinase (CPK), a muscle breakdown product.
- Alpha-dystroglycanopathies may also involve the eye and brain, so ophthalmologic evaluation and neuroimaging by magnetic resonance imaging (MRI) are recommended.
- Congenital myotonic dystrophy is a disorder presenting differently in the neonate as compared to the child or adult. Clinical features include facial diplegia, so-called cupid's bow or carp appearance to the mouth, bell-shaped chest, and talipes equinovarus. Respiratory failure is common secondary to pulmonary hypoplasia and poor intercostal muscle development. The history often reveals polyhydramnios and reduced fetal movement. This disorder displays genetic anticipation; a parent (typically the mother) is affected with facial diplegia, grip myotonia, and cardiac conduction defects.
  - Presence of grip myotonia in the mother should raise suspicion of this disorder.
  - Genetic testing of the *DMPK* gene on chromosome 19 and CTG repeat in the 3′ noncoding region should be performed. CTG repeats greater than 1000 are typically seen.
  - Mortality rates for congenital myotonic dystrophy are as high as 25%–40%; however, infants surviving the neonatal period can survive into childhood and early adulthood, with close respiratory and cardiac follow-up. Survivors typically have cognitive impairment.
- The term *congenital myopathies* refers to a group of muscle diseases that do not result in dystrophic changes on muscle biopsy. Affected individuals may present with hypotonia and weakness, as well as respiratory failure due to weak intercostal muscles and diaphragm. Electromyography (EMG) demonstrates myopathic changes, and muscle biopsy may help drive the genetic work-up.
- Spinal muscular atrophy (SMA) is a disorder of the motor neuron that occurs in approximately 1 in 10,000 live births. Neonates with SMA may have severe hypotonia and weakness affecting lower extremities > upper extremities, proximal muscles > than distal muscles. The face is spared; tongue fasciculations are often present and should be evaluated for on examination. Reflexes are absent. When suspected, it is imperative to send testing for the *SMN1* gene on chromosome 5, which is absent, as well as *SMN2*, a modifier gene. Historically, treatment

has been supportive, with death often in the first year of life without aggressive respiratory management. However, nusinersen, an antisense oligonucleotide, approved by the US Food and Drug Administration (FDA) in December 2016, has been shown to improve outcome in patients with SMA.

- Congenital myasthenic syndromes is a heterogeneous group of disorders characterized by defects in neuromuscular transmission at the neuromuscular junction. Neonates may present with hypotonia, bulbar weakness, and/or respiratory failure. CPK values and muscle biopsy are typically normal or nonspecific. Repetitive nerve stimulation obtained with nerve conduction studies suggests the diagnosis, allowing for further genetic testing.
- Congenital peripheral neuropathies are a rare cause of neonatal hypotonia. Findings on examination include the absence of reflexes and distal > proximal weakness, typically with feet abnormalities. The CPK level is normal. If EMG demonstrates neuropathic findings, further genetic evaluation indicated.
- Congenital brain malformations can result in hypotonia. The examination may indicate normal to increased reflexes, sustained clonus, encephalopathy, or seizures. Neuroimaging is indicated.
- Hypotonia with encephalopathy may be a feature in the presentation of inborn errors of metabolism. Work-up and management are discussed elsewhere in this chapter.
- The presence of specific dysmorphic features or multisystem involvement should raise concern for specific syndromes, which include trisomy 21, Smith-Lemli-Opitz syndrome, Pompe disease, and congenital disorders of glycosylation.

DIAGNOSTIC EVALUATION

Although the diagnostic evaluation should be tailored to the clinical presentation, testing that should be considered in all neonates with hypotonia is underlined.

- CPK—significantly elevated levels (five times normal) can be seen in muscular dystrophies; mildly elevated levels may be seen in congenital myopathies or SMA.
- MRI of the brain should be done.
- EMG and nerve conduction studies should be used early in the diagnostic process when a peripheral cause of weakness is suspected; these can help distinguish between a myopathic or neuropathic process. Repetitive nerve stimulation can determine a neuromuscular junction disorder.
- Muscle biopsy, testing of the *SMN1* and *SMN2* modifier genes (necessary in all neonates with hypotonia and absent reflexes for SMA) and thyroid studies should be carried out.

In infants with multisystem involvement, the following should also be considered:

- Genetic testing with karyotype—should be considered in individuals with dysmorphic features consistent with trisomy 21 (e.g., facial features, including up-slanting palpebral fissures, flat nasal bridge; brachycephaly, single palmar crease, and a short neck).
- Chromosomal microarray analysis in patients with dysmorphic features.
- DNA methylation analysis of the 15q11.2-q13 region for Prader-Willi syndrome.
- Cardiac enlargement on chest x-ray or cardiac failure with associated elevation in CPK seen in Pompe disease—confirmatory testing should be done; reduced or absent alpha-glucosidase (GAA) enzyme activity by dried blood spot, lymphocytes, or fibroblasts confirm disease; enzyme replacement therapy available for infant-onset disease.
- Carbohydrate transferrin for testing of congenital disorders of N-glycosylation.
- 7-dehydrocholesterol levels for testing of Smith-Lemli-Opitz.

MANAGEMENT

- Management of neonatal neuromuscular disorders is largely supportive, with early involvement of pulmonary services for respiratory support.
- Physical therapy and rehabilitation services, as well as consultation with neurology, should be implemented early in the evaluation.
- Early identification of SMA or Pompe disease may allow for early initiation of treatment to alter the disease course.

Arthrogryposis

BASIC INFORMATION

- The term *arthrogryposis multiplex congenita* (AMC) refers to fixed joint contractures affecting two or more limbs that are congenital and apparent at birth. This is distinguished from isolated talipes equinovarus, or dislocated hips, for example.
- AMC is a descriptive term and syndrome; further evaluation is necessary to determine the cause.

PATHOGENESIS

- Over 400 causes of specific disorders associated with AMC have been described. AMC develops secondary to decreased fetal movement, termed *fetal akinesia.*
- AMC causes can be separated into intrinsic, extrinsic, and environmental factors to aid the clinician in determining the cause.
  - Intrinsic factors include myopathic, neuropathic, central nervous system, or neuromuscular transmission disorders.
  - Environmental causes include maternal illnesses or infections affecting the fetus, maternal medications, or drug exposures.
  - Extrinsic causes include disorders resulting in compression of the fetus, such as Potter syndrome, or limitation of the in utero space by any cause, such as large uterine fibromas.

EVALUATION

- History is geared toward determining factors related to pregnancy—maternal infection or fever, trauma, and

medication exposure, as well as fetal movements in utero. Earlier onset of fetal akinesia is associated with increased severity.
- Physical examination—pay close attention to which joints are affected, whether distribution is more proximal or distal, flexor versus extensor muscles. The neonate's position at rest and degree of spontaneous movement may indicate a neuromuscular cause to the provider.
- Physical examination should be done for other associated anomalies, facial involvement, renal anomalies, or other organ involvement. Associated anomalies or dysmorphisms may help with determining causative factors.
- Imaging evaluation should include radiography of bony abnormalities or if there is concern for dislocated joints. Magnetic resonance imaging of the brain and spinal cord may be appropriate to evaluate for CNS involvement.
- The CPK level should be determined if there is a concern for neuromuscular weakness. EMG and nerve conduction studies with repetitive nerve stimulation should be performed. If these are abnormal, muscle biopsy of affected and unaffected tissue with specific staining is typically indicated.
- Genetic testing for SMA should be considered, including chromosomal microarray analysis if there are multiple anomalies.

MANAGEMENT AND OUTCOMES

- Management is geared toward determination of the cause, as well as orthopedic, rehabilitation, and multidisciplinary care.
- Outcome is based on the underlying cause; most patients have normal intelligence.
- Orthopedic complications include scoliosis, osteoporosis, and fractures; these require close monitoring to maximize outcome.

Vascular Malformations

VEIN OF GALEN MALFORMATION

- The vein of Galen malformation is the most common congenital arteriovenous (AV) shunt in the neonate.
- Although still named for the vein of Galen, this malformation stems from an embryonic precursor, the median vein of the prosencephalon, which typically regresses by the 11th week of gestation and is replaced by internal cerebral veins. The large AV shunt has feeder veins.
- The so-called vascular steal phenomenon is caused by an absence or reversal of diastolic flow due to the large size of the venous malformation, resulting in brain ischemia.
- High-output heart failure results from a decrease in cerebrovascular resistance and increased venous return to the heart. This cardiac failure may add to brain ischemia.
- Prenatally detected in some neonates by imaging, others may present in the neonatal intensive care unit (NICU) with high-output cardiac failure secondary to AV shunting. Typically, an asymmetric systolic-diastolic bruit can be auscultated over the anterior fontanel or eyeballs.
- Potential neurologic complications include worsening vascular steal phenomena, thrombosis of the vein of Galen, and hemorrhagic rupture of the vein.
- Systemic complications include worsening or refractory cardiac failure, with multiorgan involvement.
- Management includes early involvement of neurosurgery, with embolization of feeder vessels to decrease the vascular steal phenomenon.

STURGE-WEBER SYNDROME

- Port wine stains are a common finding in newborns; approximately 6% of newborns with facial port wine stain may have Sturge-Weber syndrome. This increases to 26% if the ophthalmologic distribution of the trigeminal nerve (cranial nerve V_1) is involved.
- The classic triad of Sturge-Weber syndrome includes facial hemangioma, ipsilateral increased intraocular pressure or glaucoma, and leptomeningeal involvement with vascular malformation.
- Somatic mutations in *GNAQ* are causative of Sturge-Weber syndrome, and these mutations can be found in affected skin in patients.
- Neuroimaging with MRI is recommended in neonates with port wine stain in the following cases:
  - affecting the V_1 distribution
  - also found to have ophthalmologic or neurologic involvement, V_2 or V_3 involvement, or nevus extending to the eyelid
- Seizures may occur by 2 years of age, requiring antiepileptic therapy. Stroke-like episodes, migraines, and developmental delay may also occur.

PHACES SYNDROME

- PHACES syndrome stands for **p**osterior fossa abnormalities, **h**emangiomas, **a**rterial malformations, **c**ardiac abnormalities/coarctation of the aorta, **e**ye abnormalities, and **s**ternal defects syndrome. First described in 1996, consensus-derived diagnosis and care recommendations have been recently proposed. Infants with large segmental hemangioma affecting the head, infants with a less characteristic hemangioma but additional lesions concerning for PHACES, or infants with other characteristic anomalies for PHACES without hemangioma should be screened for PHACES syndrome with physical examination, MRI, and MR angiography of the brain, neck, and aortic arch, as well as an ophthalmologic examination.

Congenital Cerebral Neoplasms

- Neonatal brain tumors are relatively uncommon, 0.5%–1.5% of all pediatric brain tumors.
- Congenital brain tumors have a predilection for the supratentorium rather than the infratentorium, which is more common in childhood.
- The most common congenital tumor in the central nervous system is teratoma. Of all teratomas, 20% emerge from the lateral ventricles, and another 10%–20% are estimated to arise from the third ventricle.
- Other congenital tumors include medulloblastomas or other primitive neuroepithelial tumors, choroid plexus tumors (papilloma or carcinoma), astrocytomas (which include subependymal giant cell tumors and glioblastoma multiforme), and craniopharyngiomas.

- The most common presentation may be incidental on fetal ultrasound or may be due to the presence of hydrocephalus found pre- or postnatally. Other common presentations include irritability and stillbirth. Neonates may also present with seizures, although incidence of this is low.

MANAGEMENT

- If there is concern for a tumor seen on prenatal imaging, further imaging evaluation is imperative to aid in diagnosis because a fetal biopsy is not feasible.
- It is necessary to formulate a birth plan to address potential complications from hydrocephalus and associated macrocrania during delivery.
- Early consultation with neurosurgery to determine potential interventions such as a ventriculoperitoneal shunt or surgical debulking should be obtained.
- Radiotherapy is used infrequently due to the potential for long-term cognitive and motor effects.

PROGNOSIS

- The prognosis of congenital brain tumors depends on several factors, including lesion histology and location and degree of fetal development. Tumors compressing the brainstem are surgically challenging to access and may result in brainstem compromise. In these cases, mortality can be high; patients with choroid plexus papillomas or astrocytomas fare better because tumors generally can be accessed more easily and do not cause brainstem compression.

Neurocutaneous Disorders

- Neurocutaneous disorders, also named *phakomatoses,* are disorders that have CNS, dermatologic, and often ocular findings. Many of these are thought to stem from the common origin of these organ systems from the ectoderm.

INCONTINENTIA PIGMENTI

- This can affect the skin, teeth, hair, nails, eyes, and CNS.
- It has four stages that occur over a span of years.
- The initial vesicular stage typically presents prior to 6 months of age and can be present in the neonatal period.
- Vesicular lesions typically are linear and are on the body with facial sparing. They can initially appear as erythema only.
- It is an X-linked disorder. Deletion in *IKBKG* is causative and is de novo in 65% of patients.
- The diagnosis can be made genetically; however, affected males may necessitate a skin biopsy for determination.
- Evaluation should include brain MRI and ophthalmology consultation because patients are at risk for retinal detachment.

HYPOMELANOSIS OF ITO

- Decreased pigmentation (hypomelanosis) following the lines of Blaschko is associated with intracranial abnormalities.
- Multiple chromosomal abnormalities have been associated with hypomelanosis of Ito, but no distinct cause is known.
- Cell mosaicism is known to occur with the various abnormalities. Cases are thought to be sporadic in nature.

TUBEROUS SCLEROSIS COMPLEX

- Tuberous sclerosis complex (TSC) occurs in as many as 1 in 5800 live births. It is caused by a mutation in the gene hamartin or tuberin and is inherited in an autosomal dominant fashion.
- Neurologically, TSC can present in infancy or childhood with seizures. Although this presentation is reported in neonates, most affected newborns are found prenatally to have cardiac rhabdomyomas. Further investigation then reveals additional factors such as subependymal giant cell tumors, neuronal migration defects, and/or cortical tubers.
- Although a neurocutaneous disorder, classic ash leaf spots, or hypopigmented macules, may be difficult to visualize in the newborn. Use of a Wood's lamp (ultraviolet, UV lamp) may help elucidate skin lesions.

Suggested Readings

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Questions

1. A 2-day-old infant born at 38 weeks requires intubation at birth secondary to poor respiratory effort. The pregnancy and delivery were otherwise uncomplicated. The following day, she fails an extubation trial. On your examination, you note an intubated baby who awakens easily to your examination but holds her mouth open around the endotracheal tube. She has bilateral talipes equinovarus. You note decreased spontaneous movements with a frog-leg position and significant head lag. You are unable to obtain deep tendon reflexes. Which of the following points in the history can lead to the final diagnosis?
   a. Maternal report of decreased fetal movements
   b. Maternal report of prior fetal losses
   c. Maternal report of hand weakness
   d. Maternal report of alcohol use during pregnancy

2. You are called to examine a 2-hour-old neonate born at 39 weeks, 6 days for possible therapeutic hypothermia secondary to concern for hypoxic-ischemic encephalopathy. He was born to a 24-year-old G1 mother with gestational diabetes. The delivery was complicated by shoulder dystocia, with Apgar scores of 1, 1, and 2 at 1, 5, and 10 minutes of life. Initial blood gas pH in the baby is 6.9, with a base deficit of 13. On examination, the neonate is noted to be lying still, with arms extended. On attempts to arouse him with stimulation, he is noted to make spontaneous movements. However, he returns to his initial state once you stop stimulation. On forced eye opening, you note small but reactive pupils. He is noted to have an incomplete Moro response and absent suck, with gag reflex present. On tests of tone, you note a frog-leg position and excessive head lag. Deep tendon reflexes are brisk, with spread to the adjacent joint. He is intubated but is noted to be breathing over the ventilator rate without difficulty. Which of the following best describes his level of encephalopathy based on his examination?
   a. Normal
   b. Mild encephalopathy
   c. Moderate encephalopathy
   d. Severe encephalopathy

SECTION 16

Neurodevelopment

ALLISON H. PAYNE

64 Incidence of Neurodevelopmental Impairments

ALLISON H. PAYNE

Background

DEFINITIONS

- Neurodevelopmental impairment (NDI) is a composite outcome that typically includes any one of the following:
  - Cerebral palsy
  - Cognitive disability (generally IQ <70; i.e., −2 standard deviations [SDs])
    - Most common disability in preterm infants
  - Severe hearing impairment (requiring at least amplification)
  - Severe visual impairment (visual acuity <20/200, despite correction)
- Additional adverse developmental outcomes are more common and may have significant impact on daily functioning.
  - Global or specific learning disabilities
  - Language delay
  - Minor neuromotor dysfunction
  - Behavioral and attention problems
    - Two to six times as prevalent in preterms compared with term peers; may not be associated with hyperactivity or conduct issues in preterms
  - Executive function disorders
  - Autism spectrum disorders: ~5% of preterms (3× general population)
  - Anxiety
  - Depression
  - Sensory impairments, especially in preterm infants
    - Retinopathy of prematurity leading to vision impairment
    - Myopia and strabismus
    - Hearing impairment (1%–10%)

INCIDENCE

- Rates of childhood neurodevelopmental disabilities increase with the number and severity of neonatal morbidities, neuroimaging abnormalities, and neonatal neurodevelopmental assessment abnormalities.
- In general, neurodevelopmental disabilities, whether mild, moderate, or severe, increase in frequency and risk with decreasing gestational age or birth weight.
  - Full term: 2%
  - Late preterm: 2%–3%
    - Cerebral palsy: 0.4% (~3× term)
    - Severe cognitive impairment: 0.8% (~2× term)
    - Lower scores than term peers—in school readiness, reading, math, and expressive language testing at school age
      - ~1.4× risk for testing below grade level compared to term peers
    - Differences between late preterms and term peers in learning disabilities or attention issues—may disappear by late adolescence
  - Moderate preterm: 3%–4%
    - Cerebral palsy: ~1%
    - Developmental delay: ~30%–35%
    - Increased behavioral and emotional concerns over term peers
    - Poorer cognitive testing
    - Poorer neuropsychological functioning in specific areas—visuospatial reasoning, attention control, inhibition, and executive function
  - Very preterm: 10%
    - Cerebral palsy: ~4%
    - Developmental delay: ~40%
    - Mild cognitive impairment: ~20%
    - Severe cognitive impairment: ~10%
  - Extremely preterm
    - 25–26 weeks' gestational age (GA): up to 40%
    - <25 weeks GA: up to 70%
      - Any disability (cognitive, motor, sensory):
        - None: ~⅓
        - Mild: ~⅓
        - Moderate–severe: ~⅓
      - Moderate cognitive impairment: 19% (~9× risk at term)
      - Severe cognitive impairment: 11% (~30× risk at term)
      - Cerebral palsy: 7%–10% (~20–40× risk at term)
      - Blindness: 1%–2%
      - Hearing impairment: 1%–2%
      - Special education needs: ~60%
      - Increased risk of neurobehavioral issues (attention, attention-deficit/hyperactivity disorder [ADHD], anxiety, autism)
      - Subject-specific learning issues: math, spelling, written language

RISK FACTORS

- Severe asphyxia
- Intraventricular hemorrhage
- Periventricular leukomalacia

- Chronic lung disease
- Sepsis or meningitis
- Neonatal seizures
- Intrauterine growth restriction
- Postnatal steroid exposure, especially early (<8 days of age) or repeated courses

POTENTIAL PROTECTIVE FACTORS IN PRETERM DELIVERIES

- Antenatal steroids, indirectly by reducing risk of intraventricular hemorrhage and duration of mechanical ventilation, bronchopulmonary dysplasia (BPD)
- Antenatal magnesium sulfate, decreased risk of severe motor dysfunction, including cerebral palsy

CAUSES

MONOCHORIONIC DIAMNIOTIC (MCDA) TWINS

- 20% of all twin gestations
- MCDA twins share a common placenta; the placental vascular anastomoses present confer a risk for:
  - Twin-twin transfusion syndrome (TTTS)
  - Twin anemia polycythemia sequence (TAPS)
  - Twin reversed arterial perfusion (TRAP)
  - Selective intrauterine growth restriction
- In the case of spontaneous fetal demise of one fetus, the co-twin may exsanguinate through the placental vascular anastomoses to the deceased twin
  - The co-twin is at risk of death (15%) of severe cerebral injury (34%).
  - There is a risk of multicystic encephalomalacia (20%), cerebral palsy (10%), other neurologic injury (porencephaly, intraventricular hemorrhage [IVH]; 10%), and multiorgan damage in survivors.
- Up to 23% of MCDA versus 4% of dichorionic diamniotic (DCDA) twins have neurologic morbidity, but this may be decreasing (to ~10%) with advances in prenatal interventions
  - Borderline motor delay, 19%
  - Language delays, 14%
  - Anxiety, 5%
  - Cerebral palsy, 2%
  - Injury to the surviving twin is at the time of the intrauterine fetal demise (IUFD).
  - Immediate delivery of survivor is not associated with improved outcome, and additional risks associated with prematurity are incurred.

Twin-Twin Transfusion Syndrome

- This affects 5%–15% of monochorionic pregnancies, but rarely in the setting of fused dichorionic placentation.
- Mortality is 80%–90% untreated, 20%–40% for both twins, in spite of aggressive therapy.
- Two-thirds of cases of a single IUFD in TTTS involve the demise of the donor twin.
- Ischemic brain lesions may result from intrauterine cardiac dysfunction or hemodynamic instability, including:
  - Leukoencephalopathy, IVH, hydranencephaly, porencephaly
- The rate of abnormality on neurologic imaging is ~7% with fetoscopic laser treatment, 17% with amnioreductions. Long-term outcomes have not shown significant differences, but studies have been limited.
- In cases diagnosed at <28 weeks' gestation, ~25% of both donor and recipient twins have abnormal findings on cranial ultrasound.
  - Severe IVH, ventricular dilation, cerebral echogenic foci, cerebral cysts, periventricular leukomalacia (PVL)
  - ~10% of abnormalities are PVL—high association with cerebral palsy
- Long-term outcomes in TTTS.
  - Amnioreduction cohorts
    - ~25% of survivors following serial amnioreduction with cerebral palsy (CP)
      - Risk of CP decreased to ~5% in cohorts with later diagnosis (<33 weeks)
    - ~20% of survivors without CP or significant cognitive impairment—have mild speech delays or special education requirement
  - Fetoscopic laser photocoagulation cohorts
    - 6%–13% with significant neurologic deficits (e.g., CP, hemiparesis, spastic quadriplegia)—many of these cases also with increased prematurity
    - 7%–11% with minor neurologic deficits (e.g., strabismus, minor motor delays, mild speech impairments)

FETAL (INTRAUTERINE) GROWTH RESTRICTION (FGR)

- Brain-sparing size does not equal normal brain development
  - Decreased total cerebral volume and total number of brain cells
  - Thinner cortical thickness and abnormal gyration
  - Reduced structural complexity of gray and white matter
  - Delay in myelination
  - Reduced posterior white matter volume
- Neurodevelopmental outcomes—influenced by timing of onset, severity of growth restriction, and gestational age at delivery
- Early-onset FGR
  - Increased risk of motor, cognitive, and behavioral concerns at age 2 years and at school age
    - These outcomes may be confounded by preterm birth
- Late-onset FGR
  - Increased risk of abnormal neurobehavior in the neonatal period and at age 2 years
- If FGR is associated with abnormal Doppler studies
  - Poorer motor and cognitive outcomes at 2 years old and school age
- FGR—risk factor for perinatal brain injury
  - Association with IVH is variable in clinical studies
  - Abnormal umbilical artery Dopplers in the setting of placental insufficiency associated with increased risk for IVH
  - In early to moderate preterm infants, IVH rates lower in FGR infants compared to appropriate for gestational age AGA preterms at given gestational age
  - In late preterm births (>34 weeks), IVH rates for FGR infants elevated compared to AGA late preterms
- Neurodevelopmental outcome

- Cognitive deficits
  - 15% of FGR with brain-sparing cohort with IQ <85 (–1 SD). At school age, abnormal umbilical artery Dopplers associated with 9-point drop in IQ compared to those with normal Dopplers
- Gross and fine motor deficits
  - 22% of spastic CP cases may be attributed to IUGR
- Reduced memory performance
- Reduced visuomotor function
- Associated with increased risks of attention-deficit/hyperactivity disorder (ADHD), anxiety, depression, poor social skills, behavioral concerns, and autism spectrum disorder
- Similar developmental and behavioral outcomes as birth weight matched controls (i.e., more preterm, AGA, not growth restricted)
- Early preterm birth (<28 weeks): AGA and small-for-gestational age (SGA) infants with similar incidence of cognitive deficits, attention deficits/hyperactivity, school difficulties
- Preterm birth 29–32 weeks—SGA infants with increased risk over AGA peers for cognitive deficits, ADHD, school difficulties
- Risk of poor outcome increased with perinatal acidosis, male gender

BRONCHOPULMONARY DYSPLASIA

- Increased risk for cognitive, language, motor, hearing, and vision deficits and CP
  - 3 years old: BPD—doubled risk for neurodevelopmental disability
  - 8 years: BPD survivors 1.5 times more likely to require special education classes compared to very low birth weight (VLBW) infants without BPD
  - Middle school: BPD associated with higher rates of subtle neurologic deficits, perceptual motor integration, motor coordination, processing speeds, and behavioral difficulties
  - Adult: deficits in problem solving, behavior awareness, organization
- Difficult to tease out direct association of BPD to outcomes because these infants may also have prolonged illness and hospitalization, increased exposure to corticosteroids or sedatives, and poor nutrition

CONGENITAL HEART DISEASE

- Among children with complex congenital heart disease (CHD) requiring surgical repair, approximately 50% have later signs of neurodevelopmental disability.
  - May include one or more of the following:
    - Cognitive impairment
    - Learning difficulties
    - Expressive speech and language abnormalities
    - Visual-spatial and visual-motor impairments
    - Motor delays
    - ADHD
    - Deficits in executive function
  - Disabilities—generally mild to moderate in severity but may occur in multiple domains and have a significant impact on academic and social functioning.
  - Increased need for special education and therapeutic support in about one-third.
- One-third of operative CHD patients have an underlying genetic disorder that may contribute to worse neurodevelopmental outcomes.
- Fetal brain development may be abnormal or injured due to abnormal fetal blood flow or increased cerebral vascular resistance associated with the CHD, leading to:
  - Immaturity of central nervous system (CNS) development
  - Microcephaly (~25% incidence in complex CHD cohorts)
  - White matter injury, stroke, hemorrhage
- Postnatal cerebral ischemia may occur before, during, and after surgical repair.
- White matter injury is the predominant injury pattern detected on MRI.
  - PVL in ~25% of preoperative and >50% of postoperative cases
  - Increased risk in those with immature brain morphology
- Brain immaturity predicts early neurodevelopmental outcome. Preoperative and postoperative injuries do not.
- Characteristics are as follows:
  - Infancy and toddler years: generalized hypotonia, delayed motor milestones.
  - Motor scores tend to improve over first 3 years, continued risk for fine motor and visuomotor impairments.
    - CP in ~2% of complex CHD cases
  - Predominant issues in school age children include language impairments (particularly expressive), memory, and slower processing speeds.
  - Most children without genetic disorders have cognitive IQ scores in the normal range; as a group, there is ~5- to 10-point decrease in mean IQ.
  - Learning difficulties may be identified only with increase D cognitive demand with increasingly complex tasks at later school ages.
  - There are problems with peer interaction and emotional symptoms and executive function disorders; difficulties may persist into adolescence and adulthood.
- Repairs using circulatory arrest show particular issues with motor and speech functioning.
- Repairs using bypass show worse scores for impulsivity and behavior.

PERSISTENT PULMONARY HYPERTENSION OF THE NEWBORN (PPHN)

- 25% neurodevelopmental impairment and 23% hearing impairment, despite early inhaled nitric oxide (iNO)
- In severe disease, mortality lower for infants placed on extracorporeal membrane oxygenation (ECMO), without increasing disability

CONGENITAL DIAPHRAGMATIC HERNIA (CDH)

- Improved respiratory and surgical management of CDH patients have improved survival rates, up to 70%–90%.
- There are multiple risk factors for neurodevelopmental impairment:

  - Prenatal adverse impact on CNS development, with cerebral circulation changes
  - Postnatal hypoxia-ischemia, emboli, reactive oxygen species, acidosis, sedation, inflammatory microvasculopathy (may affect white matter maturation)
  - Increased risks for IVH, PVL, and seizures compared to term normal peers
- Severity of illness, prenatal intrathoracic liver, the need for ECMO, and continued oxygen requirement at 28 days of life are associated with developmental delays.
- Cognition and language development:
  - 50%–60% in normal range
  - 25%–35% borderline/mild range
  - 15 %–25% severe range
  - Categorization is relatively stable over time
- Motor development:
  - Most prominent domain for developmental delays
  - 30%–50% with motor dysfunction (mild to severe)
    - May present as persistent hypotonia, delayed motor coordination
  - Recent cohort with 33% of cohort below average on visual-motor integration
    - Children with lower scores at risk for fine motor coordination, motor planning, visual processing, higher academic achievement.
  - Some evidence in older age cohorts that motor delays may be transient or improve over time
- Hearing:
  - 17%–30% sensorineural hearing loss (SNHL), about two-thirds with delayed onset
  - Risk factors: need for ECMO, increased duration of mechanical ventilation, duration of loop diuretics, aminoglycosides
  - Hearing deficits impact language acquisition, social development, academic achievement
- Behavioral
  - Increased risk for emotion and behavior regulation, poor attention, poor peer interaction and development of social skills, associated with lower acquisition of higher level academic skills and school failure
  - Emerging concerns for associations of CDH and autism
    - Recent cohort with 11% autism versus 1.5% in the general population

HYPOXIC-ISCHEMIC ENCEPHALOPATHY (HIE)

- HIE is one of many causes of neonatal encephalopathy.
- Historically, the outcome is strongly associated with Sarnat staging.
  - Mild (stage 1): ~5% of survivors with >6-month gross motor delay
  - Moderate (stage 2)
    - 4% mortality
    - ~16% of survivors with >6-month gross motor delay,
    - 21%–33% of survivors with handicap (e.g., CP, cognitive delay, severe vision or hearing impairment, severe seizures)
  - Severe (stage 3)
    - 75% mortality
    - 100% of survivors with handicap (types noted above)
- The outcome of infants with HIE can be favorably altered by the use of therapeutic hypothermia.
- Therapeutic hypothermia for moderate or severe encephalopathy initiated at <6 hours of life and continued for 72 hours decreases the risk for NDI or death. A meta-analysis of major randomized cooling trials has shown the following:
  - 24% reduction in risk of death or NDI at 2 years
  - 32%–38% reduction in risk of major disability, CP, or developmental delay
  - ~44% reduction in risk of blindness
  - Nonsignificant decrease in deafness
  - Survival without neurologic abnormality, ~1.6 times more likely if cooled (24% controls, 40% cooled)
  - For cooled infants, decrease in death does not lead to increase in neurologic abnormality among survivors
- Therapeutic hypothermia has the greatest impact on the outcomes of infants with moderate encephalopathy.
  - Moderate: 33% reduction in risk of death or NDI
  - Severe: 17% reduction in risk of death or NDI

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65 Causes and Effects of Environment on Neurodevelopmental Impairment

ALLISON H. PAYNE

Nutrition and Neurodevelopment

Nutrition plays a significant role in supporting the structural and functional development of the brain from conception into adulthood. Both the nutritional status of the mother during pregnancy and the postnatal diet of the infant can have long-term impact.

- Prenatal maternal factors
  - Maternal nutrition and health during pregnancy—additional factors in the cause of fetal growth restriction (FGR) and subsequent outcomes (see FGR section)
  - Maternal risk factors for intrauterine growth restriction (IUGR) and FGR—may include nutritional deficiency, severe anemia, smoking, toxins (e.g., warfarin, anticonvulsants, caffeine), assisted reproductive technology
- Prenatal nutrition
  - Dietary quality, not simply caloric intake, is important because specific nutrients are required during sensitive and critical periods of development.
    - Folate: neural tube development (supplement decreases risk), nucleotide synthesis, methylation, transcription; possible effects on memory and role in schizophrenia and depression
    - Choline: neural tube development, DNA methylation, epigenetics; required for formation of membranes, including gray and white matter phospholipids
    - Vitamin B_{12}: DNA methylation, epinephrine and methionine synthesis
    - Zinc: neuron formation, migration, synaptogenesis
    - Tryptophan: formation of neurotransmitters
    - Omega-3 fatty acids: development of neural cell membranes
      - Accumulation of DHA in the second half of gestation associated with rapid gray matter increases; associations with cognitive and behavioral development
    - Iodine: deficiency may lead to disruption of fetal neurogenesis, neuronal migration, synaptogenesis, myelination; associated with reduced intellectual ability, impaired executive functioning
    - Iron: necessary for myelination and development of the frontal cortex and basal ganglia, important for dopamine metabolism; iron deficiency been shown to affect cognitive, motor, socioemotional, behavioral development adversely
    - Retinoic acid (vitamin A derivative): role in molecular signaling pathways in the brain and promotion of cellular differentiation; also important in dopamine-regulated cognitive and motor activity
    - Thiamine: deficiency associated with specific language impairments (syntax and lexical retrieval)

Postnatal Nutrition

- Maternal breastfeeding and milk
  - The duration of breastfeeding is associated with IQ in some but not all studies for both term and low birth weight infants.
  - The magnitude of the effect of human milk on neurodevelopment seems to be dose dependent in premature infants, with sustained effects into toddler ages.
  - Maternal infant bonding is enhanced with breastfeeding.
    - Oxytocin serves as a neurotransmitter and directly affects maternal nurturing behaviors and maternal-infant social interactions.
- Specific nutrients
  - Iodine: deficiency associated with decreased cognitive performance
  - Iron: influences psychological functioning; deficiency in early infancy may lead to sustained poor cognitive performance, affects development of auditory processing and executive function, contributes to poor academic achievement, behavior issues
  - Zinc: deficiency associated with reduced cognitive and motor performance, higher incidence of attention-deficit/hyperactivity disorder (ADHD) and depression
  - Folate: positive association between folate intake and academic achievement
  - Protein deprivation: reduced brain weight, altered formation of the hippocampus, impairment of neurotransmitter

Non-nutritional Maternal-Infant Factors

- Maternal (prenatal) inflammation
  - Proinflammatory cytokines damage oligodendrocytes and their progenitors, potentially affecting downstream myelination.

- Chorioamnionitis in preterm infants is associated with gray matter developmental impairments.
- Breast milk is an important protective factor against sepsis and necrotizing enterocolitis.

- Maternal-infant bonding
  - The development of attachment between the parent and infant begins well before birth, perhaps as early as prepregnancy planning.
  - Influences include the parent's own childhood experiences, previous pregnancy experiences or losses, relationship status with partner, and availability of support systems.
  - Fetal exposure to maternal anxiety, depression, and stress is associated with cognitive delays, ADHD, poor executive function, dysregulation of stress responses, internalizing and externalizing problems, and greater negative emotionality in infancy and childhood.
  - Positive factors:
    - Early skin to skin contact
    - Early suckling at breast (within first hour)
    - Rooming-in
    - Parent-infant synchrony (recognition of and response to infant needs)
  - Risk factors for poor attachment:
    - Poor maternal-fetal bonding during pregnancy
    - Perinatal depression
    - Congenital malformations
    - Disruption in maternal-infant interaction in the immediate postnatal period
    - Infant requiring NICU care → anxiety and stress
    - Postpartum depression
  - Outcomes of poor bonding and attachment:
    - Breastfeeding failure
    - Child abuse, abandonment, neglect
    - Failure to thrive
    - Developmental delays
    - Increased risk of anxiety or depression in the child later in life

POTENTIAL INTERVENTIONS

- Kangaroo care
  - Improved physiologic stability of infant, including heart rate, respiratory rate, temperature
  - Improved lactation success
  - Sustained group differences to 6 months and beyond
  - Improved infant emotional and cognitive outcomes
- Parent involvement in care
  - Parent behavioral intervention programs help parents recognize infant stress and readiness for interaction cues.
    - Reduction in maternal depression and anxiety, increased confidence in parental roles, reduction in length of stay
- Positioning
  - Infants requiring neonatal intensive care, especially premature infants, are more prone to positional plagiocephaly and dolichocephaly.
  - Midline positioning of the head in preterm infants <32 weeks may be associated with decreased incidence of intraventricular hemorrhage (IVH).
    - Turned head may lead to occlusion of the jugular venous drainage system and venule leakage in the germinal matrix
  - For all infants: the Back To Sleep Campaign, while reducing the risk of sudden infant death syndrome (SIDS), has increased rates of plagiocephaly and torticollis.
  - Regular changes in posture for preterm infants at rest promote normal neuromuscular and osteoarticular function and permit development of spontaneous and functional motor activity.
    - Prone-only positioning in the 31- to 36-week gestational age (GA) range was associated with dominance of extensor muscles, hyperabduction and flexion of the arms, and global neuromuscular rigidity.
  - Neuromotor problems in preterm infants are caused by imbalances between active and passive muscle power in the extrauterine environment.
  - Prone positioning for very low birth weight (VLBW) infants has been associated with better physiologic stability:
    - Improved gas exchange (increased Pa_{O_2}, decreasing P_{CO_2})
    - Decreased respiratory rate
    - Improved chest wall synchrony
    - Increased overall sleep state and decreased energy expenditure
    - More rapid gastric emptying and less reflux

FAMILY RISK FACTORS

- Social and environmental risk factors adversely affect child development and parent well-being, in addition to medical risk factors for the infant. These include the following:
  - Separated families
  - Low socioeconomic status
  - Low caregiver educational level
- Infants with increased social risk factors may demonstrate more benefit from interventional services than infants with fewer social risks.
- The combination of medical and social-environmental risk factors is associated with particular vulnerability for poor neurodevelopmental outcome.

Early Intervention

- *Early intervention* is a nonspecific term referring to a range of interventions including, but not limited to, family support, physical therapy, occupational therapy, and speech and language therapies, introduced typically by age 3 years in the hope of taking advantage of developmental windows and neuroplasticity to optimize global and/or specific neurodevelopmental outcomes.
- Eligibility for early intervention services varies from state to state and internationally.
- Although early intervention has not been proven to prevent neurodevelopmental disability, there are many studies that demonstrate the benefit of early intervention programs.
  - There may be particular benefits of early interventions in the setting of severe hearing (hearing aids, sign

language) and severe visual impairment to promote foundations of communication, daily functioning, and quality of life.
  - Educational interventions for preterm infants have shown beneficial effects on cognition, behavior, and motor outcomes through preschool ages, but significant differences have not been seen at school age and beyond.
- Studies of early intervention, particularly of long-term effects, are difficult. Such longitudinal studies are not only costly but heavily influenced by individual differences and social and environmental factors.
- Interventions aimed at an infant's family, such as targeting maternal anxiety or depression and family coping, may improve parent functioning and outcomes and subsequently influence infant outcomes.

OTHER DEVELOPMENTAL INFLUENCES

- Vision
  - Vitamin A deficiency is the leading cause of childhood blindness.
  - Causes of congenital blindness or poor vision include the following:
    - Leber congenital amaurosis
    - Retinal dystrophies
    - Congenital cataracts
      - Significant cataracts must be removed by 6–8 weeks of age to prevent vision loss from dense amblyopia.
    - Glaucoma
      - In neonates, this is a surgical disease requiring prompt intervention. Vision loss is generally irreversible.
    - Optic nerve abnormalities
    - Uveal colobomas
    - High refractive errors
    - Congenital infections
    - Hyphema
    - Cerebral (cortical) visual impairment—normal eye, visual impairment secondary to neurologic cause
      - Greatest cause of visual impairment in children in developed countries, most often associated with neurologic deficit (e.g., cerebral palsy [CP], epilepsy)
      - Perinatal causes include intrauterine infections, cerebral dysgenesis, asphyxia, hypoglycemia, intracranial hemorrhages, periventricular leukomalacia (PVL), hydrocephalus, trauma, meningitis, and encephalitis
  - Retinoblastoma is the most common ocular malignancy of childhood.
    - Untreated: nearly uniformly fatal
    - 5-year survival >90% with timely recognition and treatment
    - Typically diagnosed between 1 and 2 years of age
  - Retinopathy of prematurity (ROP):
    - ROP is generally first diagnosed at 31–32 weeks' postmenstrual age, with progression over the next 2–5 weeks. Most VLBW infants (<1500 g) will have some degree of ROP.
    - Stages 1–3 most often spontaneously regress.
    - Stages 4–5 likely to have poor or no functional vision, despite surgical intervention.
  - Among preterm infants, myopia and strabismus are common outcomes.

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66 Clinical Features of Neurodevelopmental Impairment

ALLISON H. PAYNE

Developmental Assessments

Corrected age (age from original due date), not chronologic age (from date of birth), should be used for all assessments of milestones, cognition, language, and motor development until at least 2 years' corrected age. All ages mentioned in this section refer to corrected age.

- Timing
  - Assessments before 1 year of age are limited to detection of major motor and sensory disabilities.
  - Reliable assessment of neurodevelopmental outcome improves at ≥2 years.
    - Most transient neurologic abnormalities resolve by 18–24 months.
    - Language may be difficult to assess before the age of 3 years.
  - 4–5 years: cognitive and language function testing is more precise.
  - >6 years: subtle neurologic abnormalities, behavioral outcomes, and academic performance may be assessed.
  - Assessment at young ages likely to overestimate neurodevelopmetal impairment (NDI) rates
  - Assessment at school age or adolescence—will more accurately reflect long-term outcome
- Tools

  There is no true gold standard in developmental assessment.
  - The Bayley Scales of Infant and Toddler Development is the most common tool for cognitive and motor developmental assessment in high-risk infants up to age 3 years. Direct comparisons of cohorts tested with different Bayley editions are difficult.
    - Norm-referenced—mean, 100, standard deviation, 15
    - First and second editions include:
      - MDI (Mental Developmental Index): composite outcome of cognitive and language areas
      - PDI (Psychomotor Developmental Index): composite outcome of fine and gross motor skills
    - Third edition (2006) includes five scales:
      - Cognitive
      - Language
      - Motor
      - Socioemotional
      - Adaptive behavior
  - Cognitive assessment tools
    - Report on intelligence (a component of cognition), processing, memory, reasoning abilities, strengths and weaknesses in specific areas of learning
    - Intended to be descriptive of functioning at the time of testing, not predictive of future functioning
    - Have poor long-term validity for infant cognitive testing due to:
      - Measurement error and testing cooperation
      - Educational exposures and environmental factors experienced
    - Cognitive testing may be affected by visual, hearing, attention, behavioral issues
  - Parent reports of development (e.g., Ages and Stages Questionnaire)—can be very valuable in screening high-risk infants who may qualify for further evaluation or services

Transient Neurologic Abnormalities

- Abnormalities of
  - Muscle tone (hypotonia or hypertonia)
  - Posture
  - Primitive reflexes
- High incidence in high-risk infants: 40%–80%
- Peak prevalence for transient neurologic abnormalities is between 4–7 months' corrected age
- Generally resolve by 12 months' corrected age
- Preterm children with a history of transient neurologic abnormalities and subsequent normalized neurologic examination have:
  - Increased risk for lower cognitive and academic skills compared to preterm children with consistently normal neurologic examination
  - Better outcomes than preterms with persistently abnormal examinations

Developmental Coordination Disorder

Developmental coordination disorder (DCD) has also been previously referred to as *mild functional motor impairment* or *minor neuromotor dysfunction*.

- Common neuromotor condition
  - Affects ~5%–6% of all school age children
  - Affects ~one-third of all preterm children (~6−8x increased risk compared to term)
  - Boys > girls (2–3:1)

- Non–cerebral palsy motor impairment
  - Motor (fine or gross) coordination (e.g., issues with balance, coordination, dexterity) worse than expected for chronologic age.
    - Does not relate to a medical condition (e.g., cerebral palsy, muscular dystrophy, visual impairment, or intellectual disability)
    - Interferes with academic achievement or activities of daily living
    - Is in excess of what is expected for IQ if intellectual disability is present
  - Typically described as clumsy
    - May also show slowness and inaccuracy in motor skill performance.
  - Previous motor delays not prerequisite, but may be present in history
- Risk Factors
  - Prematurity, particularly <32 weeks gestation
  - Small for gestational age
  - Late independent walking (≥15 months)
  - Postnatal steroid exposure
  - Intraventricular hemorrhage (IVH), periventricular leukomalacia (PVL)—do not independently increase risk for DCD
- Assessment
  - Developmental Coordination Disorder Questionnaire (DCDQ)
  - Movement Assessment Battery for Children (MABC-2)
  - Bruininks-Oseretsky Test of Motor Proficiency
- Frequent comorbidities, including attention-deficit/hyperactivity disorder (ADHD), autism spectrum disorders, or specific learning disabilities
- At risk for overweight and obesity, physical injuries, psychosocial difficulties, compromised physical fitness, decreased participation in daily living, physical, and social activities
- Long-term outcomes suggest DCD may be associated with increased depression and anxiety rates, lower quality of life
  - Motor skills (e.g., driving, handwriting) and executive functioning (planning ahead, multitasking)—may continue to be problematic in adulthood

Cerebral Palsy

- Most common physical disability in childhood
  - Prevalence 1–4/1000 live births, increased in high-risk populations
    - Approximately half of all children with cerebral palsy (CP) are born at term; half are preterm
    - In general, males higher risk than females
    - Term: 0.9–1.5/1000 (~0.15%)
    - Multiples: 7/1000 (~0.7%)
    - Fetal growth restriction (>35 weeks): 3–5/1000 (~0.4%)
    - Preterm birth
      - <1000 g birth weight: 50/1000 (~5%)
      - 27–32 weeks' gestational age (GA): 60–80/1000 (6%–-8%)
      - <28 weeks' GA: 82/1000 (~8%)
      - <25 weeks' GA: 100–120/1000 (10%–12%)
  - Preterm infants at risk
    - Postnatal risk factors confer greatest risk
    - Additional risk factors—maternal infection, multiple gestation, exposure to postnatal steroids, need for high-frequency ventilation, pneumothorax, sepsis, necrotizing enterocolitis (NEC), African-American ethnicity, low socioeconomic status (SES)
    - With abnormality on head ultrasound (HUS)
      - With any IVH without PVL:
        - Infants <26 weeks have worse outcomes than infants 27–32 weeks
          - <25 weeks: normal HUS, ~10% CP; any IVH, ~20% CP
          - Week by week, stable rates of CP at 27–32 weeks for same HUS finding
          - If VP shunt needed for posthemorrhagic hydrocephalus, risk increases
        - If PVL or intraparenchymal hemorrhage:
          - CP risk, 40%–60%
          - GA does not affect CP risk
  - Term infants at risk
    - In utero factors confer greater risk in outcome of CP than perinatal or postnatal factors
      - Congenital malformations (particularly of the central nervous system [CNS]), stroke, fetal growth restriction
    - Maternal factors: infections, hypothyroidism, severe proteinuria
    - Perinatal and postnatal risk factors:
      - Ischemic stroke
      - Neonatal encephalopathy
      - 5-minute Apgar <3: 5%–7% risk of CP
      - Severe hyperbilirubinemia
- Clinical description of a group of permanent disorders of the development of movement and posture affecting motor function
  - No specific pathologic or radiographic correlates
  - Due to nonprogressive disturbance of fetal or infant brain development (injury or malformation)
- Motor aspects of CP frequently accompanied by difficulties with cognition, communication, sensation, perception, behavior, and musculoskeletal abnormalities
  - CP has a nonprogressive cause, but secondary impairments may change over time.

DIAGNOSIS

- Onset during perinatal or infancy period but diagnosis reserved until at least 2–3 years of age to establish permanent nature
- In infants with significant risk factors for CP and severe motor impairment on assessment, provisional diagnosis of CP can occur within first 2 years
- Examination may show
  - Hyper- or hypotonia
  - Difficulty with oral feeds
  - Hand preference
  - Prominent fisting
  - Asymmetric crawling
  - Persistent primitive reflexes

- Ankle clonus
- Leg scissoring
- May also show behavioral abnormalities
  - Excessive crying, jitteriness, abnormal sleep patterns, irritability
- Underlying cause not progressive, but clinical presentation of a child with CP may change over time with brain maturity

CLASSIFICATION

See Fig. 66.1.

- Spastic CP accounts for 85% of all cases (up to 90% in preterm infants) and includes increased tone with velocity-dependent resistance to passive movement and pathologic reflexes (hyperreflexive, Babinski response).
  - Spastic diplegia (~35% of overall CP)
    - Affects the lower extremities with no or minimal upper extremity involvement
      - Often first noted with a persistent commando crawl (uses arms but drags legs behind)
      - Often seen with leg scissoring and toe walking
    - Predominant type for preterm infants (~75% of cases)
      - One-third with cognitive impairment
      - Most common cause—PVL
    - Strongly associated with damage to the immature white matter
    - Most will walk but may require assistance or devices; can achieve independent care with bowel and bladder control
  - Spastic hemiplegia (~25% of overall CP)
    - Affects unilateral upper and lower extremities and trunk
      - Arm often involved more than leg
      - Typical difficulty with hand manipulation
      - Circumductive gait
    - Most common in cases of:
      - Unilateral stroke
      - Vascular malformations
      - Unilateral IVH or PVL
    - Typically able to walk by 3 years of age
    - ~Two-thirds with cognitive and learning impairments
  - Spastic quadriplegia (20% of overall CP)
    - Most severe form of CP
    - Causes: PVL, ischemia, infection
    - Low likelihood of ambulation
    - Often with flexion contractures at knees and elbows
    - High association with intellectual, speech, and visual disabilities and seizures
- Extrapyramidal (athetoid) CP (15% of overall CP)
  - Characteristically hypotonic, with poor head control and head lag, with progression over years to variable increased tone with rigidity
  - Upper extremities affected more than lower extremities
  - Feeding and speech may be difficult
  - Seizures uncommon
  - Seen in cases of basal ganglia and thalamus injury
    - Asphyxia—symmetric scars of putamen and thalamus
    - Kernicterus—scars in globus pallidus and hippocampus
    - Mitochondrial genetic disorders

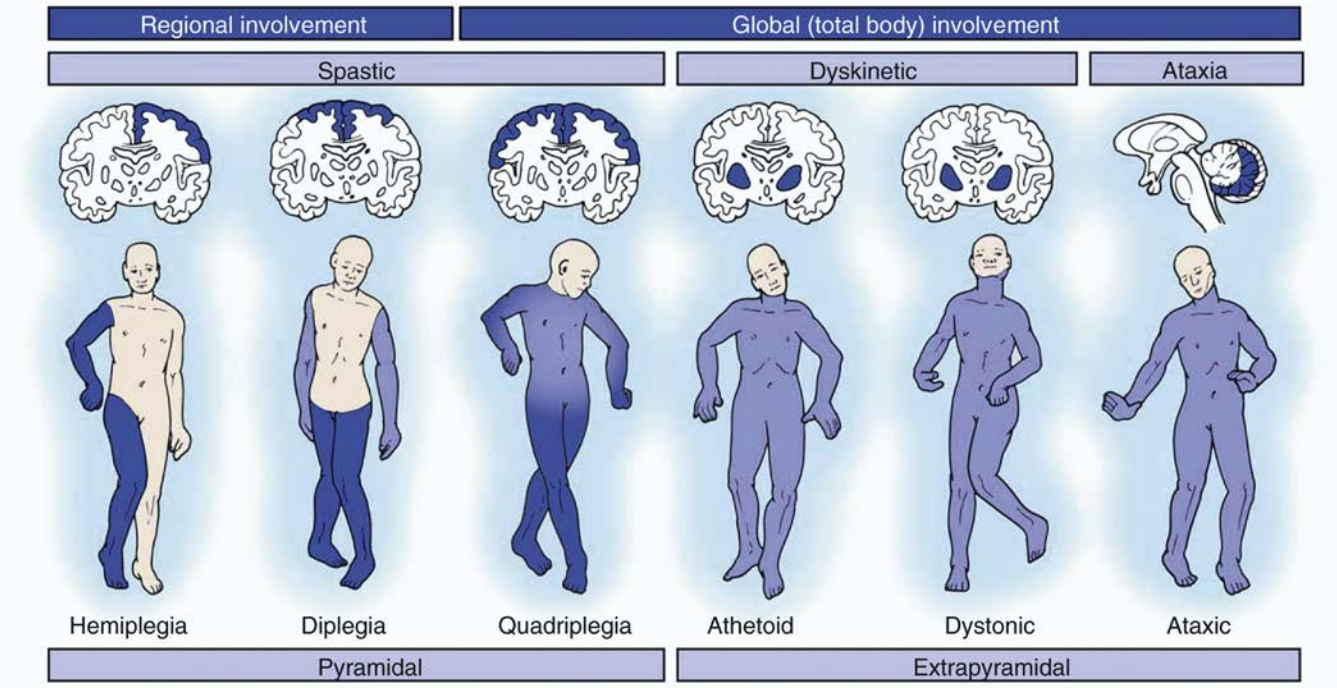

Fig. 66.1 Classification of cerebral palsy. Although overlaps in terminology exist, cerebral palsy can be classified according to distribution (regional vs. global involvement, hemiplegic, diplegic, quadriplegic), physiologic type (spastic, dyskinetic or dystonic, dyskinetic or athetoid, ataxic), or presumed neurologic substrate (pyramidal, extrapyramidal). (From *Campbell's Operative Orthopaedics*. 11th ed. Philadelphia: Elsevier/Mosby; 2008.)

FUNCTIONAL CLASSIFICATION

- Wide spectrum of severity for cerebral palsy:
  - Some children will achieve ambulation (~60% independent, ~10% assisted).
    - More common if head control by 9 months, suppression of primitive reflexes by 18–24 months, and sitting by 2 years (corrected)
    - If independent ambulation is achieved by 3 years of age, likely to be sustained through adulthood
  - ~30% of children will not achieve ambulation.
- The Gross Motor Function Classification System (GMFCS) is often used to describe mild, moderate, and severe status and better understanding of prognosis.
  - Five nonoverlapping categories
    - Level 1, most able → level 5, least able
    - Criteria for categories separated into age bands (infant, early child, school age)
  - Levels 1 and 5 usually stable over time
  - Levels 2–4 less stable over time (level may change based on age-specific criteria)
  - Levels 1–2 typically ambulate without assistance; may run, jump, climb stairs
  - Level 3 children—tend to ambulate independently with assistance (walkers, crutches, braces)
  - Levels 4–5 typically wheelchair-bound; vary in ability to control the wheelchair independently

PROGNOSIS

- CP may have associated comorbidities related to the underlying cause:
  - Pain
  - Seizures
  - Growth or nutrition failure
  - Incontinence
  - Sleep and behavioral problems
  - Autism spectrum disorders
- Children with CP require ongoing multidisciplinary care, including neurology, orthopedics, development and rehabilitation, ophthalmology, speech, audiology, and occupational and physical therapies to optimize outcome.
- Interventions should be started as early as possible (when there are any concerns, even before ability to diagnose CP definitively) to take advantage of brain plasticity and developmental windows for language, cognitive, and motor development.
- Possible treatments include the following:
  - Assistive or adaptive devices to achieve mobility
  - Communication technology, sign language
  - Baclofen (botulinum toxin) or surgical interventions for spasticity
  - Goals of treatment—to prevent deformity, optimize motor function, improve quality of life

Quality of Life

- Parents of preterm adolescents report poorer health, behavior, and physical functioning.
  - However, the self-reporting adolescent shows no differences compared to term peers.
- In young adulthood, physical functioning and cognition are reported as lower than peers, but subjective quality of life no different.
- Discrepancies may indicate differing definitions of quality of life or adaptation over time.

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SECTION 17

Eye, Ear, Nose, and Throat

MATTHEW GEARINGER, BENJAMIN HAMMOND, LYNDY J. WILCOX and CATHERINE K. HART

67 Eye Development, Retinopathy of Prematurity

MATTHEW GEARINGER and BENJAMIN HAMMOND

Normal Development and Anatomy

- Development of eye during embryonic period: weeks 3–10
  - Involves ectoderm, neural crest cells and mesenchyme
- Normal axial length, 17 mm in newborn (24 mm in adults)
- Corneal diameter, 10 mm in newborn (12 mm in adults)
- Retinal vasculature mature in most full-term infants (see Retinopathy of Prematurity section)
- Central macula underdeveloped at birth, becomes normal at 6 months
- Visual function about 20/400 at birth, becomes 20/20 by 6 months–3 years depending on measurement method

Congenital Abnormalities

Eyelids and Orbit

BASIC INFORMATION

- Congenital ptosis
  - Abnormal drooping of the upper eyelid
  - Most common cause of childhood ptosis
  - Causes of congenital ptosis
  - Simple congenital (myopathic) ptosis
    - Most common cause of congenital ptosis
    - Due to developmental myopathy of the levator muscle
    - Ptosis present at birth, remains stable throughout life
    - Unilateral, 69%
    - Coexisting strabismus in 30%
  - Blepharophimosis syndrome
    - Severe bilateral ptosis, with poor levator function
    - Palpebral fissures horizontally shortened (blepharophimosis)
    - Autosomal dominant inheritance
  - Marcus Gunn jaw-winking syndrome
    - Synkinetic (involuntary movement) ptosis
    - Predominantly unilateral
    - Sporadic, no inheritance pattern
    - Intermittent elevation of the ptotic eyelid, occurring with contraction of the muscles of mastication, leading to a "winking" movement during eating or chewing
- Acquired ptosis—includes third nerve palsy, Horner syndrome, myasthenia gravis, mechanical ptosis (birth trauma, hemangioma)

CLINICAL PRESENTATION

- Orbit malformations can cause strabismus, proptosis, or optic nerve compression.

DIAGNOSIS AND EVALUATION

- Check lid position with respect to pupil.
- Check ocular rotations for strabismus.

TREATMENT

- Early surgical repair of ptosis if amblyogenic
- Topical or systemic beta blocker for large hemangioma

Corneal Opacification

BASIC INFORMATION

- Can lead to severe amblyopia if untreated

CLINICAL PRESENTATION

- Localized or diffuse corneal clouding; may have microcystic edema or tears in Descemet membrane

DIAGNOSIS AND EVALUATION

- Forceps trauma—often with focal edema and vertical Descemet tears
- Glaucoma—diffuse clouding with enlarged diameter and microcystic edema
- Metabolic diseases—bilateral diffuse haze, with thickened stroma
- Ocular disease (Peter anomaly—sclerocornea, dermoid, ***c***ongenital ***h***ereditary ***e***ndothelial ***d***ystrophy [CHED])

TREATMENT

- Lower intraocular pressure.
- Treat underlying metabolic disease.
- Perform corneal transplantation.

Leukocoria

BASIC INFORMATION

- White pupil due to decreased red reflex from the retina

CLINICAL PRESENTATION

- Opacity of cornea or lens
- Vitreous opacity—vitritis, vitreous hemorrhage
- Retinal disease (detachment, retinoblastoma, coloboma, myelinated nerve fibers)

DIAGNOSIS AND EVALUATION

- Slit lamp examination of cornea, iris, and lens
- Dilated fundus examination of vitreous, retina, and optic nerve
- Ultrasound to evaluate posterior segment

TREATMENT

- Cataract extraction or vitrectomy for cataract, hemorrhage, or detachment
- Oncology evaluation for retinoblastoma

Congenital Cataract

BASIC INFORMATION

- Can lead to severe deprivation amblyopia if left untreated
- Congenital cataracts: noted at birth
- Infantile cataracts: occur in first year of life

CLINICAL PRESENTATION

- Abnormal or absent red reflex
- Decreased visual behavior or nystagmus
- Congenital cataracts may be associated with:
  - Trisomy 21
  - Trisomy 13
  - Trisomy 18
  - Cri du chat syndrome
  - Turner syndrome
  - Galactosemia
  - Fabry disease
  - Lowe syndrome
  - Alport syndrome
  - Congenital infections: rubella
- Nonsyndromic congenital cataract
  - One-third of all congenital cataracts are familial, not associated with other systemic disorders
  - Coppock cataract
    - Familial
    - Associated with γ-crystallin gene on chromosome 2q34-q35

DIAGNOSIS AND EVALUATION

- Slit lamp examination to determine size and morphology
- Testing for syndromic, nonsyndromic, and systemic disorders (as noted earlier)
- Genetics evaluation

TREATMENT

- If visually significant, lensectomy by 2–3 months old
- If small or faint, pharmacologic dilation
- Amblyopia management

Congenital Glaucoma

BASIC INFORMATION

- Increased intraocular pressure leading to corneal edema and optic nerve damage
- Congenital glaucoma can be inherited as an autosomal recessive: two genes identified (*CYP1B1* and *LTBP2*)

CLINICAL PRESENTATION

- Classic triad: photophobia, blepharospasm, epiphora
- Associated with systemic disease: Sturge-Weber syndrome, neurofibromatosis type 1 (NF-1), Lowe syndrome
- Associated with ocular disease: Axenfeld-Rieger syndrome, aniridia, Peter anomaly, cataract

DIAGNOSIS AND EVALUATION

- Corneal haze, increased corneal diameter (>11 mm in newborns)
- Increased intraocular pressure, optic disc cupping

TREATMENT

- Topical ocular hypotensive medication as a temporizing measure
- Surgical treatment to lower pressure (goniotomy, trabeculotomy)

Optic Nerve and Retina

BASIC INFORMATION

- Optic nerve anomalies (hypoplasia, coloboma, morning glory disc anomaly)
- Retinal disease (coloboma, Leber congenital amaurosis, rod-cone dystrophies)

CLINICAL PRESENTATION

- Decreased visual behavior, nystagmus
- Sluggish pupillary response

DIAGNOSIS AND EVALUATION

- Dilated fundus examination
- Electroretinography for retinal disease
- Endocrine evaluation in septooptic dysplasia

TREATMENT

- Management of associated systemic disorders
- Early intervention, low vision evaluation

Acquired Abnormalities

Congenital Infections

BASIC INFORMATION

- Due to transplacental or vaginal exposure to TORCH organisms (***t***oxoplasmosis, ***o***ther infections, ***r***ubella, ***c***ytomegalovirus [CMV], and ***h***erpes simplex virus [HSV])

CLINICAL PRESENTATION

- Cataract: rubella, CMV
- Cornea (keratitis): HSV, syphilis
- Retinopathy: toxoplasmosis, rubella, CMV, syphilis

DIAGNOSIS AND EVALUATION

- Titers and cultures for responsible agents

TREATMENT

- Targeted at causative agent with consideration of systemic involvement

Nasolacrimal Duct Obstruction

BASIC INFORMATION

- In 5% of newborns, due to failure of canalization of nasolacrimal duct

CLINICAL PRESENTATION

- Tearing with mucus

DIAGNOSIS AND EVALUATION

- Dye disappearance test
- Rule out congenital glaucoma

TREATMENT

- Nasolacrimal probing and possible stent if not resolved by 6–12 months

Ophthalmia Neonatorum

BASIC INFORMATION

- Conjunctivitis within the first month of life
- At risk for systemic infection (*Neisseria, Chlamydia,* HSV)

CLINICAL PRESENTATION

- Conjunctival injection, eyelid swelling, eyelid crusting, discharge (clear or mucopurulent)

DIAGNOSIS AND EVALUATION

- Culture with Gram stain
- *Neisseria:* onset 3 days to 3 weeks, copious discharge
- *Chlamydia:* onset around 1 week, mild discharge
- HSV: onset in second week of life
- Chemical: onset within 24 hours of medicine administration, self-limited

TREATMENT

- Prophylaxis (erythromycin or tetracycline)
- Systemic treatment for *Neisseria* (ceftriaxone), *Chlamydia* (erythromycin), and HSV (acyclovir)
- May need topical antibiotic or antiviral

Ocular Trauma

BASIC INFORMATION

- Difficult deliveries and shaking injuries can cause damage to the retina and cornea.

CLINICAL PRESENTATION

- Unilateral corneal opacity following forceps delivery
- Hemorrhages in the subconjunctival space or retina

DIAGNOSIS AND EVALUATION

- Breaks in Descemet membrane are seen with forceps injury. There will be no other signs of glaucoma, ocular dysgenesis, or infection,
- Look for retinal hemorrhage on dilated funduscopic examination.
- Retinal hemorrhages from birth trauma are mild and resolve within 4–6 weeks.
- Retinal hemorrhages from nonaccidental trauma can be mild or severe and often involve multiple layers of the retina.
- Retinal detachment and retinoschisis may occur after shaking injury and are exceptionally rare in other forms of trauma.

TREATMENT

- Patching when at risk for amblyopia
- Vitrectomy for severe or nonclearing vitreous hemorrhage
- Evaluation for nonaccidental trauma when clinically suspected

Retinoblastoma

BASIC INFORMATION

- This is the most common malignant pediatric ocular tumor.
- Mutations in both alleles of the retinoblastoma gene (*RB1*) on chromosome 13 are found.
- 40% of cases result from the inheritance of one mutated allele:

  - A somatic mutation to the second allele is needed to develop retinoblastoma.
  - Most bilateral cases of retinoblastoma are inherited.
- 60% result from somatic nonhereditary mutations to both alleles.
- If parent has bilateral retinoblastoma, each child has a 45% risk for the disease.
- If parent has unilateral retinoblastoma, each child has a 7%–15% risk. If a child develops retinoblastoma, which indicates a heritable mutation, each subsequent child will carry a 45% risk.
- Chromosome 13q deletion may include the *RB1* gene and result in retinoblastoma.

CLINICAL PRESENTATION

- Abnormal red reflex (leukocoria) and strabismus may be present.
- Poor vision in one or both eyes may be noted.
- Inherited and bilateral cases are typically diagnosed when the child is younger than 12 months of age.

DIAGNOSIS AND EVALUATION

- Perform dilated fundus examination to look for a retinal mass.
- Ultrasound imaging may be helpful when a fundus examination is limited.
- Larger masses may have calcifications or vitreous seeding.
- Obtain MRI scan to rule out trilateral retinoblastoma—retinoblastoma with neuroectodermal tumor of the pineal gland.
- Children who have a parent or sibling with retinoblastoma need early and regular screening.

TREATMENT

- Systemic chemotherapy is the most common primary treatment.
- Local consolidation is needed after chemotherapy or as primary therapy in small tumors (typically photocoagulation and cryotherapy).
- Intraarterial or intravitreal chemotherapy may be used in select cases and may reduce the need for systemic chemotherapy.
- The survival rate is high (>95%), and most eyes are salvaged.
- Enucleation may be needed in advanced cases (especially unilateral).
- Heritable germinal mutations put a child at risk for secondary malignancies, including pinealoma, sarcoma, melanoma, and carcinomas (incidence rate, 1%/year of life).
- Lifetime monitoring is needed.

Vascular Development of the Retina

NORMAL DEVELOPMENT

- Retinal vasculature originates from the optic nerve at around 16 weeks' gestation.
- In the relatively hypoxic, in utero environment; a gradient of proangiogenic growth factors, including vascular endothelial growth factor (VEGF), develops and drives vessel growth from the vascular retina to avascular areas.
- Full vascularization finishes between 36 and 40 weeks' gestation.

ABNORMAL DEVELOPMENT IN PREMATURE INFANTS

- Infants born prematurely are exposed to a hyperoxic environment relative to the in utero environment.
- VEGF and other growth factors decrease, delaying vessel growth into the peripheral retina, phase 1 of retinopathy of prematurity (ROP).
- Hypoxia develops in the peripheral avascular retina; accentuated by fluctuations in the supply of oxygen.
- An increase in proangiogenic factors causes abnormal vascular development at the border of the vascular and avascular retina (phase 2 of ROP).
- Most ROPs will regress, but continued growth can lead to bleeding and retinal detachment.

Retinopathy of Prematurity (ROP)

BASIC INFORMATION

- Abnormal retinal vascular development in premature infants
- A leading cause of childhood blindness and visual impairment

CLINICAL PRESENTATION

- Risk factors
  - Prematurity
  - Low birth weight
  - Prolonged duration of oxygen therapy
  - Poor weight gain
- No clinical signs until advanced—identified on routine screening

DIAGNOSIS AND EVALUATION

- Dilated fundus examination by an ophthalmologist familiar with ROP
- Screen if gestational age ≤30 weeks or birth weight ≤1500 g
- Screen if 1500–2000 g or >30 weeks when clinical course unstable
- Screening—begins at 31 weeks or 4 weeks' postgestation (later of the two dates)
- Graded based on zone and stage (Fig. 67.1)
- Zones reference geographic area to which vessels have extended:
  - Zone 1—most posterior and immature—circle with a radius twice the distance from the optic nerve to the fovea centered on the optic nerve
  - Zone 2—annulus around zone 1; outer radius is distance from optic nerve to nasal edge of the retina
  - Zone 3—residual crescent of retina anterior to zone 2

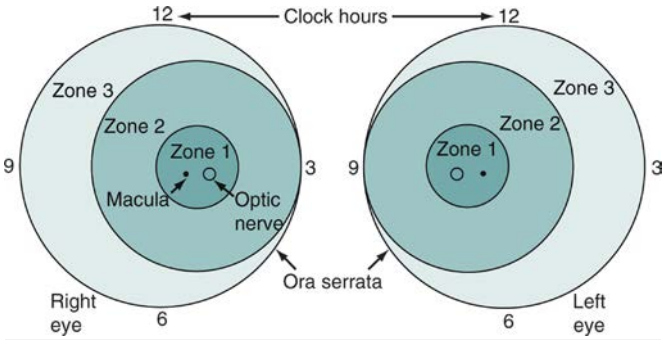

Fig. 67.1 Zones of the retina. (From Neonatology. In: Johns Hopkins Hospital, page 436, D Alexander, B Robin; Engorn B, Flerlage J. *The Harriett Lane Handbook*. St. Louis: Mosby; 2009;.)

- Stage refers to extent of anomalous vasculature
  - Stage 0—immature vasculature—no ROP
  - Stage 1—line of demarcation between vascular and avascular retina
  - Stage 2—elevated line or ridge
  - Stage 3—extraretinal fibrovascular proliferation
  - Stage 4—partial retinal detachment
    - A—extrafoveal; B—involving the fovea
  - Stage 5—total retinal detachment
- Plus disease—dilation and tortuosity of the retinal blood vessels

TREATMENT

- Prevention—prenatal care to limit risk for premature birth, avoid excessive oxygen delivery, and limit extreme fluctuations in oxygenation.
- Treat type 1 ROP:
  - Zone I, any stage with plus disease
  - Zone I, stage 3 without plus disease
  - Zone II, stage 2 or 3 with plus disease
- Laser photocoagulation of the avascular retina is the current standard of care.
- VEGF inhibitors are better at treating posterior disease (zone 1), but systemic safety is unclear.

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Questions

1. A 1-month-old girl is brought to your office because her mother thinks the right eye "looks funny." She has tearing and photophobia when examining the right eye, which shows diffuse corneal edema with a corneal diameter of 12 mm. Her left eye appears normal. The most appropriate next step is:
   a. corneal scraping for culture and institution of moxifloxacin eye drops four times a day
   b. check intra-ocular pressure and referral to ophthalmology for glaucoma surgery
   c. metabolic work-up and referral to geneticist
   d. corneal biopsy and referral for corneal transplant

2. A 10-day-old boy is brought to see you with a 2-day history of bilateral copious drainage and marked conjunctival injection. The most appropriate initial treatment is:
   a. intramuscular ceftriaxone
   b. oral erythromycin
   c. IM ceftriaxone and PO erythromycin
   d. topical sulfacetamide

3. During a 1-month well-child check, the patient's mother reports a "strange glint" in her daughter's left eye. She was full-term and is otherwise developing normally. You find a normal red reflex in the right eye, but find a white pupillary reflex in the left eye. The most likely diagnosis is:
   a. retinoblastoma
   b. retinopathy of prematurity
   c. strabismus
   d. congenital rubella

68 Ear Development and Anomalies

LYNDY J. WILCOX and CATHERINE K. HART

Outer Ear

NORMAL DEVELOPMENT

- Develops from first and second branchial arches from six hillocks of His starting at 6 weeks' gestation
- Reaches adult shape by 20 weeks' gestation
- Position of ear
  - Average distance from helical rim to scalp, 1.5–2 cm
  - Top of external auditory canal (EAC) should be on horizontal line drawn posteriorly from inferior orbital rim

PATHOLOGY

Congenital

- Preauricular tags: most common ear anomalies
  - Clinical presentation: due to extra hillocks of His
    - May be associated with branchio-oto-renal syndrome (especially if bilateral)
  - Diagnosis: clinical examination showing preauricular tag, which may include cartilage
  - Treatment: elective surgical removal
- Preauricular pits
  - Clinical presentation
    - Due to failure of fusion of the first and second arches of hillocks of His
    - May be associated with branchio-oto-renal syndrome (especially if bilateral)
  - Diagnosis: clinical examination demonstrates pit at helical root
  - Treatment
    - Antibiotics if infected or draining (occasionally requires incision and drainage [I&D])
    - Surgical excision when not infected
- Prominauris (protruding ears)
  - Clinical presentation: due to underdevelopment of antihelix, deep conchal bowl
  - Diagnosis: larger than average distance from helical rim to mastoid, usually bilateral
  - Treatment
    - Ear molding—promising results if initiated before 3 weeks of age
    - Elective otoplasty at 5–6 years of age
- Microtia: congenital abnormality in phenotype of the external ear
  - Outer ear develops early, so malformed auricle implies malformation of the middle ear, mastoid, and facial nerve
  - Clinical presentation
    - Prevalence: 1:6000–12,000
    - Usually unilateral; more commonly affects males and right side
    - 60% syndromic: Goldenhar syndrome, Treacher-Collins syndrome, CHARGE syndrome—coloboma, heart defects, atresia choanae (also known as *choanal atresia*), growth retardation, genital abnormalities, and ear abnormalities
    - Often in conjunction with aural atresia
    - Most have hearing loss (90%), usually conductive
  - Diagnosis: clinical assessment
    - Bone conduction auditory brainstem response (ABR) to assess hearing
  - Treatment
    - Prosthesis (adhesive or bone anchored)
    - Surgical repair around 6 years (with implant or costal cartilage graft)
- Aural atresia, stenosis: congenital lack of or narrowing of the EAC due to failure of resorption of the meatal plug filling the bony portion of EAC by 28 weeks' gestation
  - Clinical presentation
    - Prevalence: 1/10,000–20,000
    - Usually unilateral; more commonly affects males and right side
    - Normal auricle with canal atresia indicates abnormal development during 28th week of gestation (after ossicle and middle ear development)
    - Associated syndromes: Goldenhar syndrome, Treacher Collins syndrome, Apert syndrome, Crouzon syndrome, Pfeiffer syndrome, Turner syndrome, trisomy 21, trisomy 18, trisomy 13
  - Diagnosis
    - Bone conduction ABR to assess hearing and computed tomography (CT) scan of temporal bones
  - Treatment
    - Hearing amplification
    - Bone-anchored hearing device (BAHD) or surgical repair at 5 years

Middle and Inner Ear

NORMAL DEVELOPMENT

- Tympanic membrane
  - Two parts: pars flaccida, pars tensa
  - Three layers: epithelial (ectoderm), fibrous (mesoderm), mucosal (endoderm)
- Middle ear space, mastoid air cells, inner layer of the tympanic membrane, and eustachian tube arise from endoderm of first pharyngeal pouch

- Mastoid tip poorly developed until 1 year of age, making facial nerve more superficial and prone to injury (especially with surgery or birth trauma)
- Eustachian tube measures 17 mm at birth, grows to 35 mm by adulthood
- Ossicles—develop from first and second branchial arches from 6 to 28 weeks' gestation
- Inner ear (cochlea, vestibule, and internal auditory canal) malformations—occur due to arrest of development from 3 to 10 weeks' gestation

INNER EAR ABNORMALITIES

- Michel aplasia: complete agenesis of the petrous portion of the temporal bone due to disruption at 3 weeks' gestation
  - Clinical presentation: normal outer and middle ear with no cochlear structures present and anacusis
- Mondini aplasia: malformed cochlea (have 1.5 coils of cochlea rather than normal 2 coils), dilated vestibule, and enlarged vestibular aqueduct due to disruption at 6 weeks' gestation
  - Clinical presentation: range of normal to profound sensorineural hearing loss
  - Associated with Pendred syndrome, Waardenburg syndrome, Treacher Collins syndrome, Wildervanck syndrome, CHARGE syndrome, and cytomegalovirus (CMV) infection
- Scheibe aplasia: pars inferior dysplasia or cochleosaccular dysplasia
  - Clinical presentation
    - Most common inner ear aplasia
    - Will have varying degree of sensorineural hearing loss
    - Associated with Usher syndrome, Refsum syndrome, Waardenburg syndrome, Jervell and Lange-Nielsen syndrome, and congenital rubella
- Enlarged vestibular aqueduct
  - Clinical presentation: variable, fluctuating sensorineural hearing loss (SNHL) that decreases in stepwise fashion, worsens with head trauma or increased intracranial pressure (ICP)

CONGENITAL HEARING LOSS

- Hearing loss present at birth is genetic in 50% of patients and acquired in 50%.
- Genetic (hereditary) hearing loss is 70% nonsyndromic and 30% syndromic.

Physical Examination and Testing

- Otoscopy: evaluate external auditory canal, tympanic membrane
- External ear: evaluate auricle, preauricular pits and tags, other facial anomalies
- Hearing screen versus formal testing
- Consider genetic testing
- Consider CT of temporal bone

General Management Concepts for Hearing Loss

- Early detection by 1 month of age, early intervention by 6 months of age
- If syndromic hearing loss (HL) suspected, genetics consultation appropriate
- Hearing amplification—should be offered early to facilitate development

Infectious or Acquired

- Acute otitis media
- Otitis media with effusion
- Fetal alcohol syndrome
- TORCH infections
  - *T*oxoplasmosis (*Toxoplasma gondii*)
  - *O*ther: syphilis (*Treponema pallidum*), varicella, parvovirus B19
  - *R*ubella
  - *C*ytomegalovirus
    - Most common infectious and nongenetic causes of hearing loss
  - *H*erpes simplex virus

Genetic: Nonsyndromic Autosomal Recessive

- Connexin mutations: DFNB-1; 80% due to connexin 26 mutation (*GJB2* gene)
  - Most common cause of congenital deafness in developed countries
- Mitochondrial: maternally inherited
  - A1555G mutation; increased susceptibility to aminoglycoside-related SNHL

Genetic: Syndromic Autosomal Recessive (AR)

- Usher syndrome: most common cause of deafness and blindness in the United States (50%)
  - Clinical presentation: SNHL + retinitis pigmentosa
- Pendred syndrome
  - Clinical presentation: SNHL + euthyroid goiter
  - Associated with enlarged vestibular aqueduct (85%–100%)
  - Mutations of *SLC264A* gene or pendrin gene on chromosome 7
- Jervell and Lange-Nielsen syndrome
  - Clinical presentation: SNHL + prolonged QTc interval (>500 msec)
  - Diagnosis: genetic testing (*KCNQ1* gene)

Genetic: Syndromic Autosomal Dominant (AD)

- Waardenburg syndrome
  - Most common AD syndromic cause of hearing loss (HL)
  - Prevalence 1/10,000–20,000
  - Diagnosis: mutations in *PAX3* gene (Waardenburg syndrome types I and III), mutations in *MITF* or *SNAI2* gene (Waardenburg syndrome type II), mutations in *SOX10*, *EDN3*, or *EDNRB* gene (Waardenburg type IV)
  - Clinical presentation: four types
    - HL usually bilateral, profound, and stable over time
    - Type I: dystopia canthorum (lateral displacement of inner canthi of eyes), white forelock, SNHL in 20%
    - Type II: absence of dystopia canthorum, SNHL in 50%
    - Type III: associated with unilateral ptosis and skeletal abnormalities
    - Type IV: associated with Hirschsprung disease

- Branchio-oto-renal (BOR) syndrome
  - Second most common AD syndromic cause of HL
  - Prevalence: 1/40,000
  - Clinical presentation: ear abnormalities (preauricular pits or tags) with hearing impairment (90%)
    - Branchial cleft cysts, fistulas (25%), and renal anomalies (25%)
    - *EYA1* gene mutation
- Craniofacial dysostosis (Apert syndrome and Crouzon syndrome)
  - Clinical presentation: conductive hearing loss and craniosynostosis
  - *FGFR* gene mutation
- CHARGE syndrome: ***c***oloboma (eye), ***h***eart defects, ***a***tresia (choanal), ***r***etardation (growth), ***g***enitourinary (GU) anomalies, ***e***ar abnormalities
  - *CHD7* gene mutation
- Treacher Collins syndrome (mandibulofacial dysostosis)
  - Clinical presentation: midface hypoplasia and micrognathia, down-slanting palpebral fissures
  - Auricular deformities and conductive hearing loss
  - Mutations in *TCOF1*, *POLR1D,* or *POLR1C* gene
- Stickler syndrome (hereditary arthro-ophthalmopathy)
  - Clinical presentation: Pierre Robin sequence, hearing loss (80%), spondyloepiphyseal dysplasia
  - *COL11A1* and *COL2A1* gene defects
- Klippel-Feil syndrome
  - Clinical presentation: fusion of cervical vertebrae and hearing loss
  - Gene defects—*GDF6*, *MEOX1*, and *GDF3*—genes on chromosomes 8q22, 17q21, and 12p13, respectively

- Other syndromes associated with hearing loss
  - Goldenhar syndrome
  - DiGeorge syndrome
  - Trisomies 13, 18, 21
  - Turner syndrome
  - Congenital hypothyroidism

OTHER RISK FACTORS FOR HEARING LOSS

- Family history of permanent hearing loss in childhood
- Exposure to ototoxic medications: chemotherapy (carboplatin, cisplatin), loop diuretics (furosemide), aminoglycosides (gentamycin, tobramycin)
- Prematurity (<37 weeks) or birth weight < 1500 g
- Admission to neonatal intensive care unit (NICU) for >5 days
- Extracorporeal membrane oxygenation (ECMO)
- Prolonged mechanical ventilation (>10 days)
- Hyperbilirubinemia (>20 mg/100 mL serum or requiring exchange transfusion)
- Craniofacial anomalies or stigmata of a syndrome associated with hearing loss

NEWBORN HEARING SCREENING

- Universal newborn hearing screening (NBHS) instituted because as many as 50% of infants with hearing loss do not have identifiable risk factors
- Types of NBHS
  - Otoacoustic emissions (OAEs): acoustic emissions generated by the cochlear outer hair cells
    - Evoked OAEs—generated in response to tone or click stimulus
      - Most commonly used for NBHS
    - Benefits: fast, efficient, objective, with frequency- and ear-specific data
    - Limitations: not a sufficient screening tool for infants at high risk or in the setting of middle ear disease
    - Requirements: calm, quiet subject, normal middle ear function
  - Auditory brainstem response (ABR): tests cochlear nerve and brainstem by measuring electrical activity in response to click or tone burst stimuli
    - Not a true test of hearing, but estimates hearing thresholds
    - Automated ABR used for screening
      - Results not affected by anesthetics or sedatives
    - Diagnostic ABR
      - Not used for screening because it is time-consuming and requires an audiologist to perform and interpret results
      - Allows determination of severity, nature (conductive or sensorineural), and frequency of hearing loss
      - Results not affected by anesthetics or sedatives
- Recommendations
  - All newborns should have hearing screening during the birth admission or by 1 month of life.
  - Automated ABR is recommended for all NICU infants or those admitted to the hospital for >5 days.
  - If the infant does not pass the hearing screen, audiologic and otologic evaluations should be performed by 3 months of age.
    - Rescreening should include both ears (not just ear that failed).
  - At-risk newborns who pass the NBHS should be evaluated by an audiologist every 6 months for the first 3 years to identify changes in hearing.

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Questions

1. Genetic congenital hearing loss most commonly occurs in which of the following patterns?
   a. Syndromic and autosomal recessive
   b. Syndromic and autosomal dominant
   c. Nonsyndromic and autosomal recessive
   d. Nonsyndromic and autosomal dominant

2. The most common cause of genetic congenital deafness in developed countries is:
   a. Usher syndrome
   b. Pendred syndrome
   c. Waardenburg syndrome
   d. *DFNB-1/GJB2* (connexin 26 mutation)
   e. *DFNX-3* (congenital stapes fixation)

3. Which of the following statements is false regarding newborn hearing screening?
   a. Otoacoustic emissions and automated brainstem responses can be used for newborn hearing screening.
   b. Newborn hearing screening should be performed during the birth admission.
   c. If screening cannot be done during the birth admission, it should be done by 1 month of age.
   d. The goal of newborn hearing screening is to identify children with hearing loss prior to 12 months of age.
   e. At-risk newborns should undergo automated auditory brainstem response (ABR) screening.

4. Which of the following is considered a risk factor for hearing loss?
   a. Family history of permanent hearing loss in childhood
   b. Treatment with gentamicin
   c. Admission to the neonatal intensive care unit (NICU) for >5 days
   d. Hyperbilirubinemia
   e. Prolonged mechanical ventilation
   f. All the above are risk factors for neonatal hearing loss.

5. Which of the following is the most common infectious cause of congenital hearing loss?
   a. Toxoplasmosis
   b. Syphilis
   c. Rubella
   d. Cytomegalovirus (CMV)
   e. Herpes

6. A 2-day-old infant is noted to have bilateral preauricular pits without evidence of drainage or infection. The child does not pass the newborn hearing screen performed prior to discharge. Which of the following is the most appropriate next step?
   a. Surgical excision of the preauricular pits
   b. CT scan of the face
   c. Renal ultrasound
   d. Genetic testing
   e. Ophthalmology evaluation

7. A former 27-week premature infant with a birth weight of 1400 g passed her newborn hearing screen. Which of the following is appropriate follow-up after discharge from the NICU?
   a. Otolaryngology evaluation in 3 months
   b. Repeat audiometric evaluation in 6 months
   c. Repeat audiometric evaluation at 3 years of age
   d. Repeat audiometric evaluation only if hearing concerns develop
   e. Otolaryngology evaluation only if hearing concerns develop

69 Nose, Mouth, and Throat Development and Anomalies

LYNDY J. WILCOX and CATHERINE K. HART

Branchial (Pharyngeal) Arches

NORMAL DEVELOPMENT

- Most development occurs from 4–8 weeks' gestation
- The five branchial arches (mesoderm) develop during week 4. See Table 69.1.
- Other pertinent structures
  - Tongue
    - Anterior two-thirds derived from first branchial arch
    - Posterior third derived from third and fourth branchial arches
  - Thyroid gland
    - Thyroid diverticulum arises from endoderm at the foramen cecum (base of tongue) at 24 days' gestation
    - Thyroid descends into neck immediately anterior to hyoid bone to reach its final position anterior to the trachea by week 7 of gestation
  - Larynx, trachea, and proximal esophagus
    - The laryngotracheal groove develops in the ventral foregut at 3.5 weeks' gestation.
    - The tracheoesophageal septum forms to create two separate tubes:
      - Failure of recanalization results in laryngeal atresia and stenosis
      - Failure of separation of the tubes results in tracheoesophageal fistula (TEF) and/or esophageal atresia (EA)

ANOMALIES OF DEVELOPMENT

Syndromes Associated With Branchial Apparatus

- Pierre Robin sequence (first branchial arch)
  - Clinical presentation: triad of micrognathia, glossoptosis, and cleft palate
    - Mandibular hypoplasia displaces tongue, preventing fusion of palatal shelves
  - Diagnosis: clinical findings, assess for associated syndromes, polysomnography
  - Treatment: depends on degree of airway compromise
    - Interventions include prone positioning, nasopharyngeal airway, endotracheal intubation, lip-tongue adhesion, mandibular distraction, tracheostomy
- Other syndromes of first and second branchial arches: Goldenhar syndrome, hemifacial microsomia, Treacher Collins syndrome, and Nager syndrome
- DiGeorge syndrome (hypoplasia of first branchial arch, third and fourth branchial pouches)
  - Background information
    - Deletion of chromosome 22q11.2
    - Autosomal dominant (AD) if inherited, but usually sporadic
  - Clinical presentation: "CATCH-22"
    - *C*ardiac and aortic malformations
    - *A*bnormal facies: micrognathia, ear anomalies, telecanthus, narrow palpebral fissures, high, broad nasal bridge, long face
    - *T*hymic aplasia, hypoplasia with associated immunodeficiency
    - *C*left palate (may be submucous cleft)
    - *H*ypocalcemia with tetany due to absence of parathyroid glands
    - Associated anomalies: glottic web, TEF, tracheomalacia, hearing loss
  - Diagnosis
    - Cardiac echocardiography (echo) flow cytometry, calcium levels, parathyroid hormone (PTH) levels
  - Genetic testing: array comparative genomic hybridization (aCGH), fluorescent in situ hybridization (FISH), *TBX1* gene analysis, karyotype
  - Treatment: cardiothoracic surgery, amplification for hearing loss, cleft palate repair, manage immunodeficiency, calcium supplementation

NECK MASSES

- Branchial cleft anomalies (cysts, tracts, and fistulas)
  - Incidence unknown, but bilateral in 2%–3%
    - If bilateral, check renal ultrasound for branchio-oto-renal syndrome
  - Cyst: no opening
  - Sinus: single opening to skin or internally
  - Fistula: opening to skin and internally
  - Diagnosis: clinical findings, imaging (computed tomography [CT] scan and/or magnetic resonance imaging [MRI])
  - Treatment: excision is treatment of choice for most branchial anomalies
  - First branchial cleft anomalies
    - 1% of all branchial anomalies
    - Present as preauricular cyst (type I) or in submandibular region (type II)
  - Second branchial cleft anomalies
    - Most common type of branchial cleft cyst (95%)

Table 69.1 Branchial Apparatus: Arches, Pouches, and Clefts[a]

Arches (Mesoderm)	Key Structures
First (mandibular) branchial arch	Ossicles, external ear, mandible, muscles of mastication Cranial nerve innervation: V (trigeminal)
Second (hyoid) branchial arch	Ossicles, hyoid, external ear, facial muscles Cranial nerve innervation: VII (facial)
Third branchial arch	Hyoid, muscles of pharynx Cranial nerve innervation: IX (glossopharyngeal)
Fourth branchial arch	Thyroid cartilage, cricothyroid muscle Cranial nerve innervation: X (superior laryngeal branch of vagus)
Sixth branchial arch	Cricoid cartilage, muscles of larynx Cranial nerve innervation: X (recurrent laryngeal branch of vagus)
POUCHES (ENDODERM)	
First branchial pouch	Auditory tubes, middle ear cavity
Second branchial pouch	Palatine tonsil
Third branchial pouch	Dorsal portion: inferior parathyroids Ventral portion: thymus
Fourth branchial pouch	Dorsal portion of fourth pouch: superior parathyroids Ventral portion of fourth pouch: ultimobranchial body, differentiates into parafollicular C cells of thyroid gland
Sixth branchial pouch	Ultimobranchial body
CLEFTS (ECTODERM)	
First branchial cleft	External auditory meatus
Second, third, fourth, sixth branchial cleft	Usually obliterated (remnants may appear as cervical cysts or fistulas along the anterior boarder of the sternocleidomastoid muscle)

[a]Note: There is no fifth branchial apparatus.

- Clinical presentation: painless, fluctuant mass in anterior triangle of neck
- Third branchial cleft anomalies
  - Rare, present as mass in lower anterior neck
- Thyroglossal duct cyst
  - Most common congenital anomaly in the neck
  - Background: failure of obliteration of the thyroglossal duct tract
  - Clinical presentation: painless midline neck mass in close proximity to the hyoid bone that elevates with swallowing or tongue protrusion
  - Diagnosis: ultrasound to confirm that there is normal thyroid tissue
  - Treatment: surgical excision via Sistrunk operation
- Pseudotumor of infancy: fibrotic lesion of the distal sternocleidomastoid muscle
  - Clinical presentation: firm neck mass presents with torticollis in first weeks of life
    - Chin turned away and head tilted toward mass
    - Associated with breech and forceps delivery
  - Diagnosis: clinical examination, ultrasound
  - Treatment: physical therapy
- Dermoid cysts and teratomas: developmental anomalies composed of different germ cell layers
  - Dermoid: mesoderm and ectoderm; may contain skin appendages
  - Midline painless mass that doesn't elevate with tongue protrusion
  - Diagnosis: clinical examination and ultrasound
  - Treatment: simple surgical excision
- Teratomas: arise from misplaced embryologic germ cells containing all three germ layers
  - Occur in 1/16,000 individuals
  - Larger midline or paramedian masses, present earlier in life, cause respiratory compromise
    - 20% associated with maternal polyhydramnios
    - Termed *epignathus* when arises from the palate
  - Diagnosis: ultrasound (often prenatal) as a mixed echogenicity lesion
  - Treatment: surgical excision
  - May require emergency airway management followed by excision at birth via ex utero intrapartum treatment (EXIT) procedure

Nose

NORMAL DEVELOPMENT

- Anterior neuropore represents cranial aspect of neural tube, closes at 24th day of gestation
  - Failure of neuropore closure results in anencephaly
- Development of the skull base (third week of gestation)
  - Faulty closure of the foramen cecum at third week of development; results in skull base defects, with potential for midline nasal masses

PATHOLOGY

- Midline nasal masses (glioma, encephalocele, dermoid)
  - Incidence: 1 in 20,000–40,000 live births (Table 69.2)
  - Diagnosis: clinical examination, CT scan and MRI
  - Must determine if mass communicates with intracranial space (via MRI) and if there is a skull base defect (via CT)
  - Treatment: surgical excision with repair of skull base defect
    - Requires neurosurgery consultation if intracranial communication present
    - Left untreated, can cause abscess formation, cerebrospinal (CSF) leak, meningitis, intracranial infection, cosmetic deformity

EXTERNAL NOSE AND NASAL CAVITIES

NORMAL DEVELOPMENT

- Nasal development occurs from gestational weeks 4–8
- Frontonasal prominence eventually develops into the nose
  - Neural crest cells migrate into frontonasal prominence at fourth gestational week to form nasal placodes, oval-shaped thickenings of surface ectoderm.
  - Nasal placodes deepen into nasal pits at sixth week of gestation.
  - Nasobuccal membrane ruptures to create the primitive nasal cavity and choanae.
  - Medial and lateral nasal processes ultimately fuse with paired maxillary and mandibular processes to complete facial formation by 14 weeks' gestation.

Table 69.2 Midline Nasal Masses

Parameter	Glioma	Encephalocele	Dermoid
Pathophysiology	Sequestered glial tissue	Herniated meninges ± brain tissue	Dural tissue that does not obliterate
Connection to subarachnoid space?	No	Yes	Yes in 20%–45%
Description	Firm, nonpulsatile mass	Soft, compressible mass that gets bigger with crying, straining (Furstenberg sign)	Firm, noncompressible with pit or fistula tract connecting to nasal dorsum
Transilluminates	No	Yes	No
Location	Extranasal (60%) Intranasal (30%) Combined (10%)	Occipital (75%)	Nasal dorsum (most common), but anywhere along nose

Table 69.3 Syndromes Associated With Abnormal Nasal Development

Low Nasal Bridge	Broad Nasal Ridge	Short Anteverted Nostrils	Abnormal Philtrum
Hurler syndrome	Down syndrome	Trisomy 18	Fetal alcohol syndrome (smooth/flat)
Noonan syndrome	Valproic acid exposure in utero	Valproic acid exposure in utero	Perinatal HIV/AIDS (prominent, triangular shaped)
Osteogenesis imperfecta	Opitz G/BBB syndrome	Opitz G/BBB syndrome	Trisomy 13 (absent)
Pfeiffer syndrome	Otopalatodigital syndrome	Smith-Lemli-Opitz syndrome	Wolf-Hirschhorn syndrome (short)
Valproic acid exposure in utero	Cri du chat syndrome	Lissencephaly	
Growth hormone deficiency		Cornelia de Lange syndrome	
Congenital syphilis		Cutis laxa	
		Stickler syndrome	
		Joubert syndrome	

PATHOLOGY

- Choanal atresia
  - Failure of resorption of the nasobuccal membrane at 5 weeks' gestational age
  - Epidemiology:
    - Occurs in 1/5000 live births, with 1:2 male-to-female ratio (M:F)
    - Unilateral (right > left) twice as common as bilateral
    - 50%—have other congenital anomalies
    - Associated with CHARGE syndrome (***c***oloboma [eye], ***h***eart defects, ***a***tresia [choanal], ***r***etardation [growth], ***g***enitourinary anomalies, ***e***ar abnormalities), Treacher Collins syndrome, Apert syndrome, and Crouzon syndrome
  - Clinical presentation
    - Bilateral: cyclic cyanosis in infants relieved by crying
    - Unilateral: presents later with chronic, unilateral nasal drainage, obstruction
  - Diagnosis
    - Inability to pass a 6-Fr catheter or absence of fogging of mirror under nose
    - Confirm with nasal endoscopy and CT scan
  - Treatment
    - If bilateral: stabilize airway: oral airway, McGovern nipple, endotracheal intubation followed by early surgical repair
    - If unilateral: repair when symptomatic or before school age

SYNDROMES ASSOCIATED WITH ABNORMAL NASAL DEVELOPMENT

See Table 69.3.

Mouth and Palate

NORMAL DEVELOPMENT

- Five facial primordia arising from first arch develop around stomodeum in fourth week of gestation
  - Unpaired frontonasal prominence (superiorly)
  - Merging of medial nasal processes (5 weeks' gestation) gives rise to primary palate, philtrum of upper lip, maxilla
  - Paired maxillary prominences merge (6–7 weeks' gestation) to form upper lip, maxilla, secondary palate
  - Secondary palate fuses with primary palate and nasal septum by 12th week of gestation
  - Paired mandibular prominences (inferiorly) merge (4 weeks' gestation) to create mandible, lower lip, lower part of face

PATHOLOGY

- Cleft lip (CL) and cleft palate (CP)—most common congenital craniofacial malformations
  - Embryologic causes
    - CL ± CP: Failure of fusion of the medial nasal processes with the maxillary prominences (4-6 weeks' gestation)
    - CP: Failure of fusion of lateral palatine processes (8–12 weeks' gestation)
  - Epidemiology
    - CL ± CP occurs in 1/1000 live births
    - More common in males (M:F, 1.5–2:1)
    - Up to 30% associated with syndromes
    - Isolated CP occurs in 1/2500 live births
    - Risk for CL and CP in subsequent pregnancies if
      - Parents normal and first child affected: 3%–4%
      - One parent affected, first child affected: 10% –15%
      - Both parents affected, first child affected: 45%

- Diagnosis: physical examination findings at birth or prenatal ultrasound
  - Prior to surgical intervention
    - Manage feeding difficulties (Pigeon, McGovern, Haberman nipples)
    - Ensure adequate airway
    - Carry out audiologic and otologic assessments
  - Surgical repair
    - CL repair: rule of 10s: 10 weeks old, 10 pounds, hemoglobin of 10
    - CP repair: repair at 6–18 months of age
    - 95% will have otitis media with effusion; consider ear tubes

Neonatal Airway

SPECIAL CONSIDERATIONS FOR INTUBATION

- Anatomic differences
  - Larynx sits higher in neck, with more acute angle from oropharynx
  - Cricoid cartilage narrowest portion of airway (compared to glottis in adults)
- Normal airway size—3.5-mm endotracheal tube (ETT) for full-term neonate
  - Adjust based on weight and gestational age
  - ETT size is approximately one-tenth of gestational age (rounded down)
- Risks
  - Subglottic stenosis
    - Incidence decreasing over past several decades: 8.3% in 1970s compared to 0.63% in 1990s
    - Increased risk with prolonged, multiple or traumatic intubation, inappropriately sized tube or high cuff pressures
  - Tracheal perforation
    - Contributing factors: difficult exposure, multiple intubation attempts, excessive force, improperly placed endotracheal tubes with stylets, airway anomalies
    - Signs: subcutaneous emphysema, pneumothorax, pneumomediastinum

TRACHEOSTOMY

- Indications
  - Prolonged ventilator dependence, such as with severe bronchopulmonary dysplasia
  - Upper airway obstruction
    - Craniofacial anomalies
    - Airway stenosis or malacia
    - Vocal fold paralysis
  - Neuromuscular or cardiac disease
- Complications
  - Some complication experienced in up to 80%
  - Mortality rates as high as 42% reported, mostly due to comorbid conditions
  - Tracheostomy-specific related deaths: 0.05%–3.6%
  - Increased morbidity in children who are younger, low birth weight, have a history of heart or central nervous system (CNS) disease, or have the tracheostomy at >100 days
  - Early complications (<7 days postoperatively): bleeding, subcutaneous emphysema, pneumothorax, pneumomediastinum, TEF
  - Late complications (>7 days postoperatively): peristomal granulation tissue, laryngeal or tracheal stenosis, tracheomalacia, TEF
  - Complications occurring in both time periods: accidental decannulation, mucus plugging, skin breakdown, infection, tracheoinnominate fistula, cardiopulmonary arrest, death

Necrotizing Tracheobronchitis

- Background information: iatrogenic desquamation of the tracheobronchial mucosa, with formation of pseudomembranes of necrotic tissue
- Clinical presentation: acute airway obstruction characterized by sudden unexplained increase in ventilatory requirements, with up to 45% mortality rate
- Seen in infants on mechanical ventilation, especially oscillator or jet ventilation
- Diagnosis and treatment: rigid bronchoscopy with removal of necrotic debris ± extracorporeal membrane oxygenation (ECMO)
- Serial bronchoscopies due to risk of tracheal stenosis after resolution of acute process

EVALUATION OF STRIDOR

- Stridor: high-pitched sound created by turbulent airflow through a narrowed larynx or trachea
- History
  - Onset (birth or several weeks after)
  - Progression (getting better or worse)
  - Chronicity (constant or intermittent)
  - Alleviating and aggravating factors (positioning, feeding, agitation, sleeping)
  - Prior intubation and/or congenital anomalies
  - Feeding difficulties
- Physical examination: assess work of breathing, retractions, vital signs
  - Timing of stridor in respiratory cycle
    - Inspiratory stridor suggests supraglottic or glottic pathology.
    - Expiratory stridor suggests tracheal pathology.
    - Biphasic stridor suggests glottic or subglottic pathology.
- Flexible awake laryngoscopy to evaluate dynamics of airway, levels of obstruction
- Other studies: lateral, anteroposterior (AP) neck x-rays, chest x-ray, CT and MRI scans, barium swallow

PATHOLOGY

- Laryngomalacia: most common congenital cause of stridor
  - Clinical presentation: inspiratory stridor beginning several weeks after birth that worsens with agitation, feeding, or supine positioning
    - When severe, may have apnea and/or cyanosis, difficulty feeding, failure to thrive

- Diagnosis: flexible laryngoscopy shows omega-shaped epiglottis that curls inward, shortened aryepiglottic folds, arytenoids that prolapse on inspiration
- Treatment
  - Most infants can be managed conservatively.
  - Approximately 10% will require surgical intervention.
  - Indications for surgery include apnea and/or cyanosis, increased work of breathing, failure to thrive, and cor pulmonale.

- Vocal cord paralysis: second most common congenital cause of stridor
  - Background information: typically idiopathic in neonates, can be iatrogenic
    - Causes: cardiac surgery, central nervous system (CNS) anomalies, Chiari malformation, intubation injury, infections, trauma, some syndromes
  - Clinical presentation
    - Unilateral: may present with weak cry, feeding difficulties, and stridor
    - Bilateral: upper airway obstruction with biphasic stridor
  - Diagnosis: flexible laryngoscopy to evaluate vocal fold motion
    - If immobility identified, brain MRI to rule out CNS lesions
  - Treatment: may recover spontaneously over several years
    - Unilateral: rarely requires intervention
    - Bilateral: much more likely to require tracheostomy
- Subglottic stenosis
  - Background information: third most common cause of stridor in newborns
    - Congenital (5%): due to incomplete laryngeal lumen recanalization
    - Acquired (95%): history of prolonged or traumatic intubation
  - Clinical presentation: stridor, retractions, failure to extubate, feeding difficulties
  - Diagnosis: microlaryngoscopy and bronchoscopy with airway sizing
  - Treatment: balloon dilation, anterior, posterior cricoid split, tracheostomy, laryngotracheal reconstruction, cricotracheal resection

Other Causes of Stridor

- Laryngocele: enlarged laryngeal saccule with entrapment of air
- Saccular cyst: fluid-filled dilations of the laryngeal ventricle
  - Subglottic hemangioma: subglottic mass, often with cutaneous hemangiomas; treat with propranolol
- Recurrent respiratory papillomatosis: seen in neonates due to vertical transmission from affected mothers
- Laryngeal webs: due to incomplete recanalization of laryngeal lumen during embryogenesis
  - Typically glottic in location (75%), causing weak cry, biphasic stridor
  - Should prompt evaluation for 22.q.11 deletion

- Tracheal pathology
  - Congenital stenosis: often due to complete tracheal rings or sleeve trachea
    - Associated with pulmonary slings
  - Acquired stenosis: usually due to intubation or tracheostomy
  - Tracheomalacia: due to weak cartilage or extrinsic compression

Suggested Readings

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Questions

1. Which of the following is not a commonly described feature of the Pierre Robin sequence?
   a. U-shaped cleft palate
   b. Unilateral cleft lip
   c. Micrognathia
   d. Glossoptosis
   e. All of the above are associated with Pierre Robin sequence.

2. A newborn is noted to have abnormal facies, including micrognathia, microtia, and telecanthus, as well as tetralogy of Fallot. You suspect DiGeorge syndrome. Which of the following would not help support your diagnosis?
   a. Genetic testing showing a 22q11 deletion
   b. Presence of a submucous cleft palate
   c. Glottic web on laryngoscopy
   d. Serum calcium level of 11 mg/dL
   e. Absence of a thymus on ultrasound

3. A 3-month-old child was noted to have a small draining pit in his neck at the anterior aspect of the sternocleidomastoid muscle. The area intermittently gets swollen and drains. You suspect he has a branchial cleft cyst. Where would the fistula tract for this lesion most likely terminate?
   a. External auditory canal
   b. Parotid gland
   c. Tonsillar fossa
   d. Pyriform sinus

4. A 1-week-old infant presents with a right-sided neck mass. He was born full term and delivered via cesarean section due to breech positioning. You note that the mass is firm to palpation. The infant keeps his chin turned away from the mass and his head tilted toward the mass. What is the most appropriate course of action?
   a. Ultrasound and physical therapy
   b. Ultrasound and antibiotic therapy
   c. Biopsy and surgical excision
   d. Biopsy and chemotherapy

5. Which of the following is the narrowest portion of the airway in an infant or child and adult, respectively?
   a. True vocal cords in both
   b. True vocal cords and cricoid cartilage
   c. Cricoid cartilage and true vocal cords
   d. Cricoid cartilage in both

6. Which of the following have/has been associated with an increased risk of subglottic stenosis in neonates?
   a. Prolonged intubation
   b. Traumatic intubation
   c. Multiple reintubations
   d. High cuff pressures
   e. All of the above are associated with an increased risk of subglottic stenosis.

7. A 3-week-old infant born at 34 weeks' gestational age begins having inspiratory stridor worsened by agitation while feeding, and when lying supine. There is no oxygen requirement and no apneic or cyanotic events. The infant continues to gain weight appropriately and has a normal cry. Which of the following is not appropriate in the initial management of this patient?
   a. Directly observed prone positioning
   b. Recommend influenza vaccination for family members >6 months of age
   c. Bedside flexible laryngoscopy
   d. Supraglottoplasty
   e. All of the above are appropriate interventions at this point.

8. An 8-week-old infant born at 30 weeks' gestational age begins having soft biphasic stridor that has progressively worsened over several days. The infant's history is notable for several cutaneous hemangiomas, including one covering the right side of his cheek and chin. He was on continuous positive airway pressure (CPAP) after birth but did not require intubation and has been in room air. A bedside flexible laryngoscopy performed by an ENT consultant showed no evidence of laryngomalacia, and the vocal cords are mobile. You are suspicious for a subglottic hemangioma, which is confirmed on rigid bronchoscopy and shows 25% narrowing of the airway. What is the most appropriate intervention at this point?
   a. Tracheostomy
   b. Start propranolol therapy
   c. Biopsy the lesion to confirm the diagnosis
   d. Start steroid therapy
   e. Supplemental oxygen and racemic epinephrine

9. You admit an otherwise healthy newborn with a cleft lip and palate. There is no family history of cleft lip or cleft palate, and the parents are healthy. What is the likelihood that another child born to the same parents will also have a cleft lip and palate?
   a. 1%
   b. 4%
   c. 10%
   d. 25%
   e. 50%

10. An infant born at 36 weeks' gestation is noted immediately after birth to have increased work of breathing and cyanosis which is relieved by crying. A 6 french flexible suction catheter would not pass through his nares. An oral airway was placed with improvement in symptoms. Anterior rhinoscopy did not reveal any significant mucosal swelling or narrowing. What is the most likely diagnosis?
    a. Neonatal rhinitis
    b. Pyriform aperture stenosis
    c. Nasolacrimal duct cyst
    d. Nasal dermoid
    e. Choanal atresia

SECTION 18

Diagnostic Imaging

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70 Neurologic Imaging

MITCHELL CHESS

Germinal Matrix and Intraventricular Hemorrhage (GMH/IVH)

Ultrasound is the study of choice.
IVH grading:

- Grade I—echogenicity confined to caudothalamic groove (Fig. 70.1)
- Grade II—echogenicity extends into nondilated ventricles
  - May have similar appearance to bulky choroid (Fig. 70.2A)
  - Echogenicity in occipital horns always hemorrhage (no choroid in this location) (see Fig. 70.2B)
  - May have secondary hydrocephalus from occlusion of brain foramena or aqueduct of Sylvius (Fig. 70.3)
- Grade III—ventricles expanded by the accumulated blood (Fig. 70.4A)
  - Associated with venous infarction caused by deep terminal vein compression by pressure caused by blood (see Fig. 70.4B)
- Grade IV—bleeding extends into brain tissue around the ventricles (Fig. 70.5)
  - Cause believed to be parenchymal hemorrhage into venous infarction

Periventricular Leukomalacia (PVL)

Ultrasound

- Hyperechoic areas in the periventricular regions in mild and early cases. (Fig. 70.6)
- More severe—cysts revealed in these areas, cystic PVL (Fig. 70.7)

Magnetic resonance imaging (MRI)

- Early MR images—T1 hyperintensity/T2 hyperintensity. (see below, "Hypoxia and Ischemia")
- Subsequent periventricular cyst formation, develop after 2–6 weeks

Hypoxia and Ischemia

MRI is the most sensitive and specific imaging study.
Findings indicating ischemia:

- High T1 signal in the basal ganglia
- Cortical laminar necrosis
  - T1—gray matter: hyperintense, white matter: hypointense (Fig. 70.8A)
  - T2—gray matter: variable, white matter: hyperintense (see Fig. 70.8B)

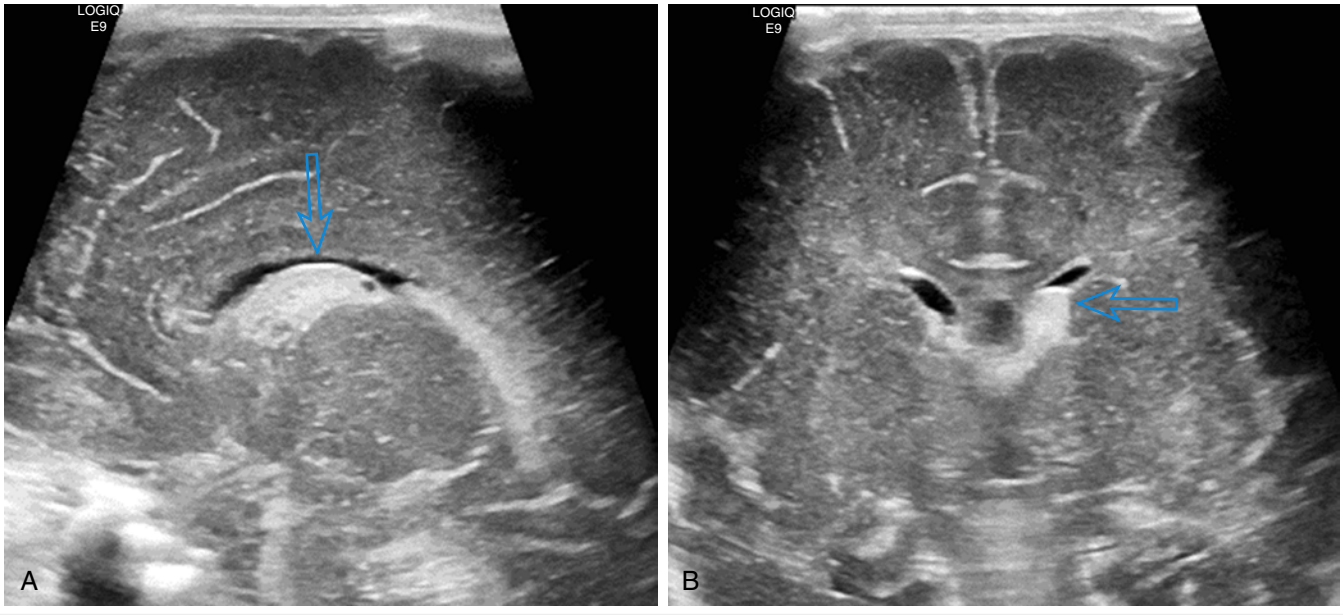

Fig. 70.1 Grade I germinal matrix and intraventricular hemorrhage *(arrow).* (A) Sagittal. (B) Coronal.

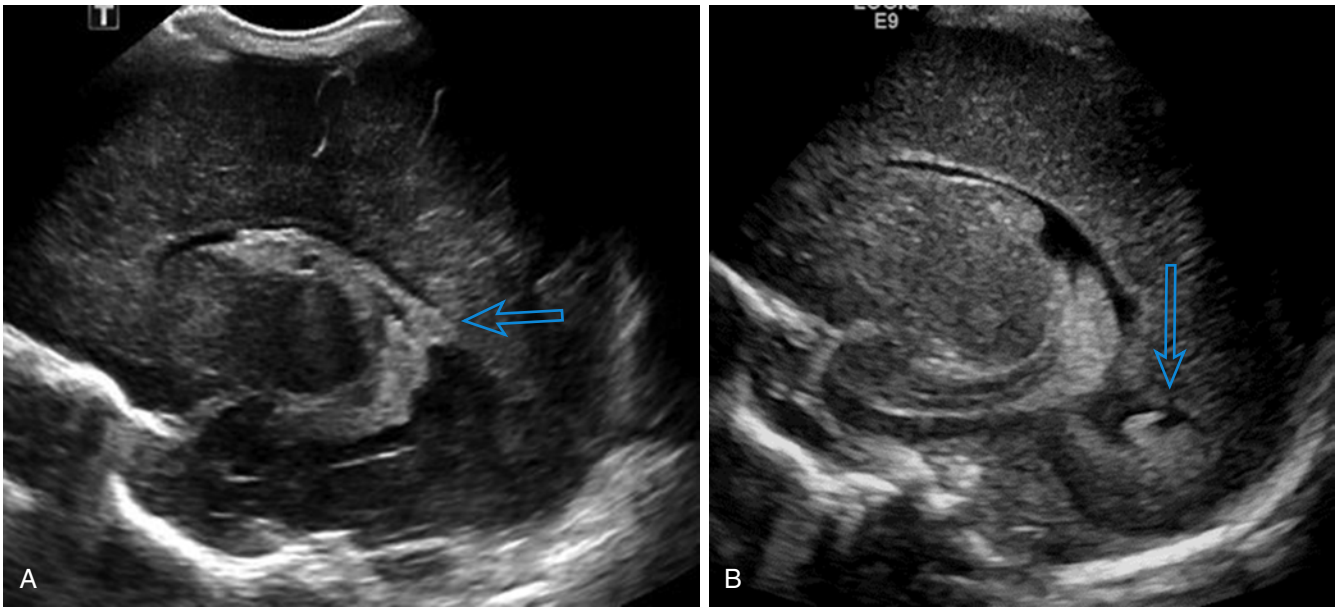

Fig. 70.2 (A and B) Grade II germinal matrix hemorrhage *(arrow)*.

Fig. 70.3 Grade II germinal matrix and intraventricular hemorrhage with hydrocephalus.

- MR spectroscopy with elevated lactate peaks (1.3 ppm; see Fig. 70.8C and D)
- Diffusion-weighted imaging (DWI), apparent diffusion coefficient (ADC)—diffusion restriction, low signal (see Fig. 70.8E)
  - ADC normalizes at 7–10 days

Mineralizing Vasculopathy

Linear echogenicity in the basal ganglia (Fig. 70.9)

- Nonspecific causes ranging from intrauterine TORCH infections, chromosomal disorders, neonatal asphyxia, and maternal drug use

Cavum Velum Interpositum

Cystic space in the pineal region (Fig. 70.10)

- Not to be mistaken for pineal or arachnoid cysts
- Internal cerebral veins below the cystic space

Chiari II Malformation

Posterior fossa (Fig. 70.11)

- Inferiorly displaced cerebellar tonsils and vermis through foramen magnum
- Low attachment of the tentorium, causing small posterior fossa

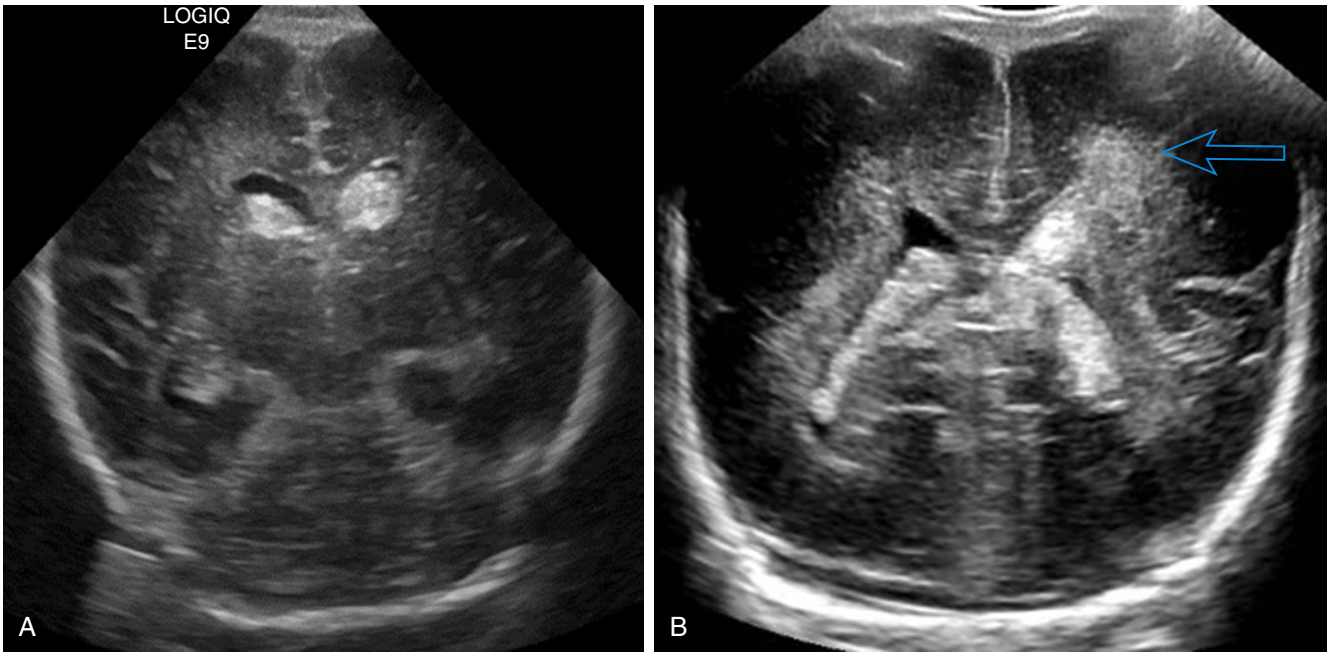

Fig. 70.4 (A and B) Grade III germinal matrix and intraventricular hemorrhage, with venous infarct *(arrow)*.

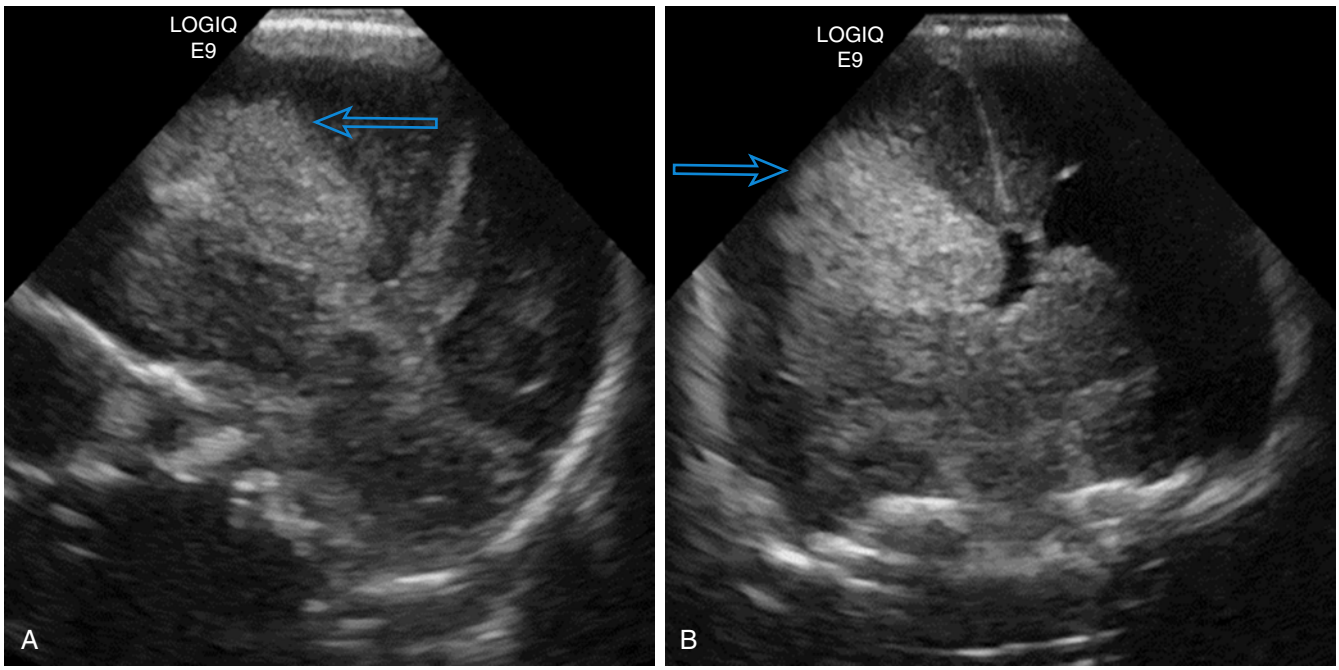

Fig. 70.5 (A and B) Grade IV germinal matrix and intraventricular hemorrhage, with intraparenchymal hemorrhage *(arrow)*. (A) Sagittal. (B) Coronal.

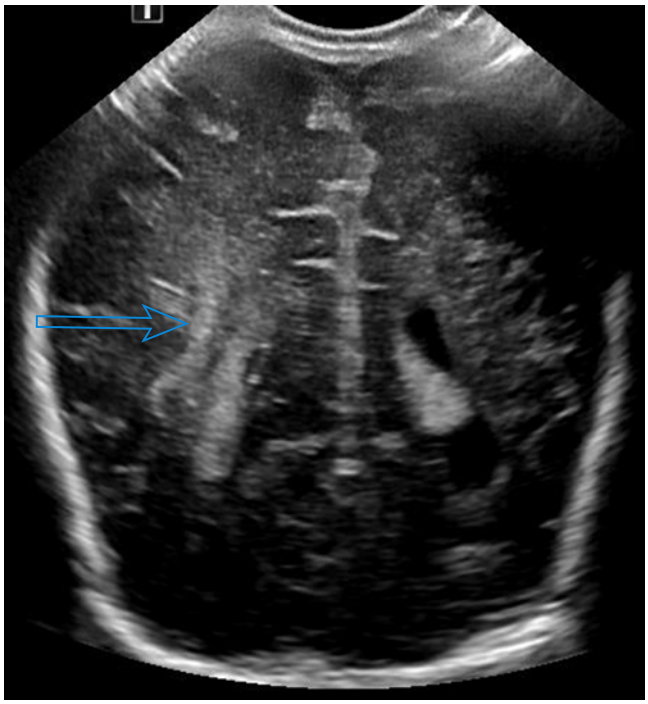

Fig. 70.6 Early periventricular leukomalacia (PVL)/ischemia *(arrow)*.

- Flattened pons
- Elongated small fourth ventricle
- Tectal beaking, causing aqueductal stenosis and hydrocephalus

Holoprosencephaly

Three general types:

Alobar holoprosencephaly
- Single cortical structure without interhemispheric fissure
- Fused thalami
- Single large ventricle
- Associated with facial abnormalities

Semilobar holoprosencephaly (Fig. 70.12)
- Cerebral lobes present fused, most commonly anteriorly and at thalami
- Absent septum pellucidum
- Olfactory tracts and bulbs usually not present
- Agenesis or hypoplasia of the corpus callosum

Lobar holoprosencephaly
- Subtle midline fusion (cingulate gyrus and thalami)
- Absent septum pellucidum
- Olfactory tracts absent or hypoplastic
- Hypoplasia or agenesis of corpus callosum

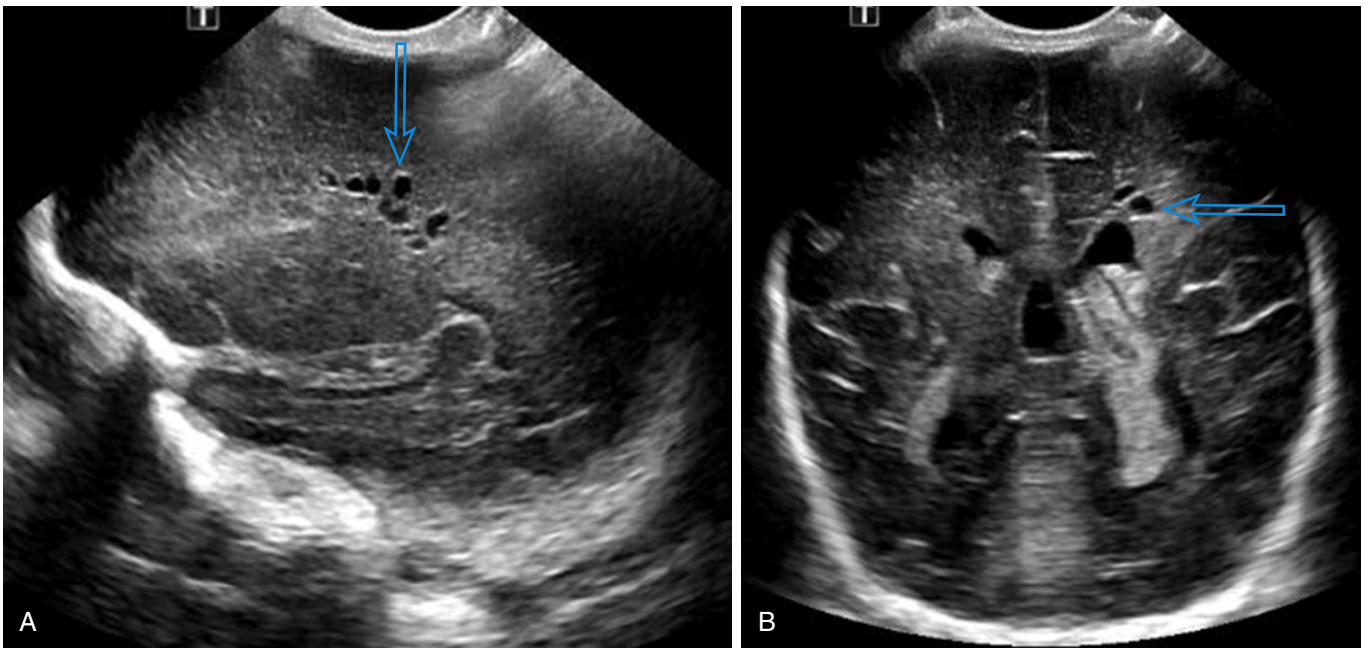

Fig. 70.7 (A and B) Periventricular leukomalacia (PVL) *(arrow)*. (A) Sagittal. (B) Coronal.

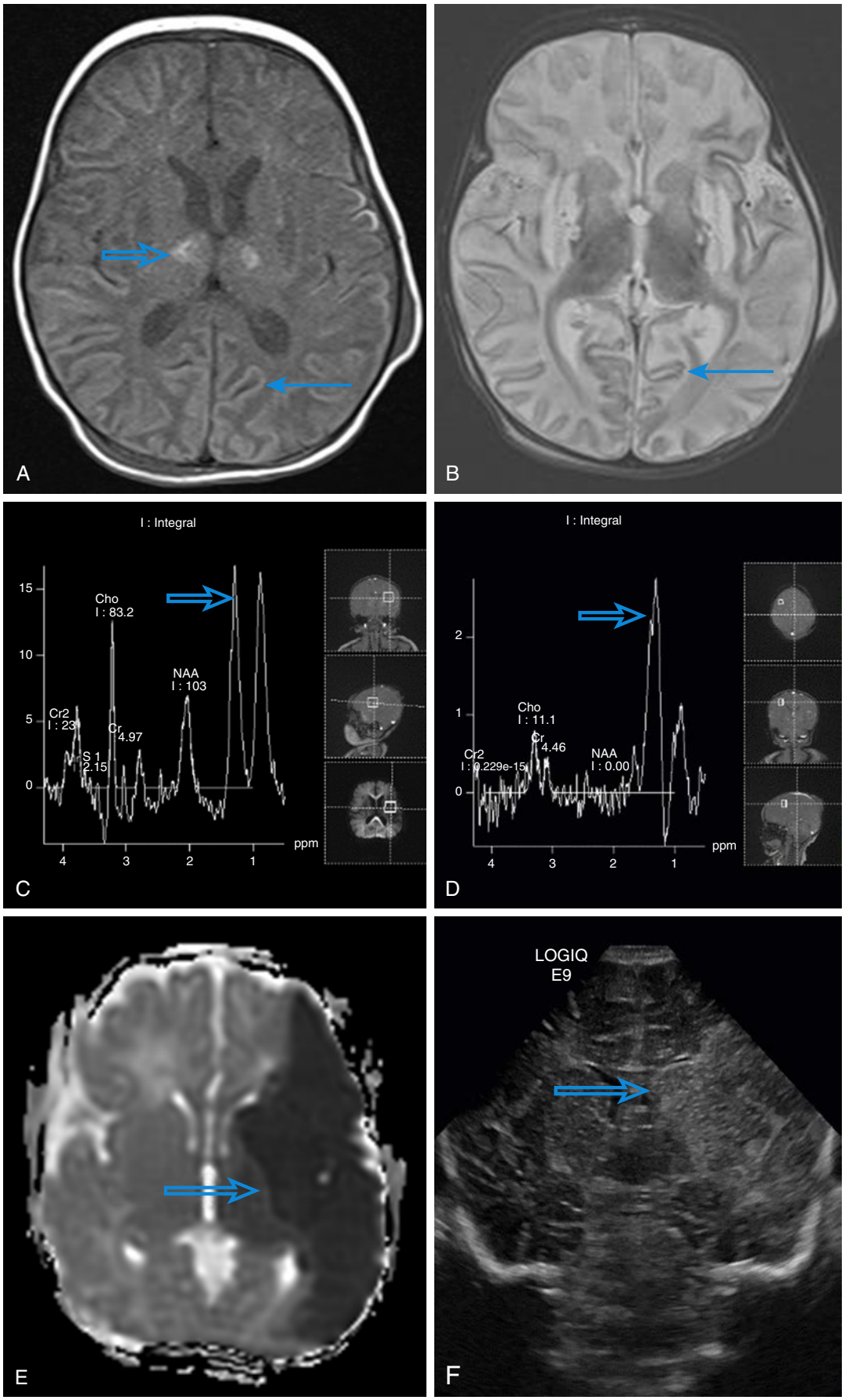

Fig. 70.8 (A -F) Hypoxic Ischemic Encephalopathy (HIE). (A) MRI T1 weighted thalamic high signal *(open arrow)* and cortical necrosis *(closed arrow)*, (B) MRI T2 weighted cortical necrosis *(closed arrow)*, (C and D) MR spectroscopy lactate peak *(arrow)*. (E) MRI diffusion weighted restricted diffusion *(arrow)*. (F) Corresponding ultrasound- increased echogenicity *(arrow)*.

Dandy-Walker Malformation (DWM) Spectrum

Most common posterior fossa malformation (Fig. 70.13)
- Hypoplasia of the vermis and cephalad rotation of the vermian remnant
- Cystic dilation of the fourth ventricle posteriorly
- Enlarged posterior fossa. with high tentorium

Syrinx

Hydromyelia—dilation of the central canal of the spinal cord

Syringomyelia—paracentral cavities lined by gliotic parenchyma due to disruption of the ependyma (Fig. 70.14)

Choanal Atresia

Assessment with axial computed tomography (CT) (Fig. 70.15) may show the following:

- Unilateral or bilateral posterior nasal narrowing, obstruction
- Airway less than 3 mm at level of the pterygoid plates
- Air-fluid level above obstruction
- Thickening of vomer
- Medial bowing of the posterior maxillary sinus

Suggested Readings

de Oliveira Schiavon JL, Grassi DC. *Neonatal and Infant Brain Imaging Evaluation. Medscape;* October 3, 2017. http://reference.medscape.com/slideshow/neonatal-infant-brain-imaging-6009107.

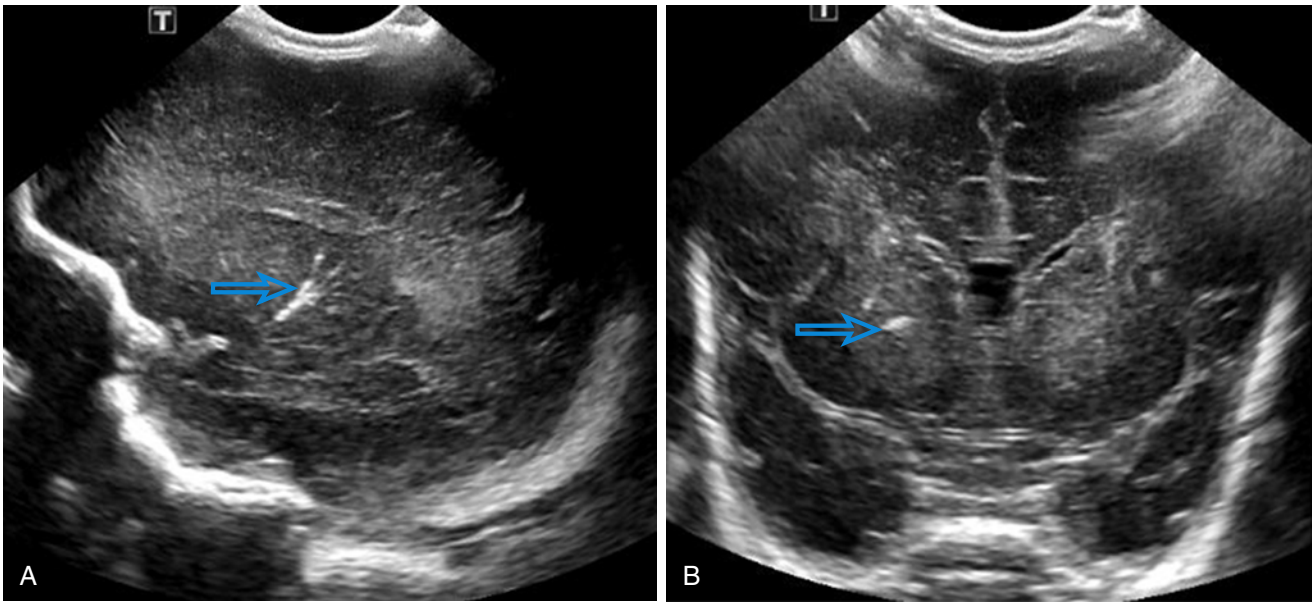

Fig. 70.9 Mineralizing vasculopathy *(arrow).* (A) Sagittal. (B) Coronal.

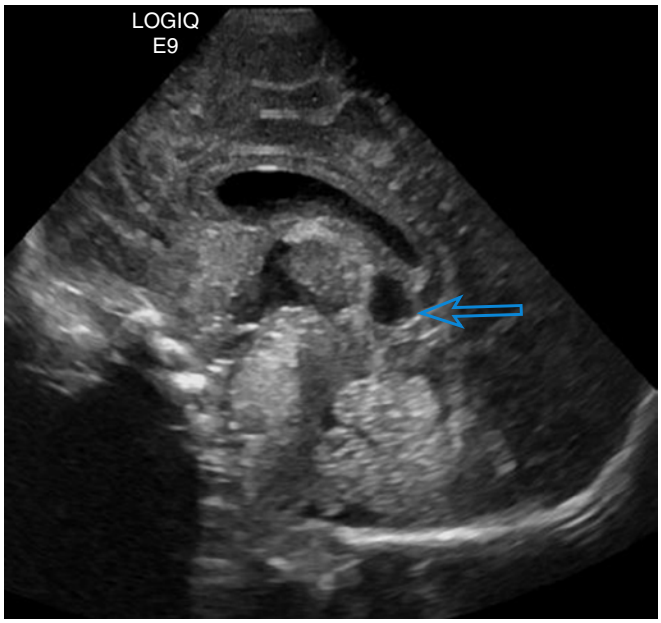

Fig. 70.10 Cavum velum interpositum *(arrow)*.

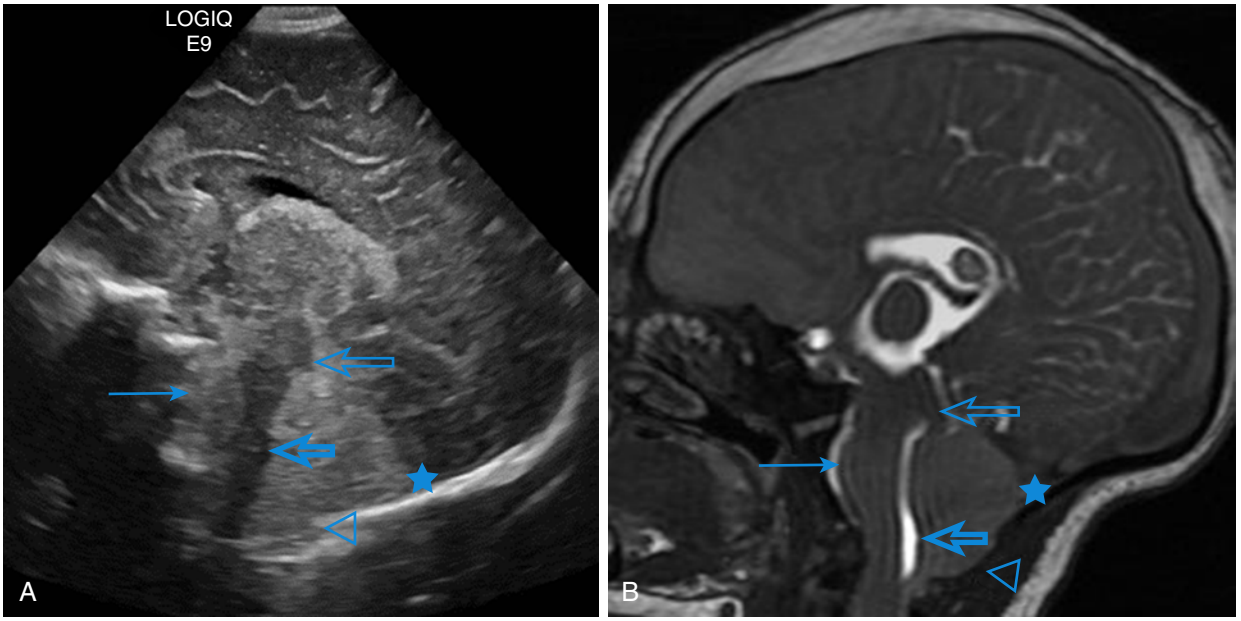

Fig. 70.11 Chiari II. Low cerebellar tonsils *(arrow head)*, low tentorial attachment *(star)*, flattened posn *(solid arrow)*, elongated 4th ventricle *(short arrow)*, tectal beaking *(long arrow)*. (A) Ultrasound. (B) MRI.

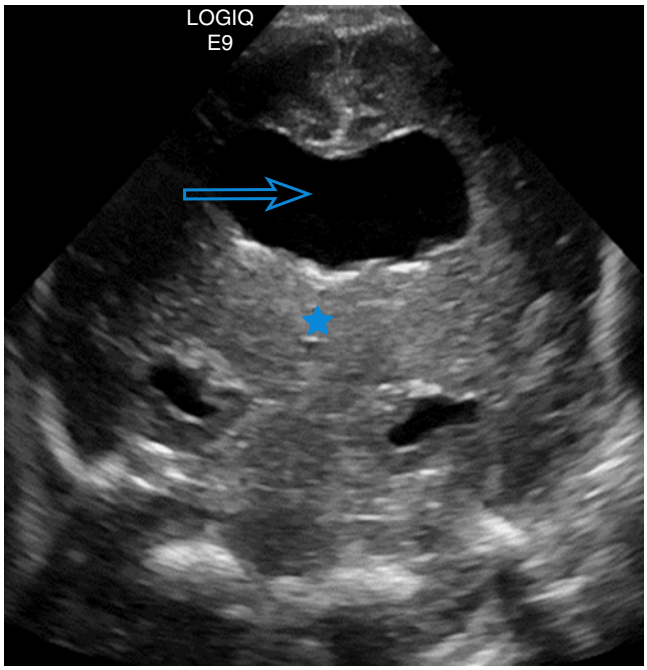

Fig. 70.12 **Semilobar holoprosencephaly. Fused thalami *(star)*, absent septum pellucidum *(arrow)*.**

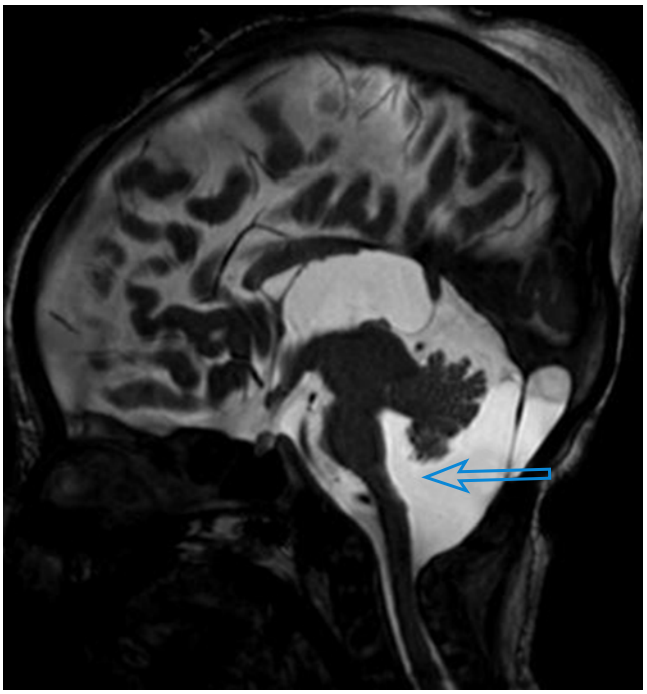

Fig. 70.13 **Dandy-Walker malformation. Hypoplasia of vermis with retrocerebellar cyst *(arrow)*.**

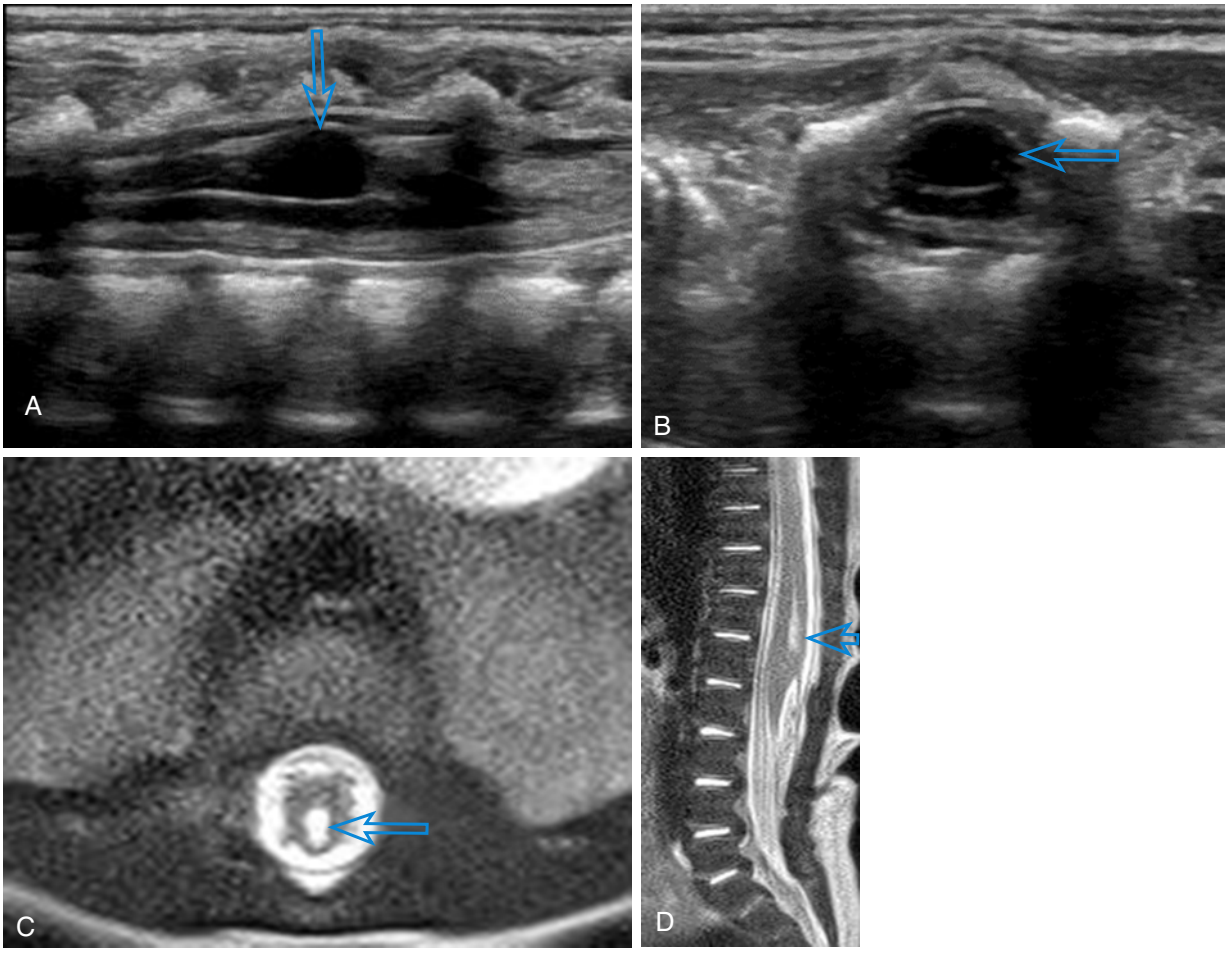

Fig. 70.14 Syrinx *(arrow)*. (A and B) Ultrasound. (C and D) MRI.

Fig. 70.15 Bilateral Choanal atresia. Membranous obstruction *(arrow)*. Thickened vomer *(star)*.

71 Chest Imaging

MITCHELL CHESS

Surfactant Deficiency

See Fig. 71.1.

- Diffuse ground-glass appearance, with fine granular pattern
- Bilateral and symmetric
- Air bronchograms
- Presents within hours of birth

Bronchopulmonary Dysplasia (BPD)

See Fig. 71.2.

- Increased interstitial markings with areas of lucency diffusely
- Hyperinflated lungs
- Cardiomegaly may suggest pulmonary hypertension

Pulmonary Interstitial Emphysema

- Cystic or linear lucencies extending from hilum
- May be focal (Fig. 71.3A) or generalized (see Fig. 71.3B)
- Hyperexpansion
- Associated with pneumothorax, pneumomediastinum, and pneumopericardium
- Increased pressure may lead to decreased venous return and smaller heart

Pneumonia

- Variable appearance from hyperexpansion, alveolar densities, interstitial disease
- May mimic surfactant deficiency
- Alveolar pattern with bilateral air space disease and air bronchograms (Fig. 71.4A)
- Round pneumonia—well-defined, rounded opacities almost exclusively pediatric (see Fig. 71.4B)

Transient Tachypnea of the Newborn (TTN)

See Fig. 71.5.

- Interstitial edema with normal heart size
- Resolves within 48 hours postpartum

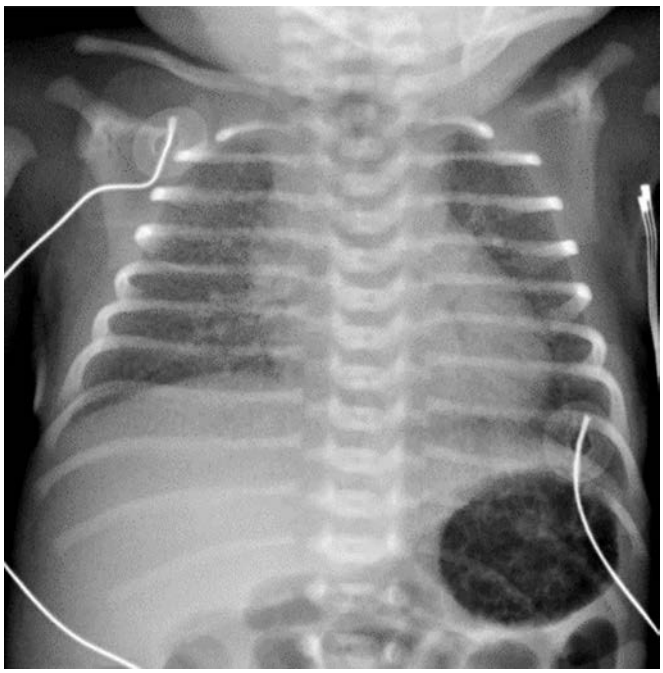

Fig. 71.1 Surfactant deficiency.

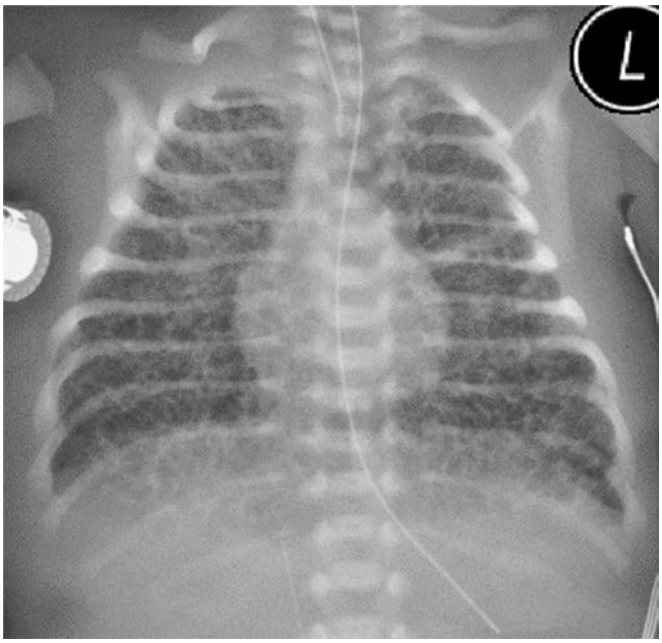

Fig. 71.2 Bronchopulmonary dysplasia (BPD).

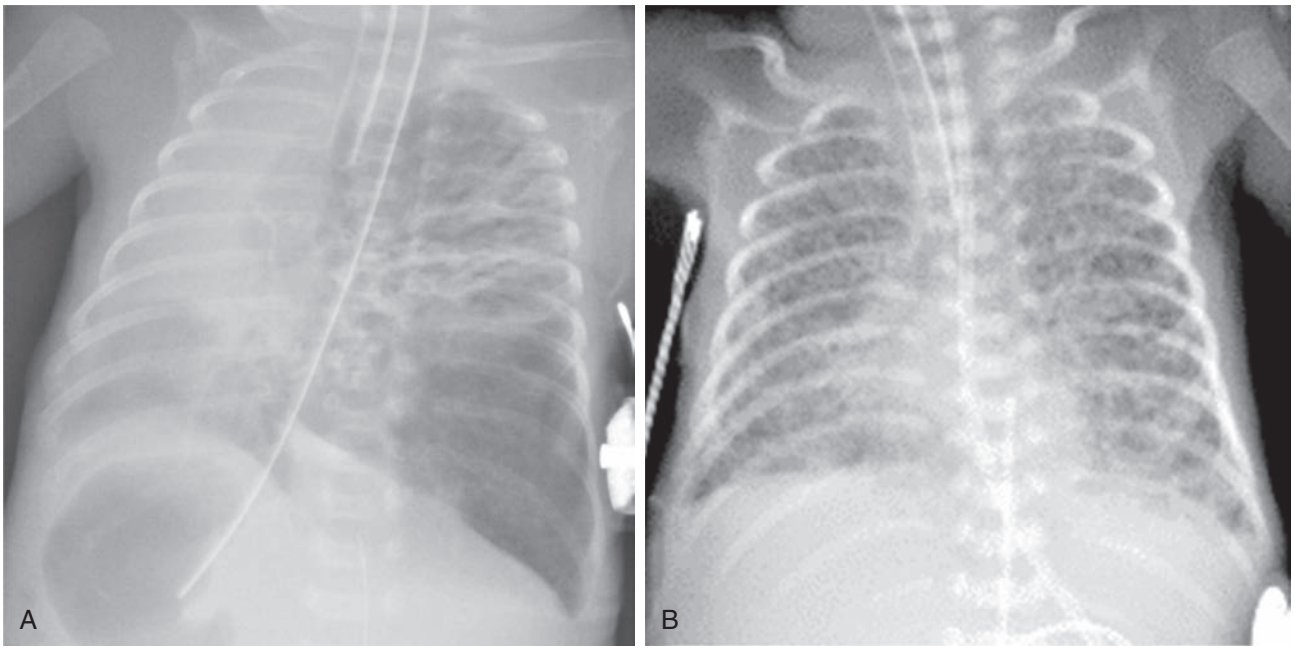

Fig. 71.3 Pulmonary interstitial emphysema. (A) Focal. (B) Generalized.

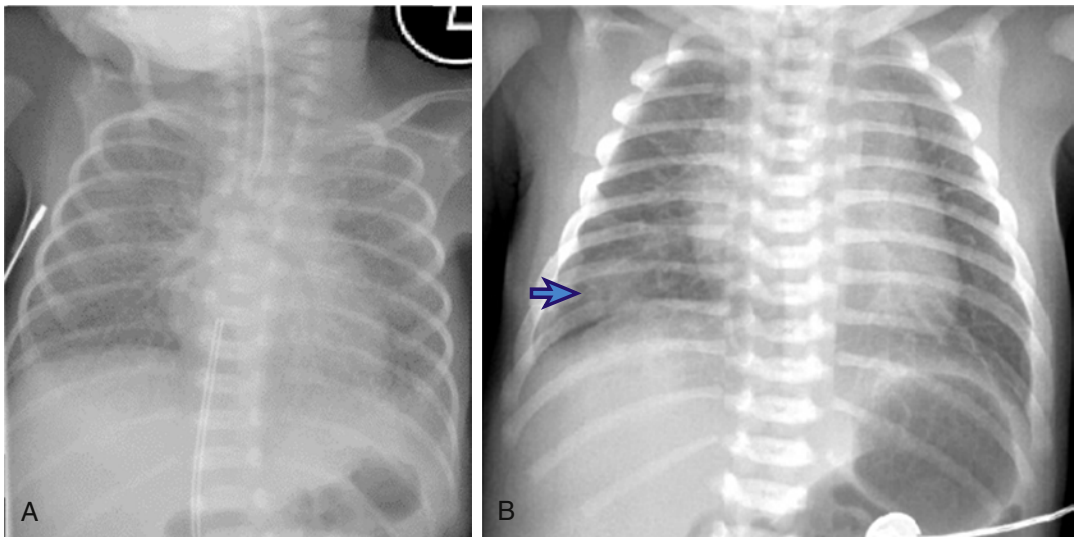

Fig. 71.4 Pneumonia. (A) Alveolar pattern. (B) Round pneumonia *(arrow)*.

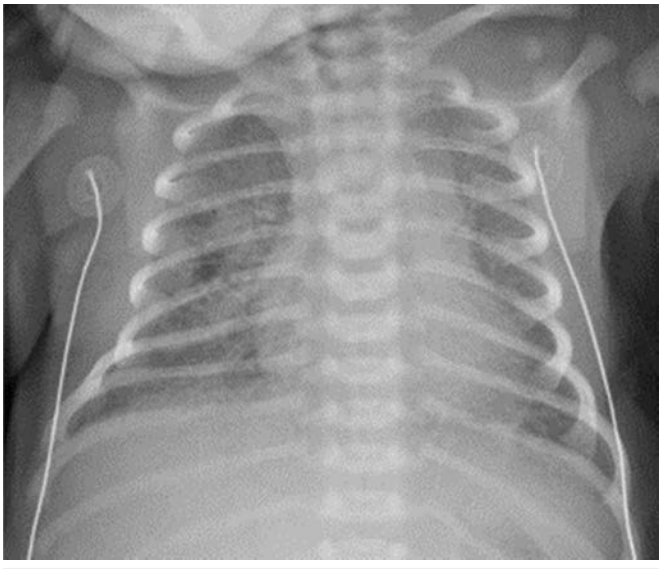

Fig. 71.5 Transient tachypnea of the newborn (TTN).

Meconium Aspiration

See Fig. 71.6.

- Hyperexpansion due to small airway obstruction
- Asymmetric, patchy opacities
- May have pleural effusions
- Pneumothorax association

Congenital Diaphragmatic Hernia (CDH)

- Indistinct diaphragm (typically left-sided)

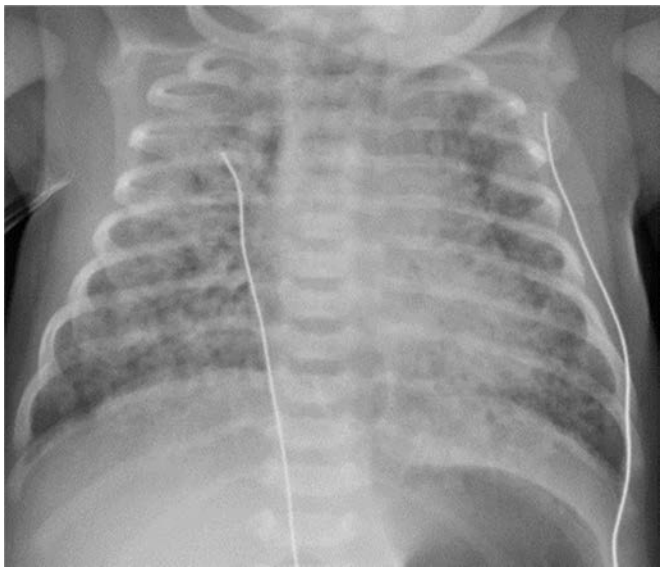

Fig. 71.6 Meconium aspiration.

- Preintubation or at intubation, bowel fluid-filled with opacification in hemithorax (Fig. 71.7A)
- Postintubation, bowel air with increased mass effect (see Fig. 71.7B)

Congenital Lobar Emphysema (CLE)

- Location
  - Left upper lobe: 40%–45%
  - Right middle lobe: 30%
  - Right upper lobe: 20%
  - Much rarer in the lower lobe
- Immediate postpartum may appear opaque and homogeneous with fetal lung fluid (Fig. 71.8A)
- Later appears hyperlucent, with paucity of vessels (see Fig. 71.8B)
- Mass effect (mediastinal shift, diaphragm depression)
- No change in lung volume on decubitus film

Congenital Pulmonary Airway Malformation (CPAM)

This was previously known as a *congenital cystic adenomatoid malformation* (CCAM).

- This is a multicystic (air-filled) lesion (Fig. 71.9A).
- It may cause mass effect (mediastinal shift, depression of diaphragm).
- Early neonatal cysts may be fluid-filled.
- Lesion may appear solid or with air-fluid levels (see Fig. 71.9B).

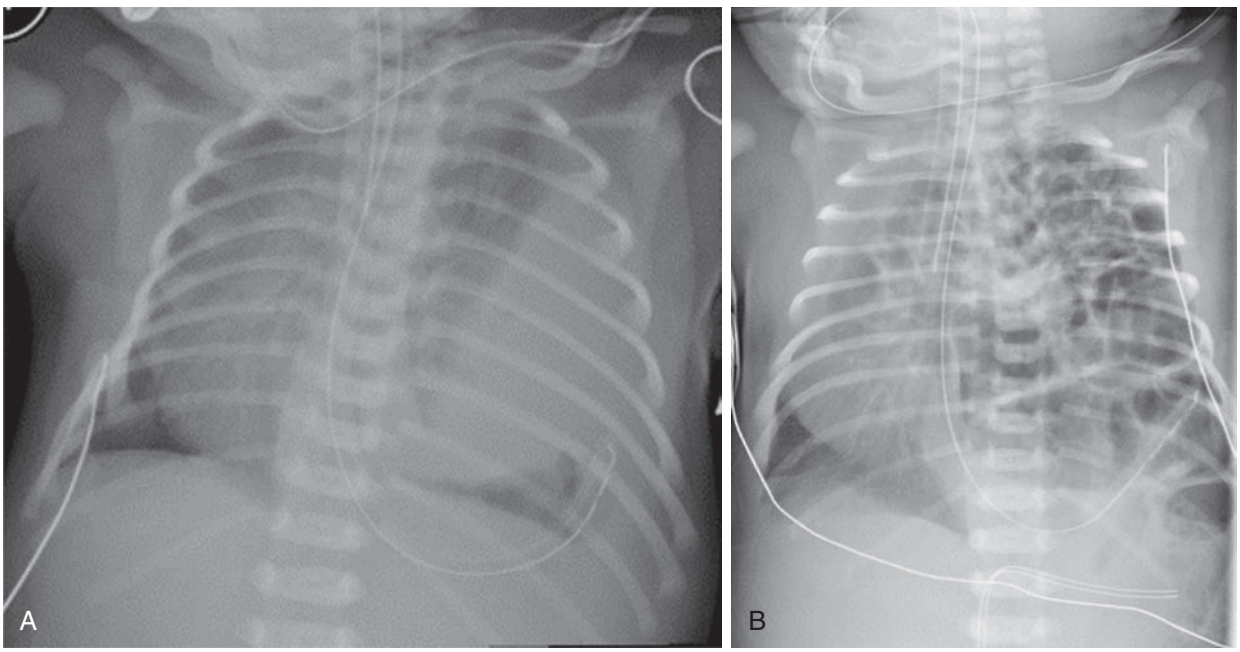

Fig. 71.7 (A and B) Congenital diaphragmatic hernia (CDH). (A) Perinatal with bowel still fluid-filled causing opacification. (B) Bowel filling with air and increasing mass effect.

- Computed tomography (CT) more accurately delineates the location and extent (see Fig. 71.9C).
- CT angiography can identify the arterial supply (systemic vs. pulmonary).

Pleural Effusion

- Most easily seen along the lateral chest wall or as a generalized hazy opacity (see Fig. 71.10) when supine because fluid layers dependently

Pneumothorax

- Accumulates in a nondependent fashion
- Supine, pneumothorax best seen as lateral chest, along diaphragm, at costophrenic angle as deep sulcus sign, or as a generalized lucency of the lung as the air layers anteriorly (Fig. 71.11A)
- Decubitus pneumothorax best seen on side that is up (see Fig. 71.11B)

Tension Pneumothorax

See Fig. 71.12.

- Increased intercostal space
- Mediastinal shift
- Hemidiaphragm depression

Pneumomediastinum and Pneumopericardium

See Fig. 71.13.

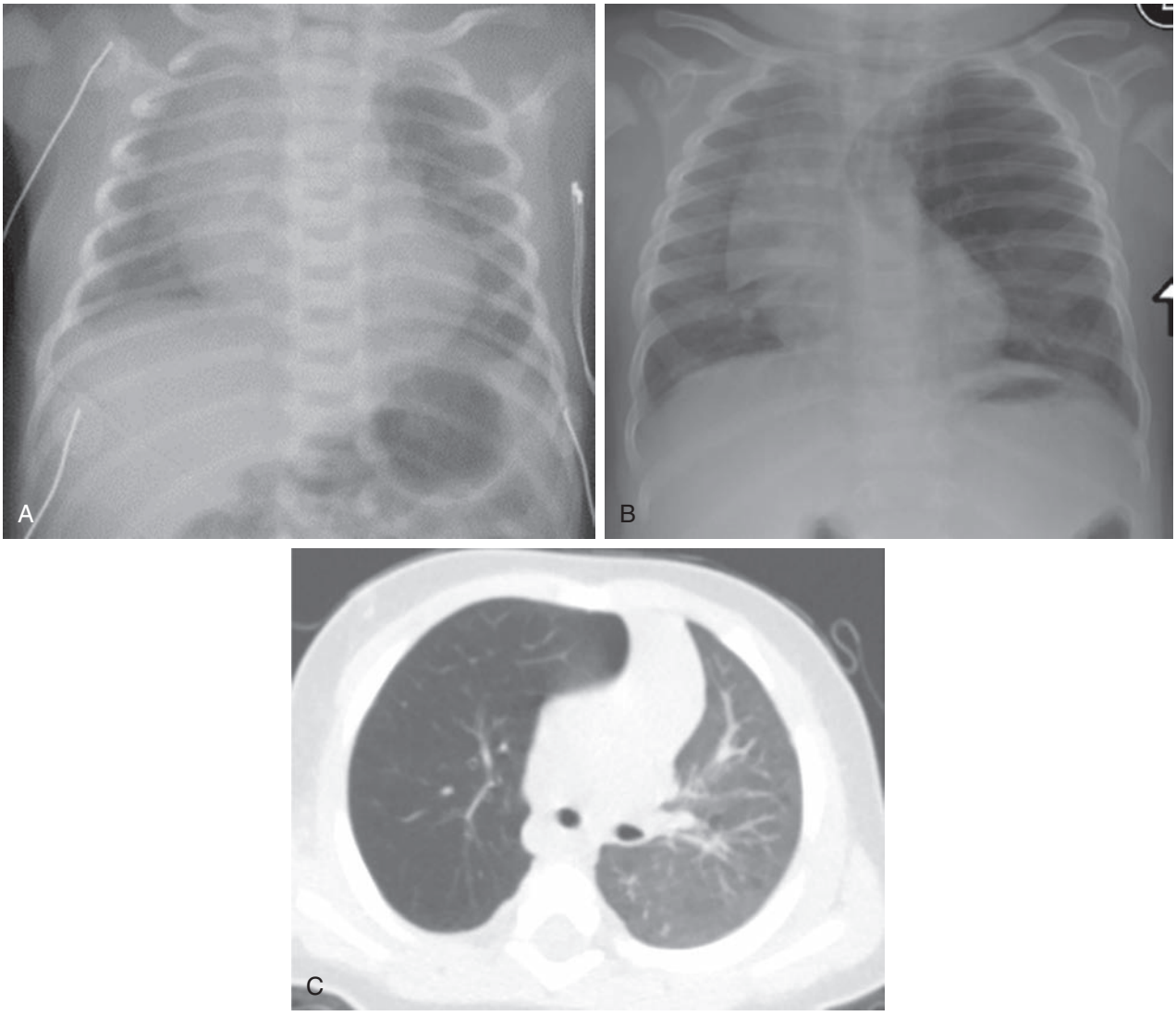

Fig. 71.8 Congenital Lobar Emphysema (CLE). (A and B) X-Ray. (A) Perinatal with mild hyperexpansion. (B) Increasing hyperexpansion over time. (C) Computed Tomography (CT scan).

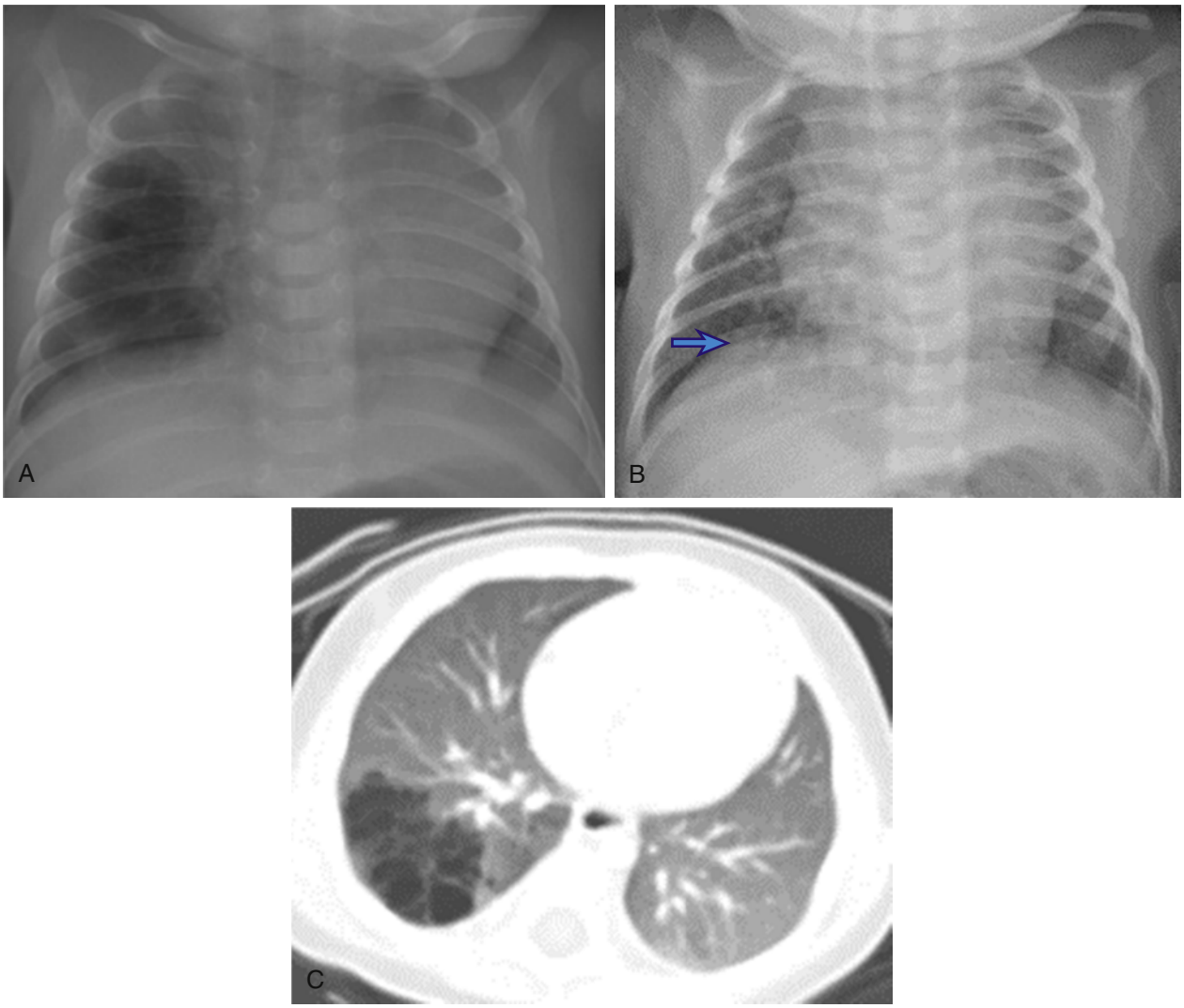

Fig. 71.9 Congenital pulmonary airway malformation. (A) X-ray Air filled malformation. (B) X-ray Fluid filled malformation (arrow) (C) Computed tomography (CT) scan.

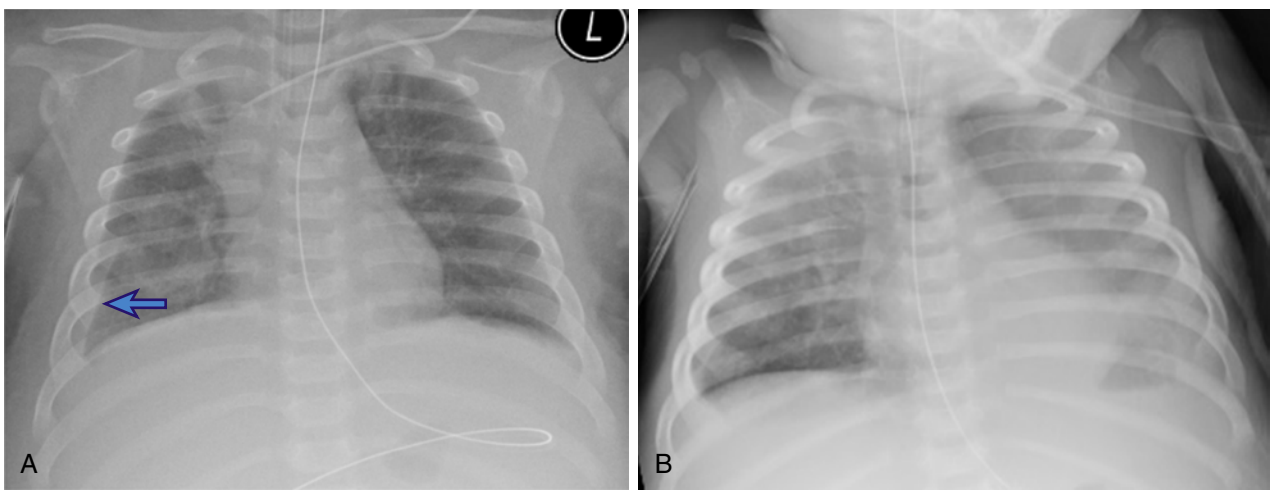

Fig. 71.10 (A and B) Pleural effusion. (A) Along lateral chest wall *(arrow)*. (B) Generalized opacity.

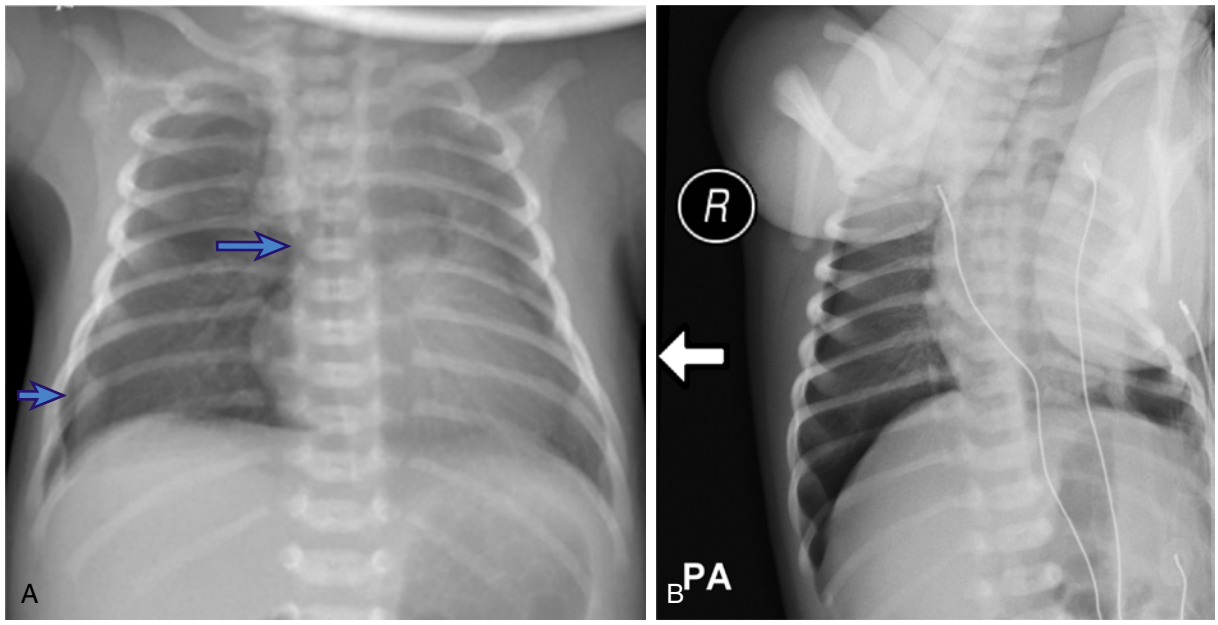

Fig. 71.11 (A) supine and (B) left lateral decubitus. Lung margin (arrow).

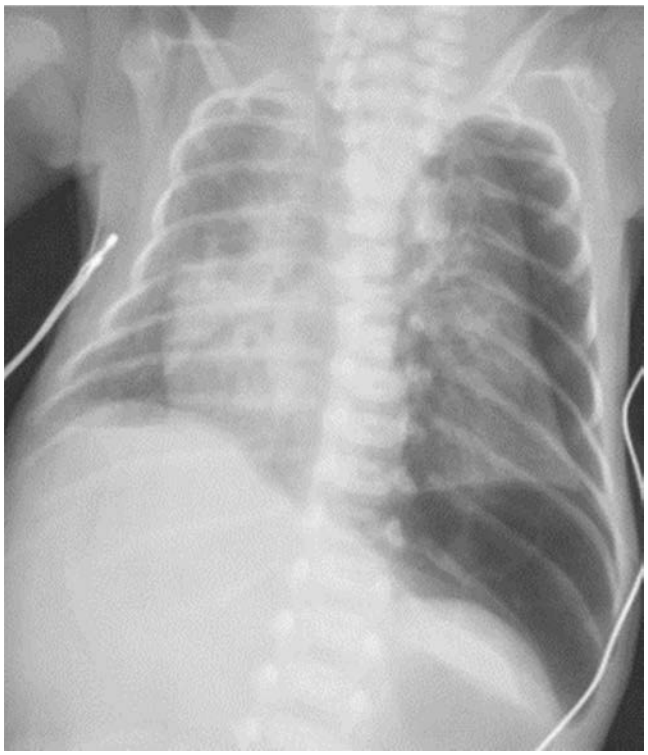

Fig. 71.12 Tension pneumothorax.

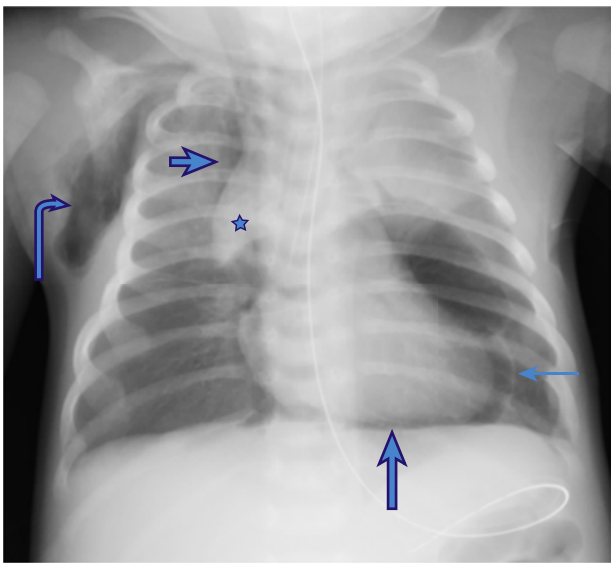

Fig. 71.13 Pneumomediastinum and pneumopericardium. Thymic wing sign *(star)*, subcutaneous emphysema *(curved arrow)*, Mediastinal air *(short arrow)*, Pericardial air *(thin arrow)*, continuous diaphragm sign *(long arrow)*.

PNEUMOMEDIASTINUM

- Elevated thymus, thymic wing sign
- Lucency outlining mediastinal contour
- Associated with subcutaneous emphysema

PNEUMOPERICARDIUM

- Pericardium sharply outlined by air
- Continuous diaphragm sign

Total Anomalous Pulmonary Venous Return (TAPVR)

- Right heart prominent due to increased flow volume
- Normal left atrium
- Cardiomegaly
- Type 1 (supracardiac) most common (Fig. 71.14)
  - Snowman appearance—left vertical vein, brachiocephalic vein, and superior vena cava (SVC) form the head, enlarged right atrium forms body

Transposition of the Great Arteries (TGA)

See Fig. 71.15.

- Cardiomegaly
- Egg-on-a-string sign—narrowed superior mediastinum with main pulmonary artery posterior to the aorta in d-transposition

Fig. 71.14 Total anomalous pulmonary venous return (TAPVR).

Tetralogy of Fallot (TOF)

See Fig. 71.16.

- Boot-shaped heart—upturned cardiac apex due to right ventricular hypertrophy and concave pulmonary artery
- Decreased pulmonary arterial flow related to pulmonary stenosis
- Right-sided aortic arch is seen in 25%

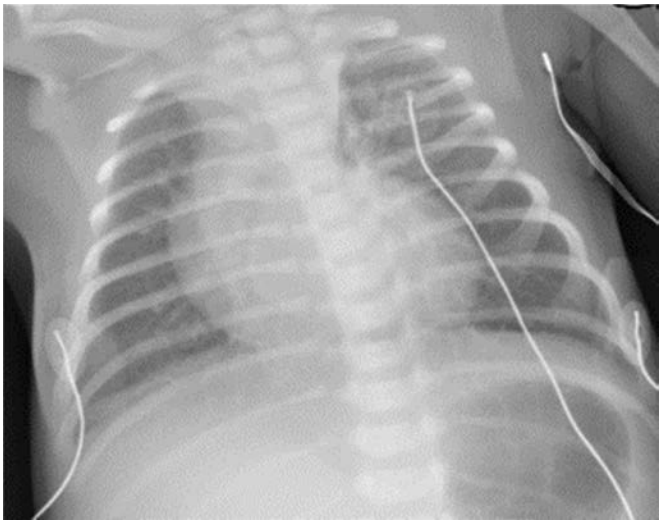

Fig. 71.15 Transposition of the great arteries (TGA).

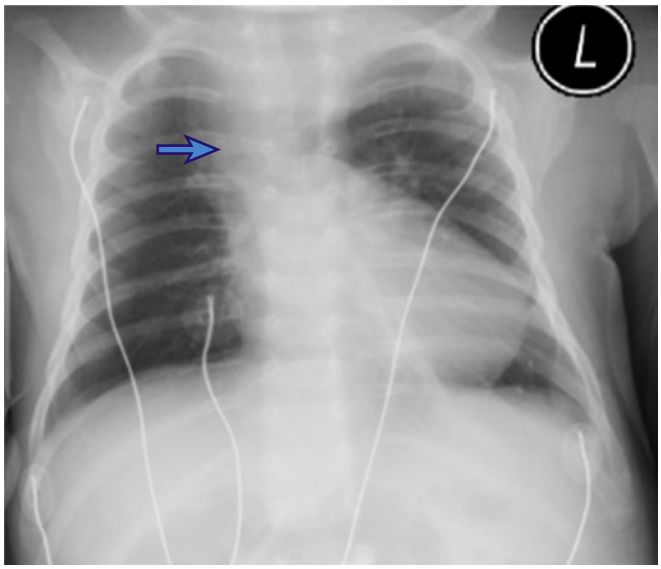

Fig. 71.16 Tetrology of Fallot. Right sided aortic arch *(arrow)*. Note lack of arch density to left of the trachea.

Suggested Readings

Eklund MJ, Hill JG, et al. *Neonatal Imaging*, 1st ed. National Certification Corporation; 2017.

72 Abdominal Imaging

MITCHELL CHESS

Necrotizing Enterocolitis

- Bowel dilation, frequently with asymmetric distribution
- "Stacking" of bowel loops (Fig. 72.1A)
- Bowel wall thickening, with separation of bowel loops (see Fig. 72.1A) or thumbprinting
- Mottled appearance of colon (see Fig. 72.1A) and linear lucency (see Fig. 72.1A) representing pneumatosis intestinalis
- Portal venous gas (see Fig. 72.1A)
- Pneumoperitoneum indicating perforation, including Rigler sign (air on both sides of the bowel) and football sign (air outlining falciform ligament; see Fig. 72.1B)

Biliary Atresia

- Nuclear medicine hepatobiliary iminodiacetic acid (HIDA) scan—good hepatic uptake with no evidence of excretion into the bowel at 24 hours
- Pretreatment with phenobarbital can increase biliary secretion by stimulating hepatic enzymes; may minimize false-positive study with patent biliary system but poor excretion
- No small bowel tracer at 6 hours (Fig. 72.2A) or 24 hours (see Fig. 72.2B)

Hirschsprung Disease

- Contrast enema for diagnosis and assessing length of involvement; transition zone on enema not always accurate transition between aganglionic and ganglionic cells
- Affected segment—small caliber, with proximal dilation (Fig. 72.3)
- Early filling views—include rectum and sigmoid colon, so rectosigmoid ratio may be determined

Microcolon

See Fig. 72.4.

- Diagnosed with contrast enema
- Differential diagnosis includes ileal atresia, meconium ileus, total colonic Hirschsprung disease

Esophageal Atresia With Fistula

See Fig. 72.5.

- Dilated air-filled pharyngeal pouch or tube insertion in blind loop turning back to neck
- Air in the stomach in the presence of esophageal atresia implies fistula

Esophageal Atresia Without Fistula

- No air in the stomach in presence of esophageal atresia—implies no fistula (Fig. 72.6A)
- Contrast via gastrostomy tube to demonstrate proximal, blind-ending, distal esophagus segment (see Fig. 72.6B)

Malrotation

- Upper gastrointestinal series is the examination of choice.
- The duodenojejunal junction fails to cross the midline to the left of the vertebral body (Fig. 72.7A).
- The duodenojejunal junction lies inferior to the duodenal bulb (see Fig. 72.7B).

Duodenal Atresia

See Fig. 72.8.

- Double-bubble sign with gas-filled distended stomach and duodenum with absence of distal gas

Hypertrophic Pyloric Stenosis

See Fig. 72.9.

- The pylorus is elongated and thick-walled.
- Remember that π [3.14] is abnormal.
  - Wall thickness > 3 mm
  - Length > 14 mm
- Stomach contents may pass through.

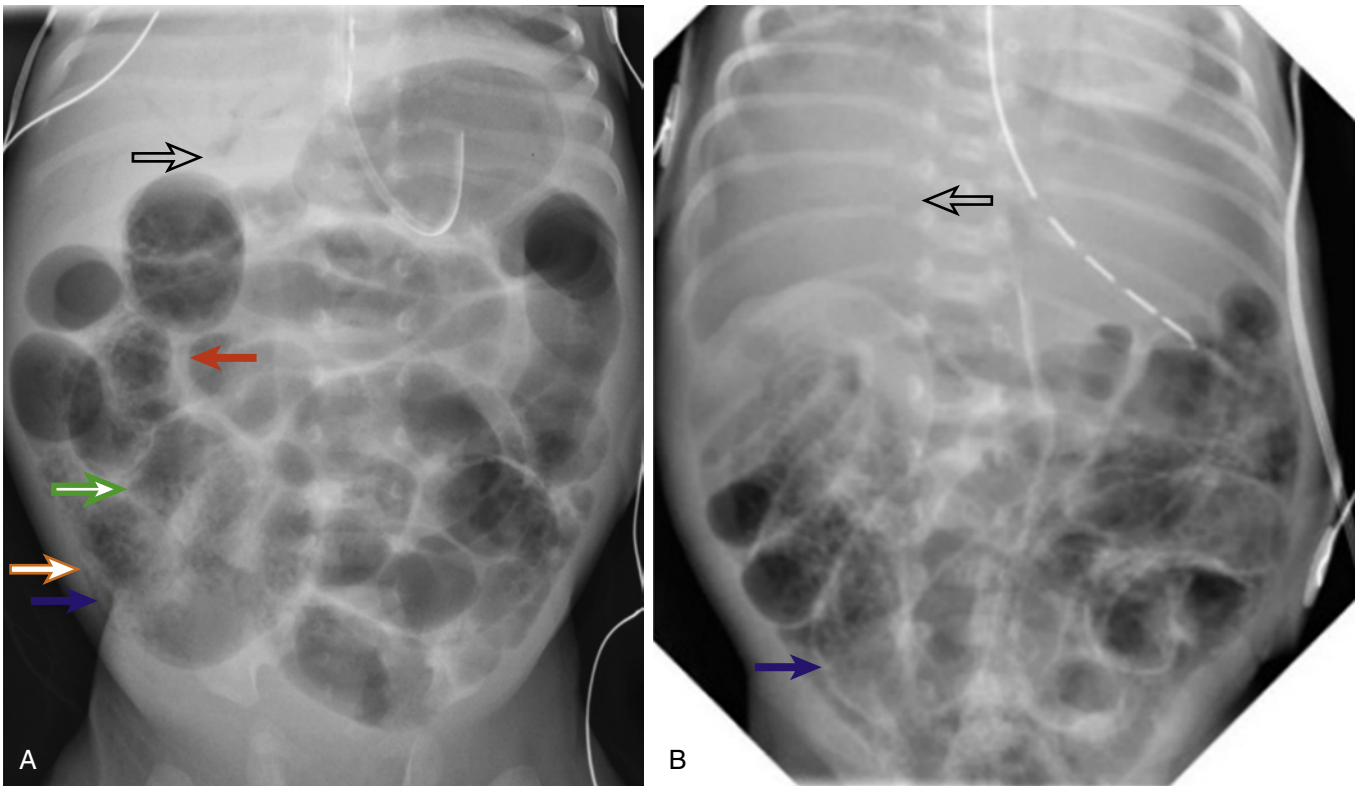

Fig. 72.1 (A and B) Necrotizing enterocolitis. (A) portal venous gas *(black arrow),* "stacking" of bowel loops *(green arrow),* separation of bowel loops *(red arrow),* mottled colon *(orange arrow)* and linear lucency *(blue arrow)* representing pneumatosis intestinalis. (B) pneumoperitoneum *(black arrow),* Rigler sign *(blue arrow).*

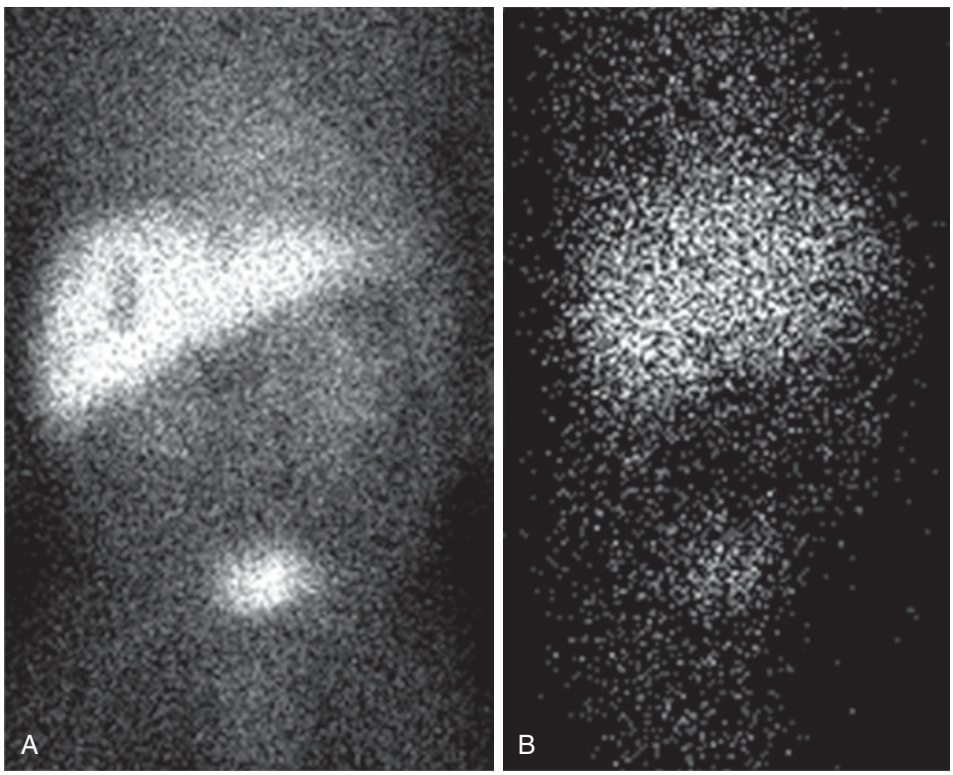

Fig. 72.2 Biliary atresia. (A) At 6 hours. (B) At 24 hours.

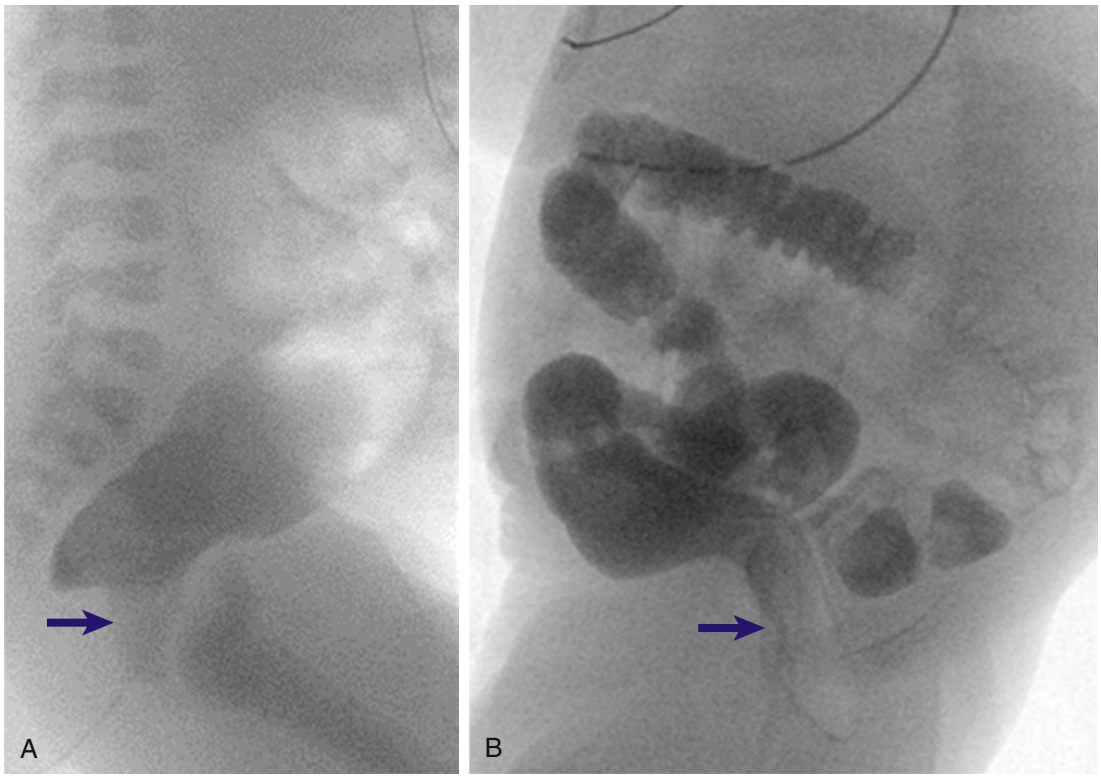

Fig. 72.3 (A and B) Hirschprung disease. Narrowed aganglionic segment *(blue arrow)*.

Fig. 72.4 Microcolon.

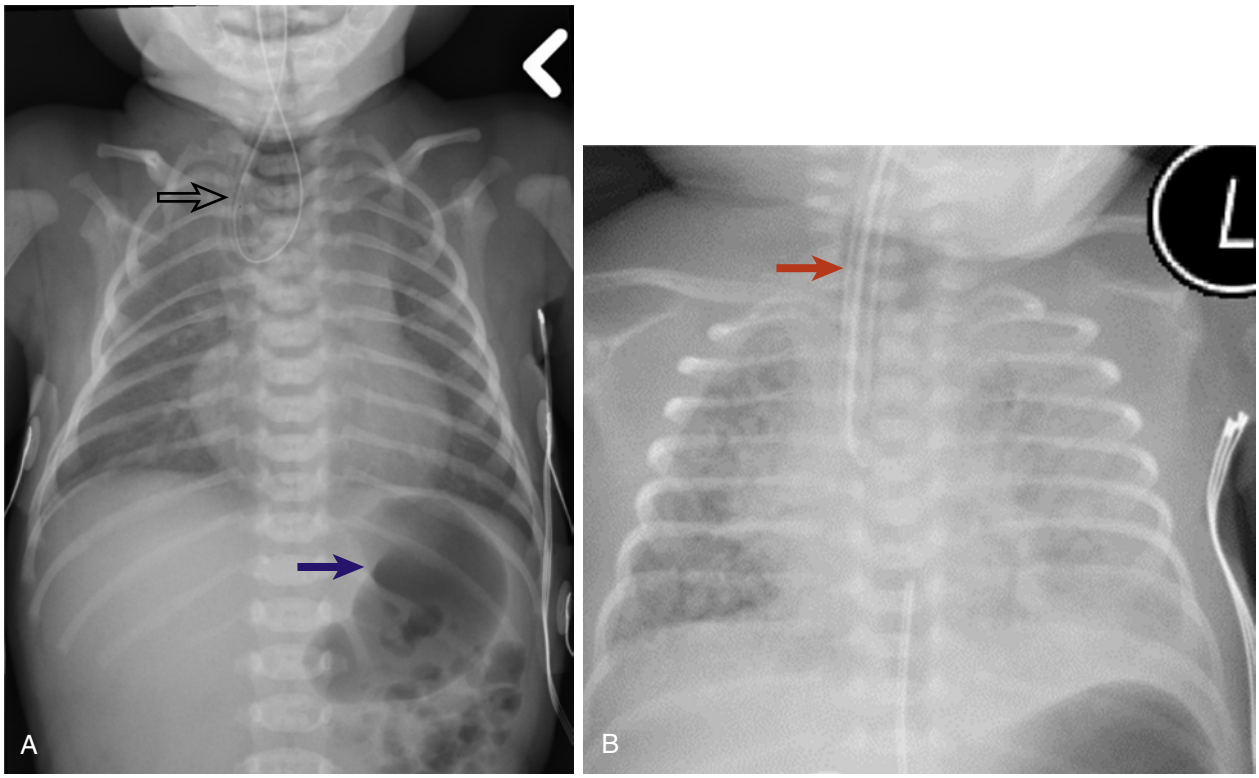

Fig. 72.5 (A and B) Esophogeal atresia with fistula. Pharyngeal pouch *(red arrow)* with tube insertion in blind loop *(black arrow)*. Air in the stomach *(blue arrow)*.

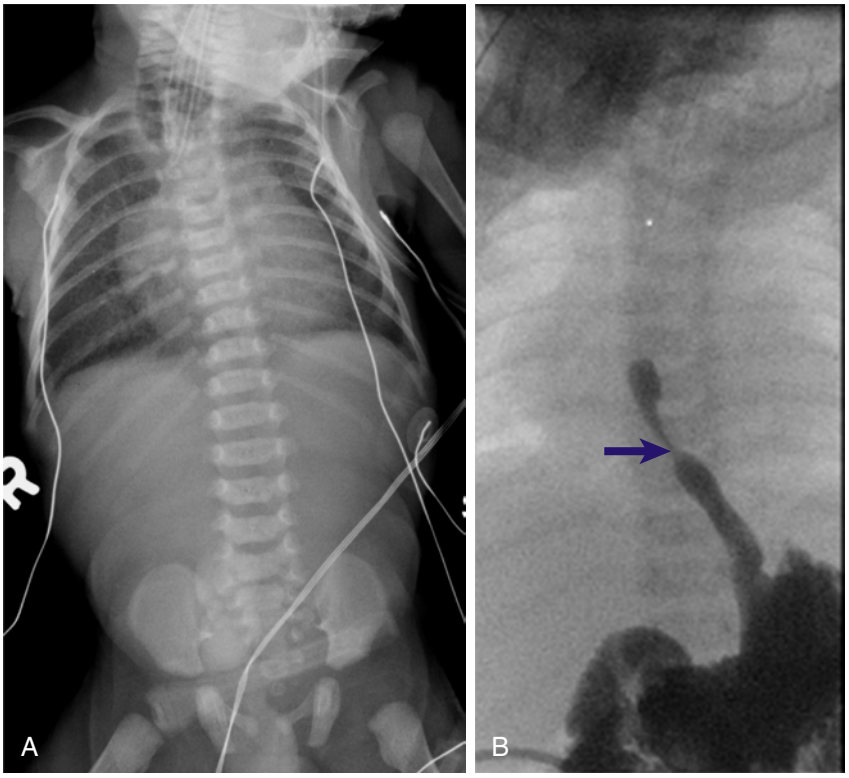

Fig. 72.6 (A and B) Esophogeal atresia without fistula. (A) x-ray. (B) Contrast via G tube demonstrates distal esophagus *(arrow)*.

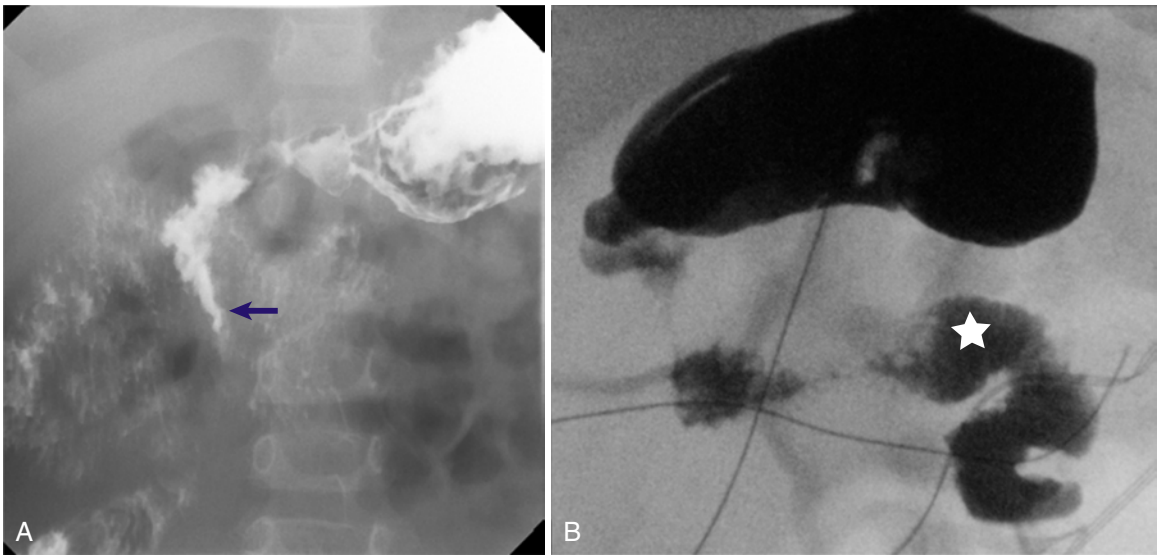

Fig. 72.7 (A and B) Malrotation. Duodenojejunal junction fails to cross the midline *(arrow)*. Duodenojejunal junction lies inferior to the duodenal bulb *(star)*.

Fig. 72.8 Duodenal atresia.

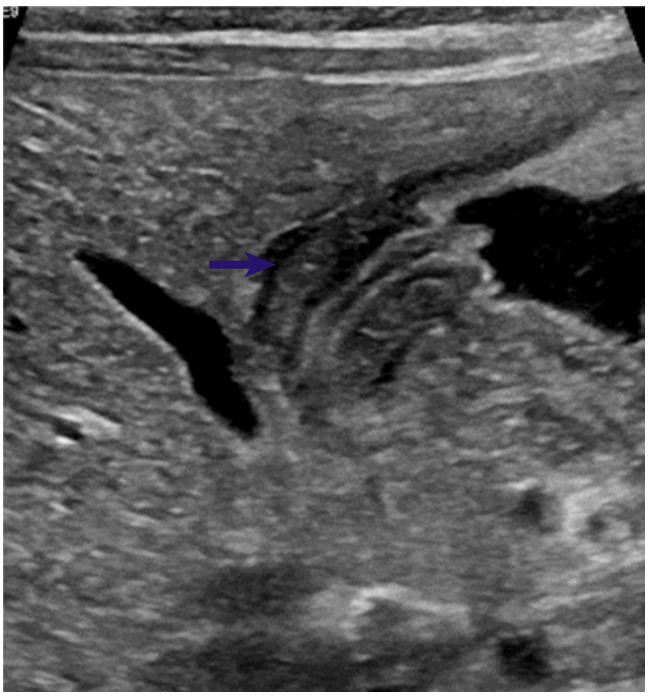

Fig. 72.9 Hypertrophic pyloric stenosis. Thickened, elongated pylorus *(arrow)*.

Suggested Reading

Eklund MJ, Hill JG, et al. Neonatal imaging, 1st ed. National Certification Corporation. 2017.

73 Miscellaneous

MITCHELL CHESS

Normal Thymus/Clavicle Fracture

See Fig. 73.1.

- Thymus triangular, frequently toward right of mediastinum, without mass effect on vascular structures or airway
- Scalloped contour from anterior rib impressions
- Clavicular fractures complete or incomplete, unilateral or bilateral
- Incidence—increases with increasing fetal weight
- Frequently related to shoulder dystocia

Lines

See Fig. 73.2.

- Umbilical vein (UV) courses anteriorly with dip posteriorly in liver through ductus venosus; final position above diaphragm
- Umbilical artery (UA) courses inferiorly to iliac artery before extending to aorta; final position between T7 and T9

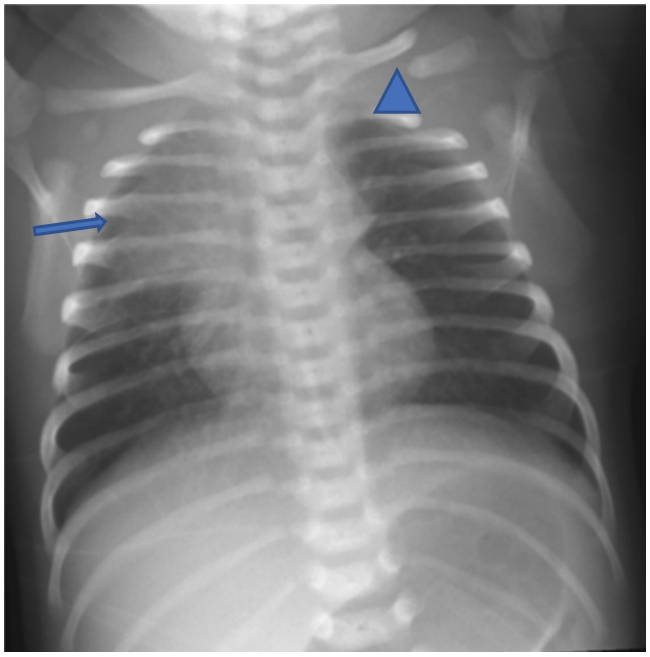

Fig. 73.1 Normal thymus *(arrow)* clavicle fracture *(arrow head)*.

Cystic Hygroma (Cystic or Nuchal Lymphangioma)

See Fig. 73.3.

- Well circumscribed
- Fluid density
- Unilocular or multilocular
- Density variable; combination of fluid, soft tissue, and fat

Thanatophoric Deformity

See Fig. 73.4.

Limbs
- Proximal limbs short, with rhizomelic appearance
- Long bones—"telephone handle" bowing and metaphyseal flaring

Iliac bones
- Hypoplastic with squared iliac wings
- May show a trident" acetabular roof

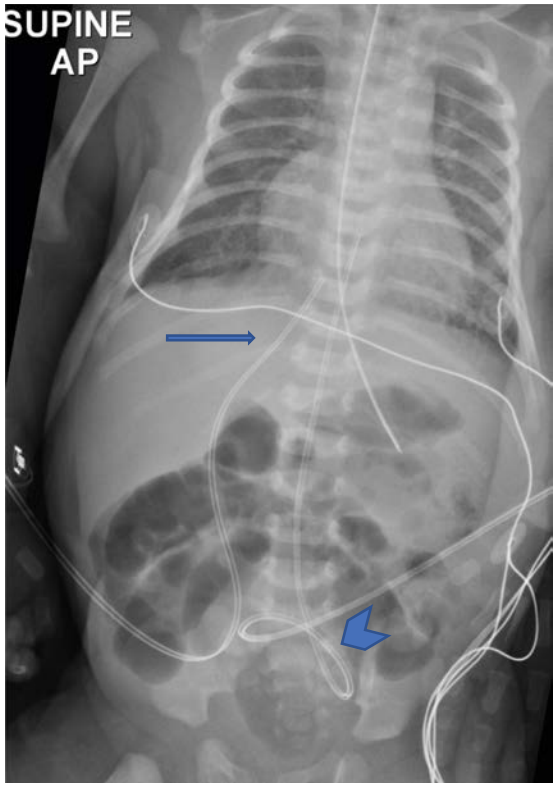

Fig. 73.2 UV *(arrow)* courses anteriorly with dip posteriorly. UA *(arrow head)* courses inferiorly to iliac artery before extending to aorta.

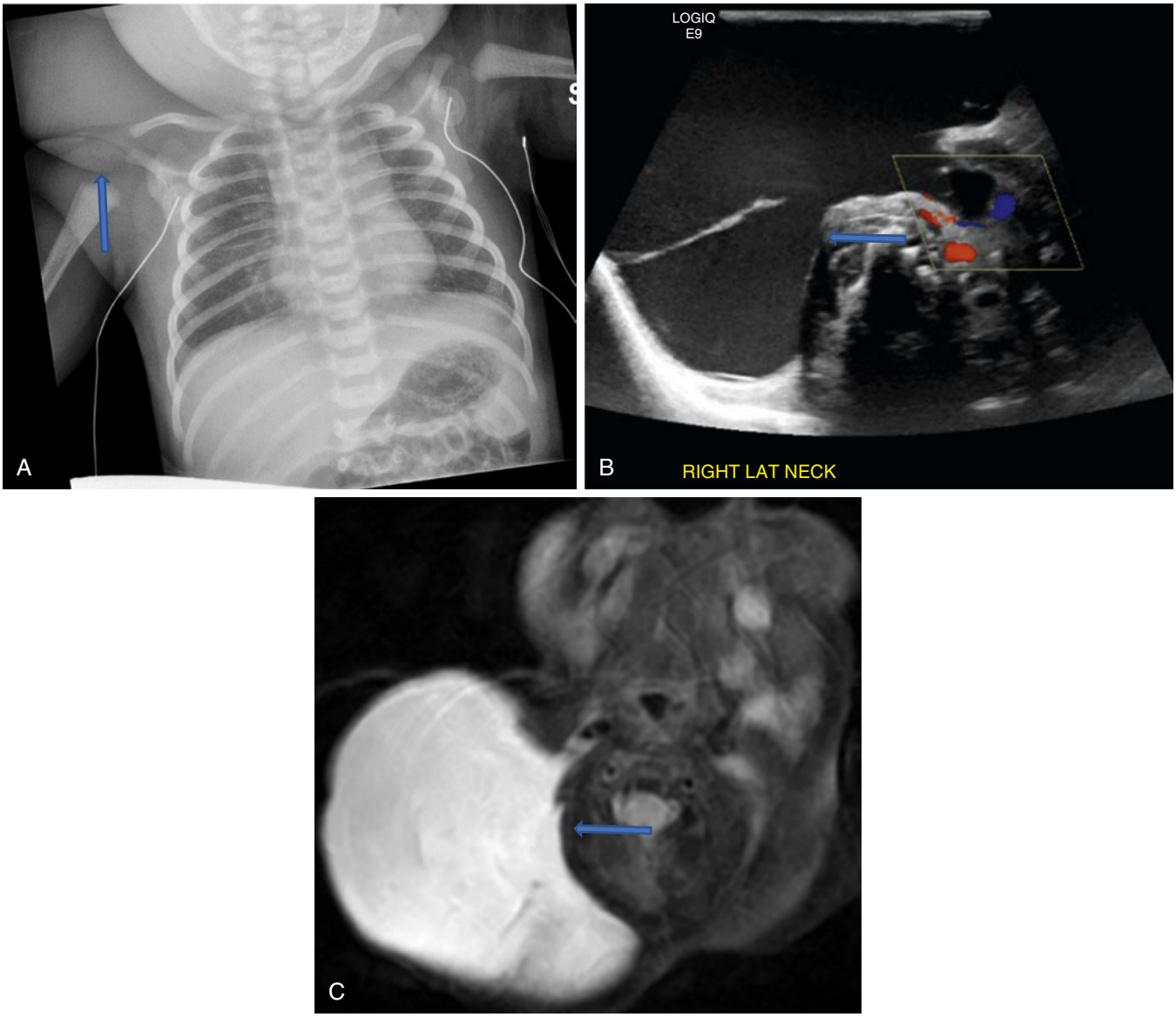

Fig. 73.3 (A–C) Cystic hygroma *(arrow)*. (A) X-ray, (B) US, (C) MRI.

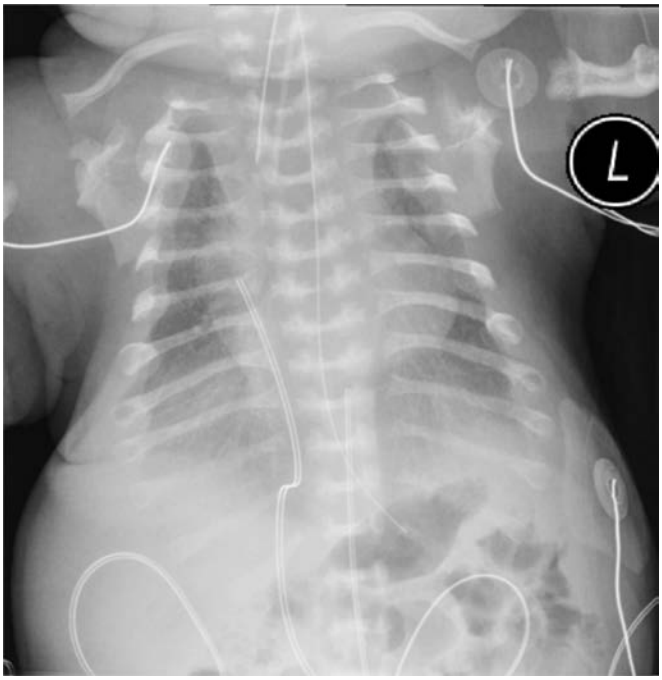

Fig. 73.4 Thanatophoric deformity.

Chest
- Narrow chest, short horizontal ribs, small scapulae

Skull and face
- Macrocephaly with frontal bossing, proptosis, and nasal bridge flattening
- May have Kleeblattschaedel (cloverleaf skull)

Spine
- Platyspondyly (flattened vertebral bodies)

Achondroplasia

See Fig. 73.5.

Chest
- Anterior flaring of the ribs, with anteroposterior narrowing of the ribs

Pelvis and hips
- Decreased acetabular angle
- Small squared iliac wings

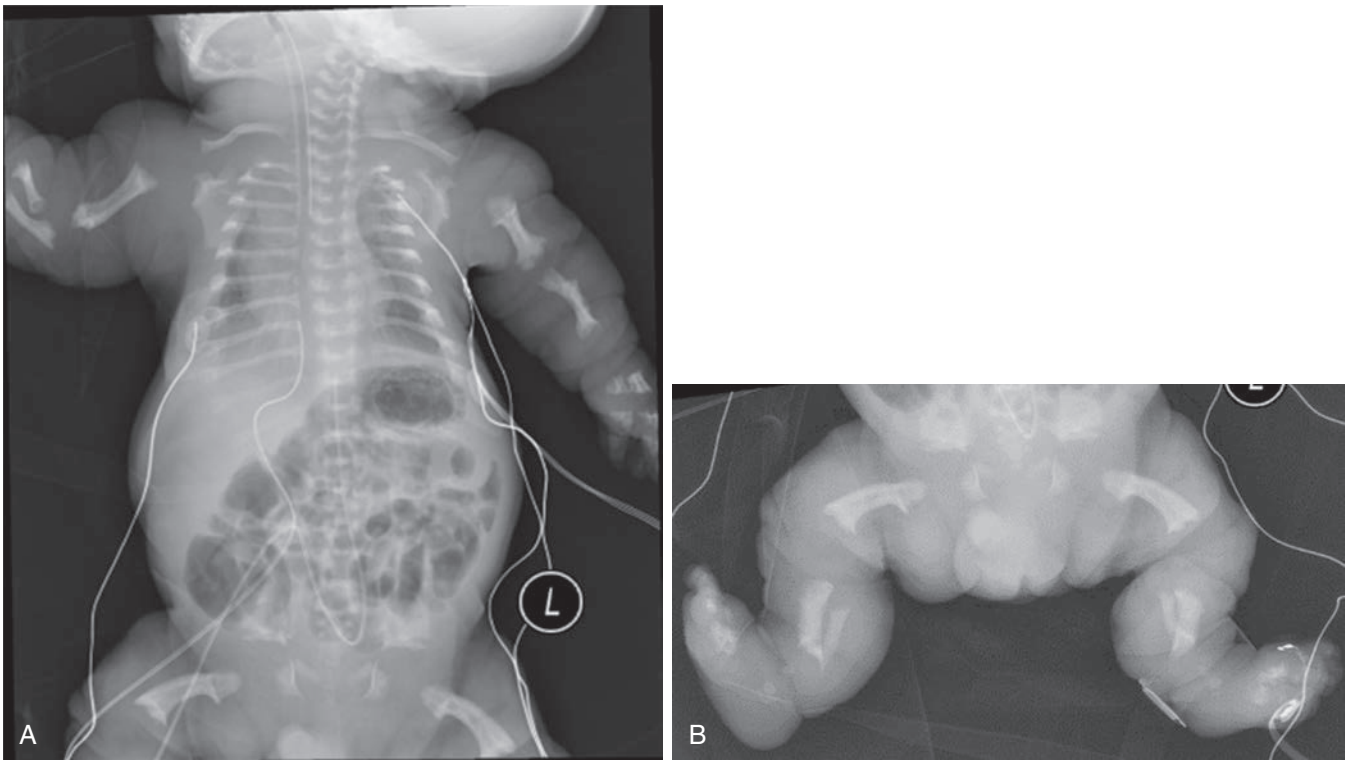

Fig. 73.5 (A and B) Achondroplasia.

- Small trident pelvis
- Champagne glass type of pelvic inlet
- Short sacroiliac notches

Limbs

- Metaphyseal flaring
- Femora and humeri most foreshortened (rhizomelic shortening)

Hydronephrosis

See Fig. 73.6.

- Abnormal dilatation of the renal collecting system, see suggested reading for more complete classification of urinary tract dilatation.
- Causes include ureteropelvic obstruction (most common), posterior urethral valves, vesicoureteral reflux, ureterocele, and other developmental anomalies of the GU tract.

Fig. 73.6 Hydronephrosis.

Urinary Tract Dilation—Posterior Urethral Valves (PUV)

Voiding cystourethrogram (VCUG) best imaging technique

- Dilation and elongation of posterior urethra (keyhole sign) (Fig. 73.7A)
- Linear lucency corresponding to the valve (see Fig. 73.7A)
- Vesicoureteral reflux frequent
- Bladder trabecula and diverticula (see Fig. 73.7B)

Ultrasound

- Bladder thick-walled and trabeculated, with an elongated and dilated posterior urethra (see Fig. 73.7C)
- Hydronephrosis (up to 10% may appear normal)
- Valve may be seen as echogenic line
- Rupture of calyceal fornix may cause urinoma (anechoic fluid collections)

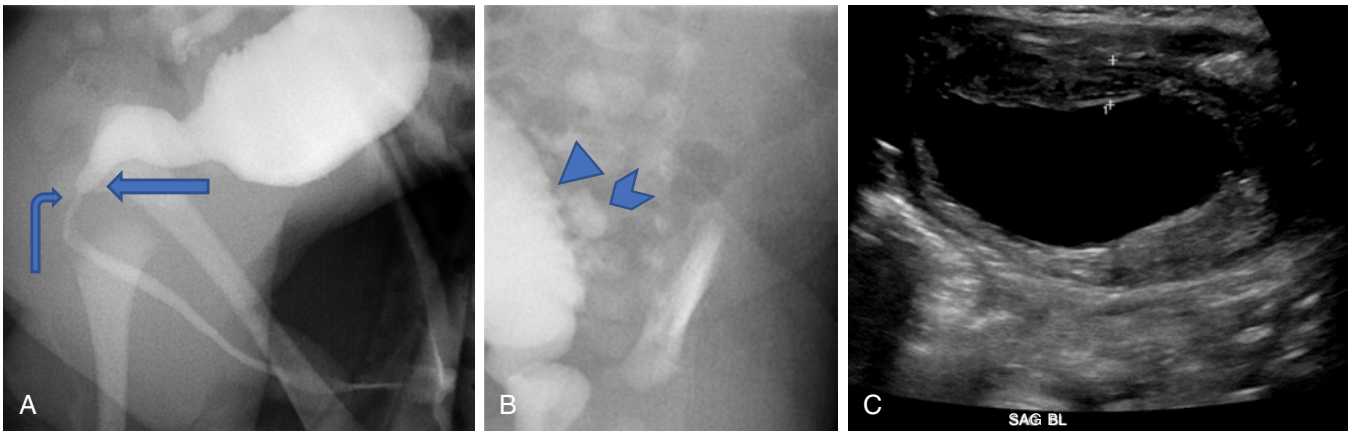

Fig. 73.7 (A–C) Posterior urethral valves (PUVs). VCUG (A and B) keyhole sign *(arrow)*, linear lucency corresponding to the valve *(curved arrow)*, bladder trabecula *(arrow head)* and diverticula *(chevron)*. US (C) bladder thick-walled and trabeculated.

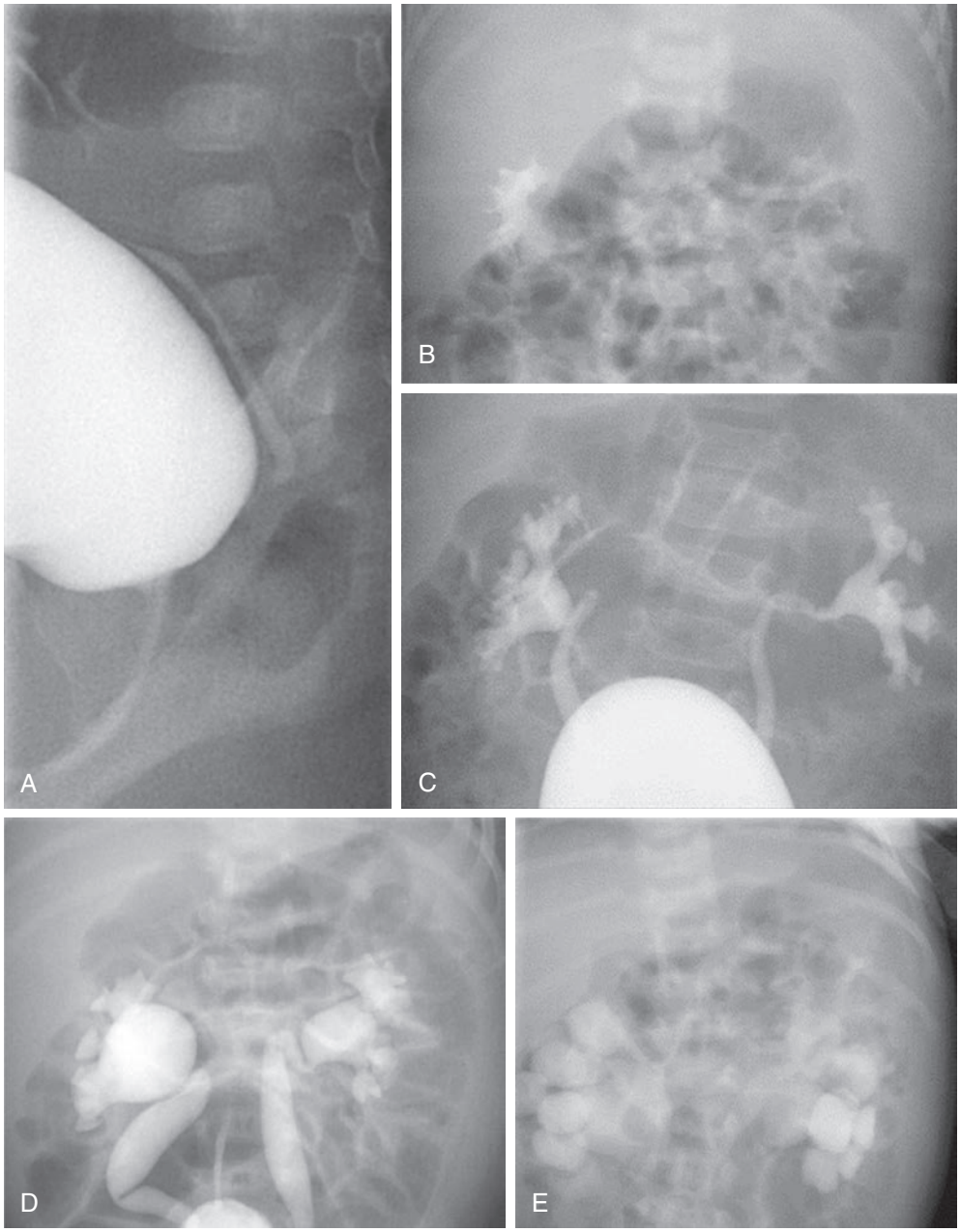

Fig. 73.8 (A–E) VCUG with VUR. (A) Grade 1. (B) Grade 2. (C) Grade 3. (D) Grade 4. (E) Grade 5.

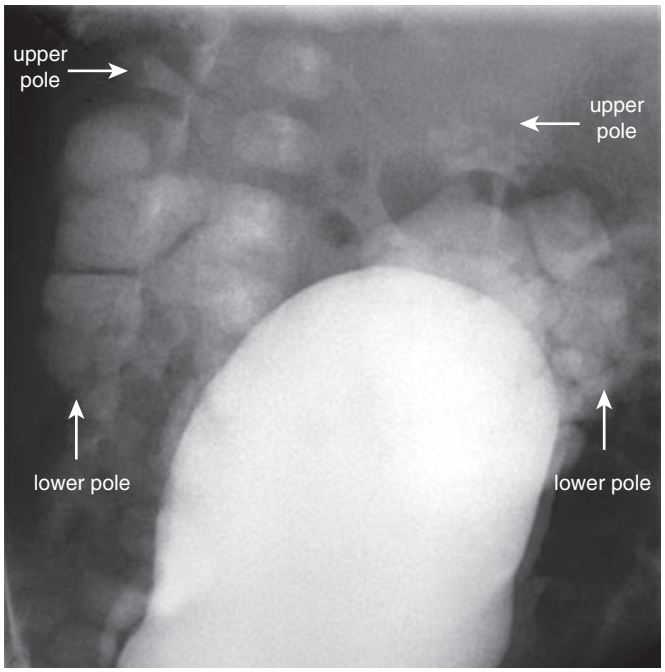

Fig. 73.9 VUR Grade 2 upper left, grade 3 upper right, grade 5 lower bilateral.

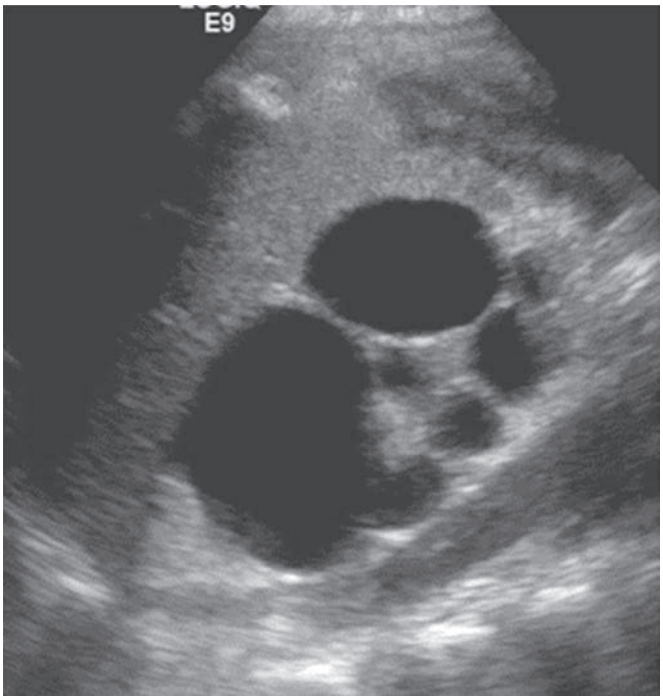

Fig. 73.10 Multicystic dysplastic Kidney (MCDK) with non-communicating cysts.

Vesicoureteral Reflux (VUR)

- Grade 1: reflux limited to the ureter (Fig. 73.8A)
- Grade 2: reflux up to the renal pelvis (see Fig. 73.8B)
- Grade 3: mild dilation of the urinary tract (see Fig. 73.8C)
- Grade 4: tortuous ureter with moderate dilation of renal collecting system, with preserved papillary impressions (see Fig. 73.8D)
- Grade 5: tortuous ureter with severe dilation of ureter and pelvicalyceal system, with loss of fornices and papillary impressions (see Fig. 73.8E)
- Reflux may not be symmetric bilaterally (Fig. 73.9)

Multicystic Dysplastic Kidney (MCDK)

See Fig. 73.10.

- Lobulated renal contour with multiple cysts of varying sizes
- Absent or small hilar vessels
- Cysts typically cluster and are noncommunicating

Suggested Reading

Chow JS, Darge K. Multidisciplinary consensus on the classification of antenatal and postnatal urinary tract dilation (UTD classification system). *Pediatr Radiol*. 2015;45(6):787–789.

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SECTION 19

Pharmacology

TRACEY L. MCCOLLUM

74 Drug Disposition and Pharmacokinetics

TRACEY L. MCCOLLUM

Pharmaceutical therapy plays an integral role in the treatment of many conditions affecting the neonate and preterm neonate. Given the paucity of evidence-based dosing regimens, it is incumbent on the provider to use knowledge of developmental pharmacology to ensure that drug therapy is effective while minimizing the risk of toxicity. A thorough understanding of the maturational changes that affect drug disposition—absorption, distribution, metabolism, and elimination—as well as clinical pharmacokinetics, will help guide this process.

Drug Disposition

ABSORPTION

- Movement of a drug from the site of administration into the systemic circulation
- Bioavailability (F): fraction of administered drug that reaches systemic circulation in active form
  - Intravascular administration = 100% bioavailability
- Extravascular absorption occurs by:
  - Passive diffusion of unionized molecules across lipophilic membranes
  - Facilitated passive diffusion involving a carrier molecule
  - Active transport by a carrier requiring energy
- Influenced by
  - Route of administration
  - Biochemical properties and formulation of the drug
    - Lipid solubility—favors absorption
    - Degree of ionization (unionized molecules favored)
    - Molecular weight (smaller molecules favored)
  - Patient-specific factors
    - Gastric pH
    - Gastric emptying time
    - Intestinal transit time
    - Blood flow to the site of administration
    - Bacterial colonization
    - Bile acid production
- Bioavailability—can be reduced by first-pass metabolism through the liver
- Table 74.1—summary of neonatal factors that affect drug absorption

DISTRIBUTION

- Movement of a drug from the bloodstream to the extravascular compartments, including fluid, organs, tissues, fat, and muscle
- Influenced by:
  - Size, composition, and pH of body compartments
  - Cardiac output (blood flow to tissues and organs)
  - Membrane permeability
  - Physiochemical properties of the drug
    - Lipid solubility, molecular weight, ionization constant, protein binding
- Volume of distribution (V_d): the theoretic volume that would be necessary to contain the total administered dose of a drug at the same concentration observed in the plasma
  - Lipophilic drugs generally have a larger V_d and longer half-life.
  - Hydrophilic and highly protein bound drugs generally have a smaller V_d.
  - Drugs that have a larger V_d require a larger dose per unit of body measure to achieve the same serum concentration.
- Protein binding
  - Free drug is the fraction of drug not bound to protein, which can penetrate cell membranes and exert pharmacologic activity.
  - Binding proteins include albumin, lipoproteins, and alpha-1-acid glycoprotein.
    - Albumin has a greater affinity for acidic drugs.
    - Alpha-1-acid glycoprotein binds drugs that are bases.
  - Protein binding is a saturable, reversible process.
  - Serum drug concentration measurements reflect the total of free and bound drug. A greater percentage of free drug may result in an enhanced response for a given serum concentration.
- Characteristics of drugs that easily cross membranes, including the placenta and blood-brain barrier:
  - Highly lipophilic
  - Low degree of ionization (neutral)
  - Low degree of protein binding (protein-bound molecules generally incapable of crossing membranes)
  - Low molecular mass
- Table 74.2—summary of neonatal factors that affect drug distribution

METABOLISM

- Biotransformation of a drug to a more water-soluble compound to facilitate elimination
- Metabolism primarily serves to weaken or inactivate drug but sometimes may result in active metabolites or intermediates, or even transform an inactive prodrug into its active form

Table 74.1 Summary of Neonatal Factors Affecting Drug Absorption

Route of Administration	Modifying Factor	Neonatal Function	Net Effect	Clinical Example(s)
Enteral, stomach	Gastric pH	Increased at birth; declines rapidly in term neonates, but can remain elevated in preterm neonates (<32 weeks) for several weeks	Decreased absorption of weakly acidic drugs; weakly basic drugs readily absorbed	Phenobarbital, phenytoin, furosemide, amoxicillin, chlorothiazide, theophylline, penicillin, erythromycin, methadone, morphine, caffeine
	Gastric emptying	Delayed (up to 6–8 hours) in the preterm infant; variable in infancy up to 6–8 months of age; dependent on type of diet	Delayed absorption and reduced peak concentration	
Enteral, intestine (primary site of drug absorption)	Transit time	Generally delayed	Delayed peak serum drug concentration; reduced AUC	Ampicillin
	Presence of pancreatic enzymes and bile salts	Reduced	Decreased absorption of fat-soluble drugs	Vitamins A, D, E, and K, zinc, clindamycin
	Bacterial colonization	Reduced	Variable	Increased bioavailability of digoxin due to lack of digoxin-reducing bacteria
Intramuscular	Muscle mass and perfusion	Reduced muscle mass and blood flow	Reduced absorption; increased potential for injury	
Percutaneous	Permeability and surface area	Increased in the preterm neonate due to immature stratum corneum and increased water content	Increased absorption; potential toxicity	Corticosteroids, alcohol-containing preparations
Rectal	Placement	Placement in lower rectum enhances absorption; placement in upper rectum subjects drugs to first-pass metabolism	Increased absorption; decreased bioavailability	Barbiturates, benzodiazepines acetaminophen

AUC, Area under the curve.

Table 74.2 Summary of Neonatal Factors Affecting Drug Distribution

Distribution Factor	Neonatal Function	Net Effect	Clinical Example(s)
Body composition	Greater percentage total body water[a]; ranges from 85% at 24 weeks–75% at term	Increased volume of distribution of polar, water-soluble drugs	Aminoglycosides, vancomycin
	Lower percentage total body fat[a]; ranges from 1% or less at 24 weeks–12% at term	Decreased volume of distribution of fat-soluble drugs	Propofol
Protein binding	Reduced concentrations of binding proteins	Increased fraction of free drug; increased volume of distribution	Digoxin, theophylline, phenobarbital
	Presence of fetal albumin	Decreased protein binding due to decreased affinity	
	Presence of unconjugated bilirubin, free fatty acids	Decreased protein binding of drugs due to competition for binding sites	Ampicillin, penicillin, phenobarbital, phenytoin[b]

[a]Compared to values in older children and adults.
[b]Note that highly protein-bound drugs such as ceftriaxone and sulfonamides can displace bilirubin from binding sites.

- Occurs primarily in the liver, with contributions from the gastrointestinal tract, kidneys, lungs, plasma, skin, and other organs
- Phase I (nonsynthetic) reactions
  - Commonly the first step in drug biotransformation, often preparing a drug for a phase II reaction
  - Include oxidation, reduction, hydrolysis, and hydroxylation
  - Cytochrome P-450 (CYP450) mixed-function oxidase system responsible for 75% of phase I oxidative metabolism
  - Total CYP450 enzyme activity is about 30% of adult level at birth.
  - Enzymes mature at different rates, but most reach maturity by 1 year.
  - This is important in drug interactions because many enzymes can be inhibited or induced by drug therapy, and drugs metabolized by the same pathway may compete for available enzyme
- Other phase I enzymes include alcohol and aldehyde dehydrogenases, esterases. monooxygenases

- Phase II (synthetic) reactions
  - Involves conjugation of endogenous substances to drugs to create highly polar compounds to facilitate excretion
  - Include sulfation, acetylation, glucuronidation, and methylation
  - Capacity for sulfation and methylation present at birth, whereas acetylation and glucuronidation develop over weeks to months (Fig. 74.1)
- Overall, capacity for drug biotransformation is reduced in preterm and term neonates compared to adults.
  - Decreased hepatic blood flow and reduced cellular uptake limit delivery of drug to the liver.
  - Activity of phase I and phase II enzymes are generally decreased, with variable rates of maturation.
  - Expression of hepatic enzymes is also associated with large interpatient variability, making overall capacity for metabolism difficult to characterize.
  - At various stages of development, a more developed metabolic pathway may compensate for one that is less developed.
- Modification of drug therapy in hepatic impairment
  - Reduce doses of drugs that are primarily hepatically metabolized as a result of:
    - Decreased metabolizing capacity of the hepatocytes
    - Increased bioavailability caused by a reduction in first-pass metabolism, as well as decreased protein binding
    - Impaired biliary elimination

ELIMINATION

- Removal of a drug or metabolite from the body, primarily via renal excretion
- Minor routes of elimination—include biliary, pulmonary, and fecal, as well as various body fluids
- Renal clearance—volume of plasma from which a drug is completely removed by the kidneys per unit of time; sum of glomerular filtration, tubular secretion, and tubular reabsorption
- Glomerular filtration rate (GFR)
  - Free drug, in solution, is filtered in the renal tubule.
    - Highly protein-bound drugs will have a low rate of glomerular filtration.
  - GFR is approximately 30% of adult value per unit surface area at birth in term infants.
  - It increases rapidly in response to decreased renal vascular resistance, higher cardiac output, and increased renal blood flow, doubling by the end of the first month of life (see Fig. 74.1).
  - GFR in the preterm neonate is markedly reduced and may not reach adult values until 1–2 years of age.
- Tubular secretion and reabsorption
  - Drugs, particularly weak acids and bases, are secreted into the lumen of the renal tubule via active transporters in proximal tubule cells.
  - Secretion is not affected by protein binding.
  - Reabsorption of lipid soluble drugs across the tubular epithelium occurs as the concentration of drug in the tubular fluid increases.
  - Tubular secretion is immature at birth, particularly in the preterm infant. It matures more slowly than GFR, not reaching adult values until at least 6 months of age, longer for preterm infants (see Fig. 74.1).
  - Drugs that require tubular secretion for elimination include penicillins, cephalosporins, furosemide, digoxin, and morphine. Neonates may have a reduced ability to clear these drugs.
- Renal elimination is largely dependent on cardiac output and renal blood flow. It is reduced in the setting of
  - Cardiovascular disease—heart failure, significant patent ductus arteriosus (PDA), left ventricular (LV) dysfunction
  - Hypotension—dehydration, sepsis, postsurgical
  - Renal disease or administration of nephrotoxic drugs
- Modification of drug therapy in renal impairment
  - Dose should be reduced for drugs that have a time-dependent profile (require maintenance of a minimum concentration) and/or exhibit toxicity at high concentrations (e.g., penicillins).
  - Interval should be extended for drugs that have a concentration-dependent profile (require achievement of a peak concentration for efficacy) and/or exhibit toxicity if not fully eliminated (e.g., aminoglycosides).

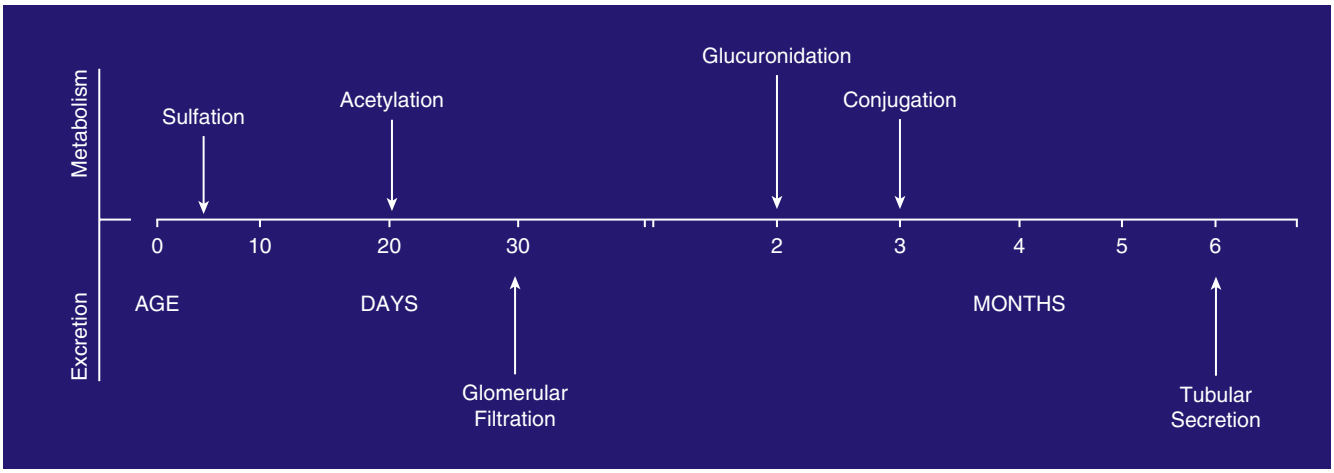

Fig. 74.1 Time line of expected maturation of metabolic and renal pathways in the neonate to 6-month-old infant. (From Reed MD, Besunder JB. Developmental pharmacology: ontogenic basis of drug disposition. *Pediatr Clin North Am.* 1989;36:1064.)

Quantitative Pharmacokinetics

- Application of mathematical principles to predict changes in concentration of a drug in the body over time
- Compartmental models (Fig. 74.2) used to describe a drug's distribution in the body:
  - A compartment represents a space (fluid or tissue) into which drug can distribute.
    - The term *central compartment* generally refers to the blood (plasma) and highly perfused tissues (heart, lungs, liver, and kidneys).
    - Peripheral compartment(s) include fat, muscle, and cerebrospinal fluid.
    - Compartments are not necessarily equivalent to physiologic or anatomic volumes.
  - The one-compartment model assumes the following:
    - All fluids and tissues belong to one compartment.
    - After administration, the drug distributes equally to all body areas instantaneously.
    - Changes to concentrations in plasma represent changes taking place in tissues.
    - A plot of the log drug concentration versus time will be linear (first-order elimination).
    - It is best used to describe polar drugs that are largely confined to the central compartment (e.g., aminoglycosides).
  - The multiple-compartment model assumes the following:
    - Drug distributes between a central and peripheral compartment(s) in such a way that maintains equilibrium.
    - After administration, the drug does not achieve instantaneous distribution and equilibration.
    - Rapid distribution to the central compartment
    - Slow distribution to peripheral compartment(s)
    - Best used to describe lipophilic drugs with extensive distribution (e.g., benzodiazepines)
- First-order, single-compartment elimination (linear pharmacokinetics)
  - The amount of drug eliminated over a given time is directly proportional to the amount or concentration in the body.
  - The fraction of drug in the body eliminated over a given time is constant.
  - First-order kinetics will demonstrate an exponential decay curve when plotted as plasma concentration versus time, but the curve will become linear when plotted as log plasma concentration versus time (Fig. 74.3).
  - First-order, one-compartment models can be used to describe the elimination of most drugs administered to neonates.
- First-order, multiple-compartment elimination
  - Rate of elimination is biphasic.
  - Drug concentration declines rapidly during the initial distribution phase, followed by a slower, steady elimination phase once equilibrium is achieved.
  - Because serum sampling is seldom done during the distribution phase, most pharmaceutical models assume first-order, single-compartment elimination.
- Zero-order elimination (nonlinear pharmacokinetics)
  - The amount of drug eliminated in a given amount of time is constant.
  - The fraction of drug eliminated over a given time varies.

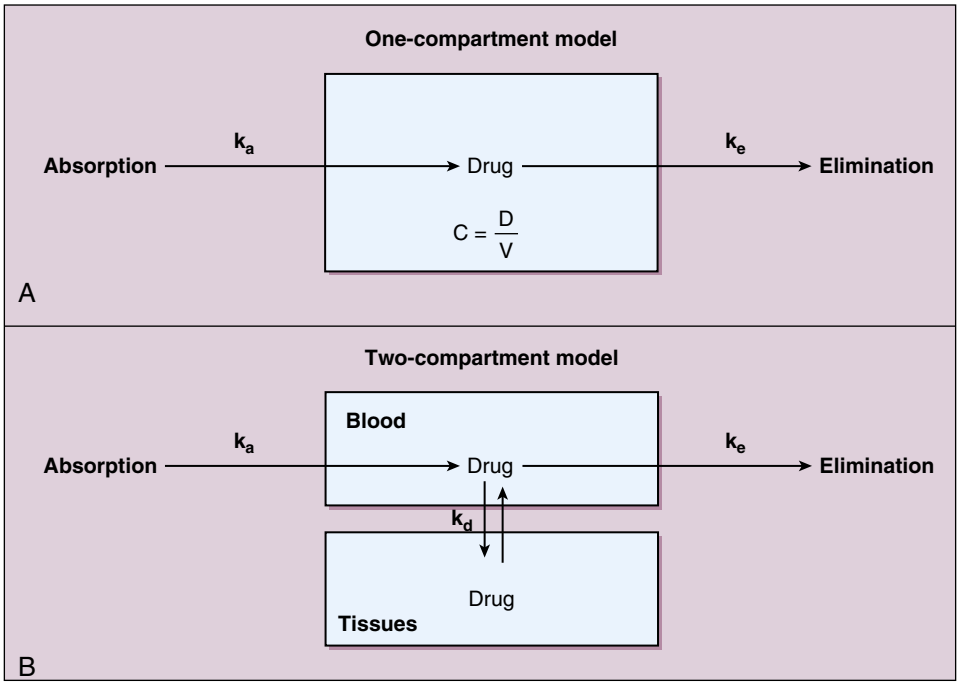

Fig. 74.2 (A) In the one-compartment model, the drug concentration at any time, *C*, is the amount of drug in the body at that time, *D*, divided by the volume of the compartment, *V*. Thus *D* is a function of the dose administered and the rates of absorption and elimination represented by k_a and k_e, respectively. (B) In the two-compartment model, the drug concentration in the central compartment (the blood) is a function of the dose administered and the rates of drug absorption, distribution to the peripheral compartment (the tissues), and elimination from the central compartment. (From Brenner GM, Stevens CW. *Pharmacology*. 4th ed. Philadelphia: Elsevier; 2013:9–25.)

- Zero-order kinetics will produce a straight line when plotted as plasma concentration versus time and a curvilinear shape when plotted as log plasma concentration versus time.
- Also known as *saturation kinetics*, drugs can display zero-order kinetics in situations of overdose or impaired clearance when enzymes or transport systems become completely saturated with drug, thus limiting the rate of metabolism or transport (Fig. 74.4).
- When a drug is exhibiting saturation kinetics, small dose changes may lead to large increases in serum concentration.
- See Table 74.3 for examples of drugs that exhibit zero-order kinetics.

- Volume of distribution
  - Dose (D): the amount of drug administered, in mg/kg
  - Concentration (C): the amount of drug in the serum at a given time, in mg/L (C_0 is serum concentration immediately following a dose; may have to be back-extrapolated in a two-compartment model)
  - Volume of distribution (V_d): a proportionality factor that relates the amount of drug in the body (dose) to the serum concentration, in L/kg
  - Thus:
    $V_d = D/C_0$
  - This equation—can be rearranged to calculate a loading dose or dose increase
- Elimination rate constant (k_e)
  - The fraction of drug eliminated from the body per unit of time. It can be calculated using the measurement of drug concentration at two different points in time:
  - $k_e = Ln(C1/C2)/\Delta T$

where C1 = serum concentration at time T1, C2 = serum concentration at time T2, and ΔT = the time between the two measured concentrations.

- In first-order kinetics, the amount of drug removed is concentration-dependent, but the fraction of drug removed is constant.
- Elimination half-life ($t_{½}$):
  - The time required for the serum concentration to decrease by 50% (in hours [hr])
  - Can be calculated from the elimination rate constant
  - $t_{½} = 0.693/k_e(hr^{-1})$
  - Determines the appropriate dosing interval
- Clearance (Cl_s)
  - This is the volume of plasma from which a drug is cleared in a given time period.
  - It is the sum of clearances by various mechanisms.
  - The rate of clearance is a constant, but the amount of drug cleared per unit of time is dependent on the serum concentration.
  - It determines the steady state concentration for a given dose:
    Cl_s (L/kg/hr) = V_d(L/kg) × k_e (hr^{-1})
- Steady-state concentration (Css)
  - This refers to the point of therapy where the amount of drug being administered is equal to the amount of drug being cleared (in = out).
  - The length of time required to reach steady state is directly proportional to $t_{1/2}$, the half-life (~5 half-lives), and is independent of dose or dosing interval (Fig. 74.5).
    Css = (dose [D]/dosing interval [τ])/Cl_s

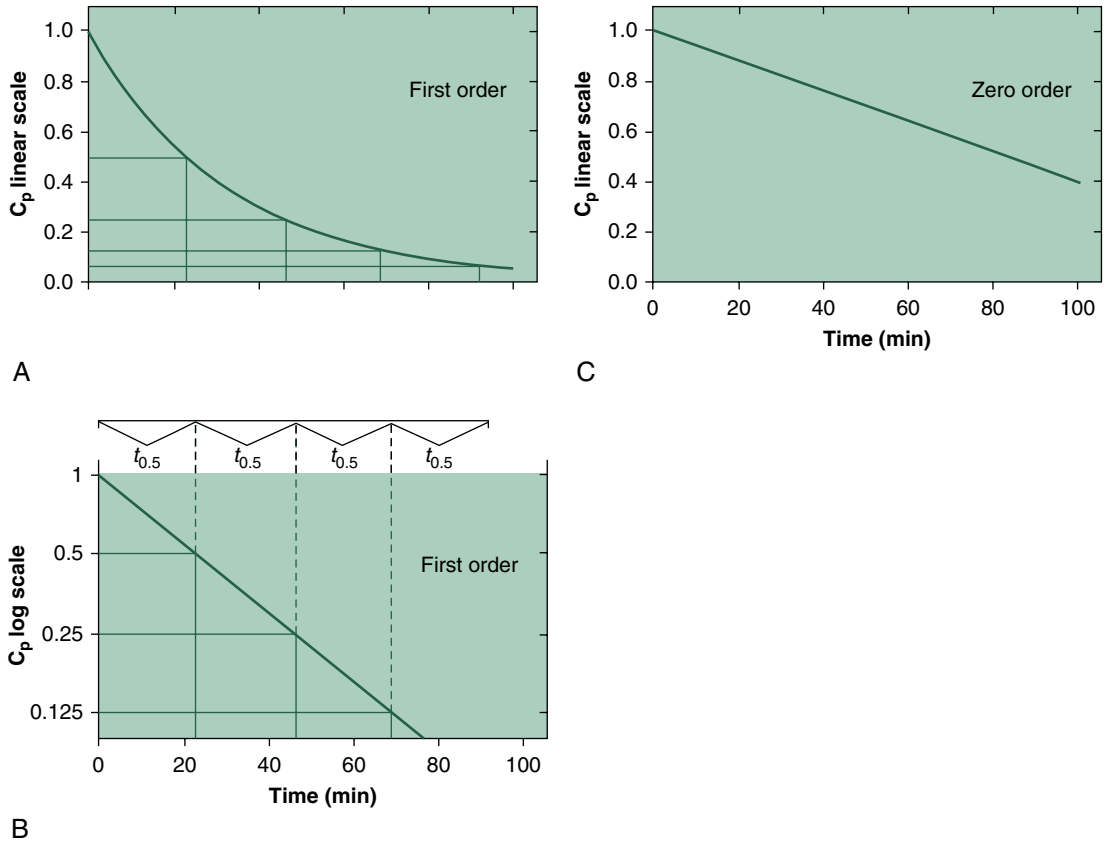

Fig. 74.3 Elimination of drugs. (A) First-order, linear concentration scale. (B) First-order, logarithmic scale. (C) Zero-order kinetics, linear concentration scale. (From Dale MM, Hatlett DG. *Pharmacology Condensed*. 2nd ed. Philadelphia: Elsevier; 2009:24–25.)

- Basic calculations of dosages
  - The pharmacokinetic parameters described above, along with serum drug sampling, can be used to guide drug therapy.
  - This example uses gentamicin and assumes first-order kinetics at steady state.
    - A dose of 3 mg/kg administered every 12 hours results in a peak concentration of 5.2 micrograms/mL (note micrograms/mL = mg/L) at a steady state.
    - A trough level drawn 12 hours after the dose results at 2.6 micrograms/mL.
    - These concentrations can be used to determine the V_d:

$$V_d\ (\text{L/Kg}) = \frac{\text{dose (mg/kg)}}{\Delta C\ (\text{mg/L})} = \frac{3\ \text{mg/kg}}{5.2 - 2.6\frac{\text{mg}}{\text{L}}} = 1.15\ \text{L/kg}$$

    - As the serum level decreased by 50% (5.2 micrograms/mL to 2.6 micrograms/mL) over 12 hours, it is noted that the $t_{1/2}$ = 12 hours. After another 12 hours, the serum level would be expected to decrease to 1.3 micrograms/mL, within the desired range of 0.5–2 micrograms/mL, necessitating a 24- to 36-hour dosing interval (2–2.5 half-lives).
    - By rearranging the equation used to calculate V_d, one can determine the dose required to achieve a therapeutic peak level (6–10 micrograms/mL). Assume a desired peak of 7 micrograms/mL and dosing every 24 hours, as calculated above.
    - Dose (mg/kg) = V_d (L/kg) × ΔC (mg/L) = 1.15 L/kg (7 mg/L − 1.3 mg/L) = 6.5 mg/kg every 24 hours.

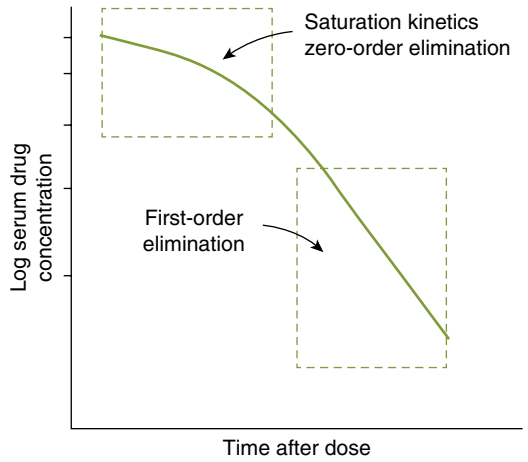

Fig. 74.4 Saturation, or zero-order and first-order pharmacokinetics. (From Allegaert K, Ward RM, Van Den Anker JN. *Avery's Diseases of the Newborn.* 10th ed. Philadelphia: Elsevier; 2018;419–431.)

Suggested Readings

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Table 74.3 Kinetics of Drugs Commonly Used in Newborns

Zero-Order Kinetics	Saturation Kinetics[a]
Alcohol (as an excipient)	Caffeine
Heparin	Diazepam
Phenytoin	Furosemide
Theophylline	Indomethacin

[a]Even when administered at therapeutic doses.

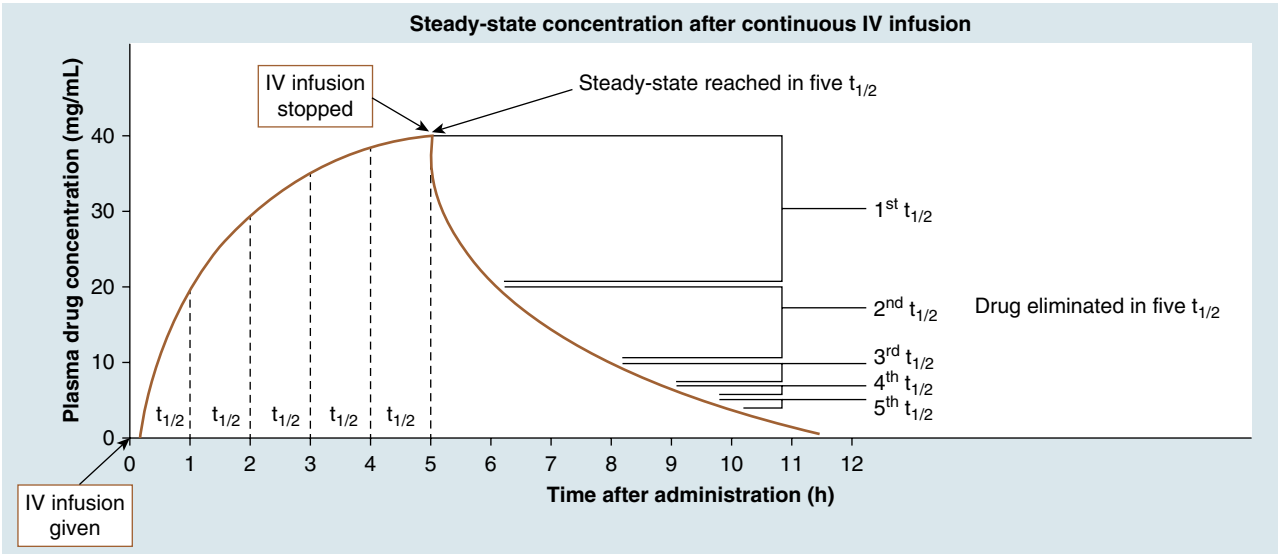

Fig. 74.5 Drug accumulation to the steady state. The time required to reach the steady state depends on the half-life ($t_{1/2}$); it does not depend on the dose or dosage interval. The steady-state drug concentration depends on the dose administered per unit of time and on the drug's clearance or half-life. (From Brenner GM, Stevens CW. *Pharmacology.* 5th ed. Philadelphia: Elsevier; 2018:11–26.)

75 Clinical Toxicology

TRACEY L. MCCOLLUM

The use of pharmaceuticals and other substances in pregnancy, childbirth, and lactation is common and often necessary. An understanding of the factors that determine fetal and infant exposure to these substances will assist the clinician in modifying risk while providing optimal care to both mother and baby.

General Considerations

- US Food and Drug Administration (FDA) pregnancy risk categories (A–D and X)—replaced by the Pregnancy and Lactation Labeling Rule, which requires drug labeling to include
  - Pregnancy exposure registry
  - Risk summary
    - Identifies if drug is contraindicated in pregnancy
    - Prioritizes human data, followed by animal data, then pharmacologic considerations
    - Describes adverse developmental outcomes
      - Structural abnormalities
      - Embryo, fetal, and infant mortality
      - Functional impairment
      - Alterations to growth
    - Includes information on background population risk
    - Established adverse outcome risk summarized based on incidence, seriousness, reversibility, and relation to dose, duration, and gestational timing of exposure
  - Clinical considerations
    - Includes risk of untreated disease to both mother and fetus
    - Provides recommended dose adjustments for pregnancy
    - Describes potential maternal or fetal adverse reactions
    - Describes potential effects on labor and delivery
  - Data—provides all available human and animal data
- Lactation labeling follows same format
  - Risk summary
    - Describes the extent that drug crosses into breast milk
    - Includes effects of drug on milk production
    - Lists potential effects on the infant
  - Clinical considerations
    - Provides recommendations for dose adjustments, if required
    - Provides strategies to minimize infant exposure
    - Describes monitoring parameters for the infant
  - Data—includes all sources from which information was gathered
- Drug use during pregnancy and lactation—should be guided by the principle that maternal benefit clearly outweighs risk to the fetus or infant
- Treatment principles
  - Review treatment options to select drugs with significant safety data in pregnancy and lactation.
  - Consult multiple references to assess the most complete and up-to-date information.
  - Titrate maternal dose to the lowest effective dose, and use the shortest possible course.
  - Avoid use of newer agents because risks may not be identified for many years after marketing.

Drugs in Pregnancy

- The risk of harm based on exposure to drugs in pregnancy is dependent on
  - The teratogenic potential of the drug
  - The extent of fetal exposure
  - The developmental stage at the time of exposure
- Fetal harm caused by drugs can be divided into two categories
  - Teratogenic effects
    - Occur primarily during the embryonic period (2–8 weeks after fertilization)
    - Result in a disruption in tissue development or organ formation
    - Examples—neural tube defects, limb malformations, craniofacial abnormalities
  - Adverse fetal effects
    - Affect organs or systems that are already formed
    - Usually result in postnatal concerns
- Overall, the risk of fetal malformations due to drugs is very low.
- See Table 75.1 for examples of drugs with known teratogenic effects in pregnancy.
- See Table 75.2 for examples of drugs that can cause fetal or neonatal adverse effects.

Drugs in Lactation

- There are very few drugs that are truly contraindicated in breastfeeding (Box 75.1).
- For other agents, consider
  - Maternal need for the drug
  - Effects of the drug on milk production
  - Amount of drug excreted into breast milk (milk-to-plasma ratio)
  - Extent of absorption by the infant

Table 75.1 Select Drugs With Known Teratogenic Effects in Pregnancy

Agent	Effects in Humans (With Examples)
Angiotensin-converting enzyme inhibitors (ACEIs)	In second and third trimesters: renal tubular dysgenesis, severe renal dysfunction with oligohydramnios, anuria, oliguria, hypotension, skull ossification defects (hypocalvaria), intrauterine growth retardation (IUGR); fetal death In first trimester: congenital heart disease, central nervous system (CNS) malformations Examples: captopril, enalapril, lisinopril
Angiotensin II receptor antagonists (ARBs)	In second and third trimesters: renal tubular dysgenesis, severe renal dysfunction with oligohydramnios, anuria, oliguria, hypotension, skull ossification defects (hypocalvaria), limb contractions, fetal death Early data do not demonstrate risk in first trimester. Examples: losartan, valsartan, candesartan
Antiepileptic drugs (AEDs)[a, b]	Carbamazepine—neural tube defects (esp. meningomyelocele), IUGR, craniofacial defects, developmental delays Lamotrigine—facial cleft Phenytoin—fetal hydantoin syndrome (FHS): facial clefting, epicanthal folds, hypertelorism, short nose with broad nasal bridge, short neck, microcephaly, wide fontanel, low-set, abnormally formed ears, IUGR, digit and nail hypoplasia, mental deficiency (FHS features seen with other AEDs as well) Topiramate—oral cleft, hypospadias Valproic acid—neural tube defects (esp. meningomyelocele), cardiac defects; mental deficiency, FHS features as above
Antiretroviral drugs	Zidovudine—neuromitochondrial disease, congenital heart disease Efavirenz—neurologic defects
Cyclophosphamide	CNS malformations: facial and palate defects, absent fingers and toes, single coronary artery, imperforate anus, hernias, growth retardation, multiple eye defects, microcephaly, hypotonia, pancytopenia
Cocaine	Fetal loss, microcephaly, growth retardation, limb reduction, urinary tract malformations, cardiac abnormalities, placental abruption, poor neurodevelopmental outcomes
Ethanol	Fetal alcohol syndrome: IUGR, craniofacial abnormalities (short palpebral fissures, hypoplastic philtrum, maxillary hypoplasia, short nose, flat nasal bridge), microcephaly, growth retardation, developmental delay, behavioral abnormalities
Isotretinoin (retinoids)	Spontaneous abortion, multiple cardiac defects, craniofacial defects: microtia, anotia, low-set ears, hypertelorism, hypoplastic maxilla and mandible, narrow sloping forehead; hydrocephalus, thymic hypoplasia
Lithium	Ebstein anomaly
Methotrexate	Neural tube defects, anencephaly, microcephaly, IUGR, craniofacial abnormalities: synostosis of lambdoid, coronal sutures, and frontal bone, low-set ears, broad nasal bridge; syndactyly; tetralogy of Fallot
Misoprostol	Neural tube defects, limb defects, Möbius syndrome
Tetracyclines	Malformations of tooth enamel (including permanent discoloration) and bone
Thalidomide	Limb-shortening defects, hearing loss, abducens paralysis, facial paralysis, anotia, microtia, cardiovascular and gastrointestinal anomalies
Warfarin	Fetal warfarin syndrome: nasal hypoplasia, epiphyseal stippling, limb and digit hypoplasia, ophthalmic anomalies (e.g., optic atrophy, microphthalmia, blindness), low birth weight; CNS defects with exposure after first trimester: agenesis of corpus callosum, Dandy-Walker syndrome

[a]Risk of defects increases with use of multiple agents and higher doses.
[b]Folic acid supplementation may reduce the risk of AED-induced teratogenic effects.

Table 75.2 Select Drugs Known to Cause Fetal or Neonatal Adverse Effects

Agent	Fetal or Neonatal Adverse Effects
Antipsychotic agents	Difficult adaption, breathing difficulties, jitteriness, irritability, poor feeding
Beta blockers	Neonatal hypoglycemia
Hypoglycemic agents	Neonatal hypoglycemia
Nicotine	Intrauterine growth retardation (IUGR), preterm delivery
Nonsteroidal antiinflammatory drugs (NSAIDs)	Indomethacin, ibuprofen administered near term, at delivery Premature closure of the ductus arteriosus, necrotizing enterocolitis
Opioids, heroin	Neonatal abstinence syndrome
Selective serotonin reuptake inhibitors (SSRIs)	Preterm birth (low risk), persistent pulmonary hypertension, respiratory distress, difficult adaption, irritability, crying, poor feeding, sleep disturbances, increased tone, convulsions

Box 75.1 Drugs Contraindicated in Breastfeeding

Illicit drugs
Radiopharmaceuticals
Antineoplastic chemotherapy agents

- Potential adverse effects to the infant
- Age and comorbid conditions of the infant

- Estimated infant drug exposure can be calculated
  - The infant's daily dose (mg/kg/day) can be calculated by multiplying the average concentration in milk (mg/mL) × the volume (mL) of milk ingested in 24 hours.
  - Calculate the relative infant dose using the equation in Fig. 75.1.
  - A relative infant dose (RID) of <10% is generally considered to be compatible with breastfeeding, although the toxicity of the drug should be considered.

$$\text{Relative Infant Dose (RID)} = \frac{\text{Dose.infant}\ \left(\frac{mg/kg}{day}\right)}{\text{Dose.mother}\ \left(\frac{mg/kg}{day}\right)}$$

Dose.infant = dose in infant/day

Dose.mother = dose in mother/day

Fig. 75.1 The relative infant dose (RID) expresses the infant's dose as a percentage of the mother's dose. (From Rowe H, Baker T, Hale TW. Maternal medication, drug use, and breastfeeding. *Pediatr Clin North Am.* 2013;60(1):274–294)

- The infant's daily dose (mg/kg/day) should fall well below the normal dosing range.

- See Table 75.3 for a listing of select drugs of concern in breastfeeding.

Table 75.3 Select Drugs With Concerns in Breastfeeding

Agent	Infant risk	Considerations
Alcohol	Psychomotor delay, drowsiness, decreased milk intake	Delay breastfeeding 2 hours for each drink consumed to allow for alcohol metabolism.
Amiodarone	Depressed thyroid function	Monitor infant cardiac and thyroid function.
Ergotamine	Vomiting, diarrhea, convulsions; may also decrease milk production	Use with caution; consider alternative agents.
Anticonvulsants, phenobarbital, primidone, ethosuximide	Sedation, levels approaching therapeutic, potential for seizures on withdrawal	Monitor serum levels, and reduce maternal dose if possible.
Cyclosporine	Immune suppression, renal toxicity	Monitor infant cyclosporine and serum creatinine levels.
Lithium	Changes to thyroid and/or renal function	Use only when alternatives are not suitable and only with healthy, full-term infants; monitor infant lithium, TSH, BUN, and creatinine levels frequently.

BUN, Blood urea nitrogen; *TSH,* thyroid-stimulating hormone.

Suggested Readings

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76 Indications, Mechanisms, and Adverse Reactions for Common Drugs

TRACEY L. MCCOLLUM

Pharmaceutical therapy is a critical component in the care of the sick neonate. Babies in the neonatal intensive care unit receive dozens of medications a day, many of them unlicensed or off-label. This chapter will examine the most commonly used medications and discuss the implications of unlicensed and off-label use.

Antimicrobial Drugs

ANTIBACTERIALS

Aminoglycosides (Amikacin, Gentamicin, Tobramycin)

- Indications: treatment of infections caused by aerobic gram-negative bacilli, including *Pseudomonas*; commonly used in combination with a β-lactam antibiotic for synergy in treating early-onset sepsis, meningitis, endocarditis
- Mechanism of action: inhibit protein synthesis in susceptible bacteria by binding to the 30S ribosomal subunit
- Adverse effects: decreased creatinine clearance, renal tubular dysfunction resulting in electrolyte disturbances (e.g., hyponatremia, hypocalcemia, hypokalemia, hypomagnesemia), intrinsic neuromuscular blocking properties, potentiation of neuromuscular blockade in the presence of other neuromuscular blockers or hyper magnesemia
- Toxicity: renal toxicity with high trough levels, ototoxicity with high peak levels; toxicity is increased in combination with other ototoxic/nephrotoxic agents (e.g., vancomycin, furosemide)

Penicillins (β-Lactam)—Ampicillin, Penicillin G, Nafcillin, Oxacillin (Penicillinase-Resistant), Piperacillin-Tazobactam (Antipseudomonal)

- Indications: broad-spectrum agents useful in treating disorders such as sepsis, meningitis, pneumonia, urinary tract infections (UTIs); active against group B streptococcus, *Listeria monocytogenes*, susceptible *Staphylococcus aureus* and enterococci, *Neisseria meningitidis*, and susceptible *Haemophilus influenzae* and *Escherichia coli* spp.; penicillin is also used to treat neonatal gonococcal and syphilis infections
- Mechanism of action: β-lactam antibiotics exert bactericidal action by binding to penicillin-binding proteins and inhibiting bacterial cell wall synthesis
- Adverse effects include diarrhea; extended-spectrum agents can cause elevations in aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels
- Toxicity: high doses can cause central nervous system (CNS) excitation, leading to seizures; piperacillin-tazobactam is nephrotoxic, this is increased in combination with other nephrotoxic agents, particularly vancomycin

Cephalosporins (Beta-Lactam)

See Table 76.1 for classification and indications for cephalosporins.

- Mechanism of action: β-lactam antibiotics exert bactericidal action by binding to penicillin-binding proteins and inhibiting bacterial cell wall synthesis

Table 76.1 Classification of Cephalosporins Commonly Used in the Neonatal Intensive Care Unit

Generation	Antimicrobial Coverage	Indications
First generation (cefazolin, cephalexin)	Primarily gram-positive cocci[a] plus *E. coli, Klebsiella,* and *Proteus*	Surgical prophylaxis, urinary tract infections (UTIs), skin and soft tissue infections
Second generation (cefoxitin)	Increased gram-negative coverage, including anaerobes (e.g., *Bacteroides fragilis*), *H. influenzae*, and *Neisseria gonorrhoeae*; reduced gram-positive coverage	Intraabdominal, UTIs, skin and soft tissue infections
Third generation (cefotaxime, ceftriaxone[b] ceftazidime)	Broad spectrum, effective against most gram-positive and gram-negative organisms; ceftazidime covers *Pseudomonas*	Sepsis, meningitis (excellent CNS penetration)
Fourth generation (cefepime)	Similar coverage to third generation, but with increased resistance to β-lactamases	Sepsis, meningitis

[a]None of the cephalosporins covers *Listeria* or *Enterococcus* spp.
[b]Ceftriaxone may displace bilirubin from albumin.

- Adverse effects are rare but include rash, diarrhea, elevated hepatic transaminase levels, transient eosinophilia, and positive Coombs test

Vancomycin

- Indications: serious infections caused by methicillin-resistant staphylococci and penicillin-resistant pneumococci, including late-onset sepsis, meningitis, pneumonia
- Mechanism of action: inhibits bacterial cell wall synthesis by inhibiting peptidoglycan synthesis; requires higher doses to be bactericidal
- Adverse effects: rash, hypotension (red man syndrome); can be relieved by extending the infusion time; phlebitis, neutropenia with prolonged therapy
- Toxicity: ototoxicity with elevated peak levels, nephrotoxicity, which is increased when used with other nephrotoxic agents (piperacillin-tazobactam, aminoglycosides)

ANTIFUNGALS

Amphotericin B (Conventional, Lipid Complex, or Liposomal)

- Indications: treatment of systemic fungal infections; lipid complex or liposomal formulation indicated for patients with renal or hepatic impairment
- Mechanism of action: binds to ergosterol in the fungal cell wall, leading to alteration of cell membrane permeability; leakage of cell components, with subsequent cell death
- Adverse effects: decreased renal blood flow and glomerular filtration rate (increased hydration required with conventional form), renal losses of sodium, potassium, and magnesium, renal tubular acidosis; anemia, thrombocytopenia, fever and chills
- Toxicity: nephrotoxic; caution advised in dosing because of fivefold to tenfold difference in dosing between conventional and lipid-based products

Fluconazole

- Indications: treatment of systemic infections caused by *Candida* and *Cryptococcus*, including meningitis, and superficial mycoses not relieved by topical treatment
- Mechanism of action: decreases ergosterol synthesis in the fungal cell membrane by interrupting fungal cytochrome P450 activity, thus inhibiting fungal cell membrane formation
- Adverse effects: elevation of hepatic transaminase levels, hepatitis, jaundice, rash
- Toxicity: hepatic

ANTIVIRALS

Acyclovir

- Indications: treatment of infections caused by herpes simplex virus (HSV) or varicella zoster (VZV), including CNS and pulmonary infections
- Mechanism of action: acyclovir triphosphate (a metabolite of acyclovir) acts as specific inhibitor of herpesvirus DNA polymerase, thus inhibiting DNA synthesis and viral replication
- Adverse effects: neutropenia, crystalluria (adequate hydration is required), transient renal dysfunction

Cardiovascular Drugs

Alprostadil (Prostaglandin E1)

- Indications: maintenance of ductus arteriosus patency necessary for patients with congenital heart disease dependent on ductal shunting for oxygenation and perfusion
- Mechanism of action: vasodilation of vascular and ductus arteriosus smooth muscle
- Adverse effects: apnea, bradycardia, hypotension, fever, cutaneous flushing, leukocytosis; hypokalemia with long-term infusion

Vasoactive Drugs (Table 76.2)

- Indications: used to increase perfusion due to hypotension, cardiac failure, and shock; agents affect cardiac contractility (inotropic effect), heart rate (chronotropic effect), and systemic vascular resistance (SVR)

Ibuprofen and Indomethacin

- Indications: closure of patent ductus arteriosus (PDA); indomethacin also used for prophylaxis of intraventricular hemorrhage
- Mechanism of action: nonsteroidal antiinflammatory drugs that inhibit prostaglandin synthesis
- Adverse effects: decreased cerebral, renal, and gastrointestinal (GI) blood flow, oliguria, hypoglycemia, platelet dysfunction, risk of gastrointestinal perforation if used in conjunction with steroids
- Toxicity: renal

Sildenafil

- Indications: treatment of persistent pulmonary hypertension
- Mechanism of action: phosphodiesterase type-5 (PDE5) inhibitor limits the breakdown of cyclic guanosine monophosphate (cGMP), causing relaxation of the pulmonary vasculature
- Adverse effects: systemic hypotension, exacerbation of dyspnea, visual disturbances, increased liver enzymes, increased V/Q mismatch
- Toxicity: possibly hepatic (case reports)

Central Nervous System Drugs

BENZODIAZEPINES

These include diazepam, lorazepam, and midazolam.

- Indications: status epilepticus (refractory to standard anticonvulsants), maintenance of sedation, skeletal muscle spasticity
- Mechanism of action: enhancement of the effect of gamma-aminobutyric acid (GABA) at the $GABA_A$ receptor
- Adverse effects: respiratory depression, hypotension, hypotonia, seizure-like myoclonus in premature infants
- Toxicity: flumazenil is reversal agent

Table 76.2 Vasoactive Dugs

Agent	Contractility	HR	SVR	Adverse Effects[a] and Comments
Dobutamine	↑↑	↑	↓	Adverse effects: tachycardia, arrhythmias at high dose (ectopic beats), hypotension if volume depleted Synthetic catecholamine with primarily β_1-adrenergic activity; useful for cardiogenic shock and myocardial dysfunction; no increase in afterload; no effect on renal blood flow
Dopamine	↑↑	↑↑	↑↑	Adverse effects: tachycardia/arrhythmias (ectopic beats), hypoxemia due to pulmonary vascular constriction, azotemia Catecholamine with α-adrenergic effects; effects vary with dosage; increases renal blood flow at low dose
Epinephrine	↑↑↑	↑↑↑	↑↑↑	Adverse effects: hypokalemia, arrhythmias (PVCs and VT), severe hypertension, renal vascular ischemia; stimulates alpha and beta receptors
Isoproterenol	↑↑↑	↑↑↑	↓↓↓	Adverse effects: tachycardia, arrhythmias, decreased coronary blood flow, hypoglycemia Stimulates beta-1 and beta-2 receptors; useful in bradycardia and to increase cardiac output; less helpful in shock due to decreased vascular resistance
Milrinone	↑↑	↑↑	↓↓	Adverse effects: hypotension if volume-depleted, thrombocytopenia, arrhythmias Phosphodiesterase inhibitor, decreases cAMP breakdown; decreases afterload

[a]Note that all vasoactive agents can cause tissue ischemia and necrosis if extravasation occurs.
cAMP, Cyclic adenosine monophosphate; *HR,* heart rate; *PVC,* premature ventricular contraction; *SVR,* systemic vascular resistance; *VT,* ventricular tachycardia.

OPIOIDS

These include fentanyl, morphine, and methadone.

- Indications: analgesia, sedation, anesthesia; methadone useful in narcotic weaning
- Mechanism of action: bind to opioid receptors in the CNS, inhibit ascending pain pathways
- Adverse effects: respiratory depression (fentanyl < morphine), hypotension, bradycardia, urinary retention, ileus and delayed gastric emptying, pruritus, seizures (especially with rapid weaning); fentanyl has been associated with chest wall rigidity, especially with rapid administration; tolerance with prolonged infusion (>5 days), requiring slow weaning to avoid withdrawal
- Toxicity: naloxone is reversal agent

PHENOBARBITAL

- Indications: seizures, sedation, narcotic withdrawal, hyperbilirubinemia
- Mechanism of action: largely unknown, depresses the sensory cortex and limits the spread of seizure activity, possibly by increasing inhibitory neurotransmission
- Adverse effects: CNS depression, sedation, respiratory depression at elevated serum concentrations, apnea with rapid IV administration
- Toxicity: reports of hepatic toxicity with prolonged use

US Food and Drug Administration (FDA) Approval

- The FDA approves drugs based on adequate and well-controlled trials, which provide substantial evidence of efficacy and safety.
- These trials rarely include neonatal or pediatric populations, so these populations are excluded from the approved labeling for many drugs.
- Off-label use refers to the use of a drug for an unapproved indication or an unapproved age group, dosage, or route of administration.
  - Lack of labeling does not imply that a drug is contraindicated or inappropriate for use in a disorder or population.
  - Off-label use is not illegal nor is it considered investigational use.
- Professional standards for off-label use dictate that the drug is used:
  - In good faith
  - In the best interest of the patient
  - Without fraudulent intent
- Therapeutic decision making should be guided by
  - Benefit to the individual patient
  - Best available evidence, including:
    - Published literature
    - Expert opinion
    - American Academy of Pediatrics Practice Guidelines and Policy Statements
    - Handbooks and databases
  - Practitioners have a duty to add to the body of knowledge by publishing or reporting notable experiences with off-label use.
- The Best Pharmaceuticals for Children Act (BPCA) and Pediatric Research Equity Act (PREA) have helped increase the number of drugs with pediatric labeling, but there is still a deficit in the neonatal and preterm populations.

Suggested Readings

American Academy of Pediatrics Committee on Drugs. Off-label use of drugs in children. *Pediatrics.* 2014;133(3):563–567.
Hsieh EM, Hornik CP, Clark RH, et al. Best Pharmaceuticals for Children Act—Pediatric Trials Network. Medication use in the neonatal intensive care unit. *Am J Perinatol.* 2014;31(9):811–821.
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SECTION 20

Ethics and Health Services Delivery

MARLYSE HAWARD and ANNIE JANVIER

77 Organization of Perinatal Care

MARLYSE HAWARD and ANNIE JANVIER

Issues in Organization and Perinatal Care

1. These include regionalization, transport, practice guidelines, benchmarking data, and quality improvement.
2. Issues in perinatal care have focused on decreasing maternal and neonatal morbidity and mortality through efforts in regionalization, transport, evidence-based practice guidelines, quality assessment, and quality improvement processes.
3. Improved neonatal survival has been demonstrated with regionalization strategies (Epicure cohort 1 and 2): neonatal mortality of small preterm infants can be improved if more children are born in large tertiary centers.
4. Lack of regionalization can lead to increased mortality. In countries with socialized health care, regionalization is generally improved.

Regionalization

The goal is efficient and effective use of resources.

1. Access to comprehensive perinatal health care services
   a. Early, ongoing risk assessments matched to appropriate level of care (basic to subspecialty)
   b. System of referrals and consultations between institutions in one region (ensures access to all care levels)
   c. Simplification: larger centers as opposed to multiple smaller centers with less volume (e.g., benefits extremely-low-birth-weight [ELBW] infants, extracorporeal membrane oxygenation [ECMO], cardiac surgery)
2. Patient-centered, family-centered approach
   a. "Family" as defined by the patient and mother; maternal preferences dictate family decision-making roles
   b. Incorporate maternal preferences and values (respect, communicate, support, collaborate)
3. Culturally and linguistically sensitive and appropriate care
   a. Address and improve disparities in health care via federal, state, and local collaborations
4. Public—should be educated about reproductive health
   a. High percentage of unwanted pregnancies across ethnicities; start education prenatally
5. Accountability: all components of health care delivery system by all members involved
   a. Physicians, families, health maintenance organizations (HMOs), government agencies, insurance, programs, and systems
   b. Includes patient safety and quality improvement
6. Challenges
   a. Financial competition; lack of governmental oversight
7. Organization of perinatal services
   a. Preconception care; prenatal care (basic, specialty, subspecialty, in-hospital care) and postnatal care
   b. Neonatal intensive care unit (NICU) designation: level I, II, III, or IV; birth at level III and IV improves outcomes for ELBW and premature infants
      1) Level I: Well-baby nursery with delivery room; 35–37 weeks to term
      2) Level II: >32 weeks; >1500 g; mechanical ventilation <24 hours
      3) Level III: level II ≤32 weeks, <1500 g + High frequency oscillatory ventilation (HFOV), iNO, medical and surgical subspecialties; advanced imaging
      4) Level IV: level III plus full range of surgical repairs, including complex cardiac disease

Transport

This is an essential component in regionalization, as is determining the appropriate level of care for mother and infant.

1. Three types: maternal, neonatal, return; modes: ground, air (helicopter, plane)
   a. Antepartum transport preferable; avoids separation; even if in labor if delivery not imminent
   b. Teams from referring hospital, accepting hospital, or third hospital for transport only
   c. Acuity, weather, and other circumstances determine mode of transport
2. Adherence to federal and state law
   a. Emergency Medical Treatment and Labor Act: emergency screening required if Medicare accepted
3. Components of a transport system
   a. Predetermined alliances and formal transfer plans between hospitals (ensures appropriate level of care for infant and mother)
   b. Risk identification and anticipated benefits of transfer
   c. Assessment of perinatal capabilities and conditions recommended for consultation and transfer
   d. Safe, efficient, effective resource management
   e. Financial and personnel support
   f. Comprehensive and reliable communication systems
   g. Clear responsibility of functions for transport team, receiving and referring institutions

4. Transport team responsibilities
   a. Medical care: referring hospital team retains responsibility until arrival at receiving hospital; receiving hospital team assumes responsibility on departure from referring hospital
   b. Procedures: proper identification of the newborn, medical records and tests; secure venous line, endotracheal tube (ETT) placement, STABLE protocol (***s***ugar, ***t***emperature, ***a***irway, ***b***lood ***p***ressure, and ***e***motional support); monitor, perform patient care; appropriate consents
   c. Equipment: checked regularly to ensure functionality
5. Staff responsibilities
   a. Appropriate level of training for transport team; Director (subspecialist in maternal-fetal medicine [MFM] or neonatologist)
   b. Maintains database, protocols, and safety standards; alternative plans if transport not possible
6. Legal issues
   a. Policies and protocols in place for level of care, consultation, and transfer
   b. Consent for transport, procedures, telephone consent for surgical procedures
   c. Continued contact with supervising physician during transport
7. Continual quality evaluation and improvement procedures

Practice Guidelines

The goal is to decrease variations in outcomes, minimize harm, be cost-effective, improve outcomes, and promote quality.

1. *Evidence-based:* strong recommendation, recommendation, optional, no recommendation
2. *Process:* determine quality of evidence (individual and aggregate assessments)

A: well-designed, randomized controlled trial (RCT), sample and target population match
B: RCT or study with minor limitations; consistent evidence from observational studies
C: observational studies
D: expert opinion, case reports
X: exceptional studies cannot be confirmed, but overwhelmingly beneficial or harmful

Systematic reviews helpful; such as the Cochrane Database

- Standardized approach consisting of six criteria for assessing quality of evidence and determining strength of recommendation developed by Grading of Recommendations Assessment, Development and Evaluation (GRADE) working group
- Standard for guideline development; methodology meets methodologic standards for the conduct of new Cochrane Intervention Reviews (MECIR), see <http://www.gradeworkinggroup.org>

Benchmarking Data: Quality Control

1. Quality control is vital in neonatology, and neonatologists are leaders in quality control research. Many countries, states, and provinces have large databases of neonatal data (including follow-up data) for all NICU children (e.g., Canada, Denmark, United Kingdom, Sweden). Comparing outcome data to these databases (benchmarking) optimizes quality control within and between units, thereby improving outcomes. Data must comply with Health Insurance Portability and Accountability Act (HIPPA) regulations.
   a. There could be a single database (e.g., Canada) versus multiple databases (United States): such as Vermont Oxford Network (VON) (fee-based), Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) (request), and Pediatrix (ICD-10 based).
   b. NICHD is a source of randomized control trials and birth and death statistics that is mandatory in the United States.
2. Nonanonymizing centers have shown dramatic improvement in outcomes (e.g., pediatric heart surgery in the UK), leading to questions about whether data should be private or made accessible to the public.

Quality Improvement

The Institute of Medicine (IOM) has defined quality as "the degree to which health services for individuals and populations increase the likelihood of desired health outcomes and are consistent with current professional knowledge."

1. Crossing the Quality Chasm by the IOM: six characteristics when implementing quality improvement (QI) projects
   a. Safety (e.g., highly reliable organizations): preoccupation with failure, sensitivity to operations, reluctance to simplify, commitment to resilience, deference to expertise
      1) American Academy of Pediatrics (AAP) endorses the following:
         a) Culture of safety (systems of care not individuals
         b) Confidential reporting
         c) Educate not penalize
         d) Team functioning
         e) Situational awareness—safe medication practices (automated systems, avoid nonstandard abbreviations, eliminate verbal orders)
         f) Reduction of surgical errors (time out to avoid wrong site, wrong procedure, wrong patient)
         g) Improve communication (most common cause of preventable adverse outcome is communication error; disclose errors; includes patient and family, entire team)
      2) Also endorsed by Toward Improving the Outcome of Pregnancy III by the March of Dimes
   b. Effectiveness: preventing overuse, underuse, or misuse of resources
   c. Patient centeredness: respectful of patient preferences and values
   d. Timeliness: avoiding delays that could cause harm
   e. Efficiency: avoiding excess waste (resources, ideas, energy)
   f. Equitable: care that is equal for all patients, regardless of patient characteristics

2. Goals are to decrease variability, increase patient safety, improve performance
   a. Assessed by looking at structure, process, and outcome and benchmarking data with large databases
      1) Structural assessments such as day versus nighttime coverage; process assessments such as overuse: postnatal steroid use, such as misuse; patient satisfaction reflecting ineffective communication; outcome assessments such as temperature on admission
      2) Consider case mix when benchmarking (differences in risks and comorbidities); helps identify best practices such as delayed cord clamping, golden hour, development of order sets
3. Five components of a QI program include the following:
   a. Leadership: responsive (medical staff and administration); may be separate officer
   b. Peer review: retrospective analysis of outcomes to assess consistency with standard of care or recommended guidelines; multidisciplinary; may need to outsource
   c. Reducing variation: creation of protocols
      1) Institute for Clinical Systems Improvement: guidance for developing procedures and protocols
   d. Quality metrics: measures to identify processes that could be improved
      1) Lists at Agency for Healthcare Research and Quality: http://www.quality measures.ahrq.gov. (e.g., maternal: mortality; elective cesarean section at <39 weeks; neonatal: <32 weeks delivered at institution without NICU)
   e. Data collection and analysis: regional data collection, databases for benchmarking, standardized collection methods, tools, guidelines
      1) National Fetal and Infant Mortality Review: review by multidisciplinary team of sentinel events
4. Accountability: ability to respond to process improvements to achieve desired outcomes
   a. Observed and expected NMR (neonatal mortality rate) versus SMR (standardized mortality rate)
   b. Physician contribution to quality: written in the AMA Code of Ethics; includes continuing medical education (CME), critical reviews
5. Reporting QI projects should follow SQUIRE guidelines (http://www.squire-statement.org), which provide a framework for studying QI projects similar to CONSORT statement (http://www.consort-statement.org) for randomized clinical trials
6. Electronic health records: improves communication and collaboration between physicians; helps standardization; reduces medication error; improves workflow; data for QI

Table 77.1 Perinatal, Neonatal, Postneonatal, and Infant Mortality

Term	Definition
Perinatal death (PD) = fetal death (FD) + neonatal death (ND); three definitions	1: ND <7 d + FD >8 wk 2: ND <28 d + FD >20 wk (most used) 3: ND <7 d + FD >20 wk
Perinatal mortality	Stillbirth + neonatal death
Fetal death (FD): >8 wk; no LB; any gestational age (GA)	Miscarriage: 8–20 wk Stillbirth: >28 wk Early: 20–27 wk Late: 28–term
Infant death (ID) = neonatal death (ND) + postneonatal death (PND)	Any live birth resulting in death at <365 days
Early neonatal death:	<7 days
Late neonatal death:	7–28 days
Postneonatal death:	29–364 days
Live birth (LB)	Any GA completely out of uterus with umbilical pulsations, heartbeat, respirations, movement

Awareness of Public Health Issues, Services, and Delivery

1. See Table 77.1.
2. Cause of death: neonatal deaths (NDs) most likely due to prematurity, congenital anomalies, newborn affected by complications from pregnancy; postneonatal deaths (PNDs) most likely due to infections
3. Industrialized countries, higher NDs (2:1); underdeveloped countries, higher PNDs
4. Model State Vital Statistics Act and Regulations (the Model Law)
   a. Vital statistics reporting for infants born weighing more than 350 g at or more than 20 weeks completed gestation
   b. States need to report on live births, fetal deaths, and infant deaths but variability in reporting criteria between states, despite the Model Law

Suggested Readings

AAP Committee on Fetus and Newborn; ACOG Committee on Obstetric Practice. In: Riley LE, Stark AR, eds. *Guidelines in Perinatal Care*. 7th ed. Elk Grove Village, IL: American Academy of Pediatrics; 2012.

American Academy of Pediatrics Committee on Fetus and Newborn. Levels of neonatal care. *Pediatrics*. 2012;130(3):587–597.

Barfield WD, COFN. 2016 Standard terminology for fetal, infant, and perinatal deaths. *Pediatrics*. 2016;137(5):e1–e5.

Steering Committee on Quality Improvement and Management. Classifying recommendations for clinical practice guidelines. *Pediatrics*. 2004;114:874–877.

Woodward G, Kirsch R, Stone Trautman M, et al. Stabilization and transport of the high-risk infant. In: Gleason K, Devaskar S, eds. *Avery's Diseases of the Newborn*. 9th ed. Philadelphia: Elsevier; 2012:341–356.

Questions

1. The most common cause of preventable adverse outcome is:
   a. communication error
   b. medication error
   c. allergic error
   d. pharmacy error
   e. surgical error

2. True or False: Industrialized countries tend to have more postneonatal than neonatal deaths.

3. Regionalization helps to:
   a. decrease maternal morbidity
   b. decrease neonatal morbidity
   c. a and b
   d. none of the above

4. An infant born at 30 weeks requiring ventilation for >24 hours can be cared for in the following level NICUs (mark all that apply):
   a. I
   b. II
   c. III
   d. IV

5. Evidence from an observational study is considered level of evidence:
   a. A
   b. B
   c. C
   d. D
   e. X

78 Ethical and Legal Issues in Neonatology

MARLYSE HAWARD and ANNIE JANVIER

Ethical and Legal Issues and Death and Dying

1. Basic information and general ethical concepts
   a. Ethics: set of morals and values guiding what is considered good or bad in a society
   b. Bioethics: application of morals and values in the context of medical care or research
   c. Clinical ethics: subset of bioethics in the clinical context; patient care dilemmas
   d. Pediatric and neonatal ethics: subset of bioethics related to children and neonates
      1) Models of decision making
         a) Paternalism: physician makes decision for patient; historical approach to decision making
         b) Shared decision making: parents and physicians partner in making decisions for children, share information, express preferences and values, agree on interventions, family-centered
         c) Fully autonomous: Patient with capacity makes decision

Each model has been debated. Personalized decision making models have been suggested as alternatives, where the patient decides which approach works best for him or her.

      2) Informed consent doctrine: based on the principle respect for autonomy
         a) Three types of disclosure: professional, reasonable person, and subjective standard
         b) Five tenets: competence, disclosure, understanding, voluntariness, consent
         c) Physician's obligations: inform, provide alternative options, review risks and benefits of having or forgoing treatment, ensure comprehension, answer questions
      3) Decision-making capacity (lacking in neonates and young children)
         a) Ability to perform cognitive tasks necessary to act autonomously
         b) Increases with age: none at birth, assent or dissent in midchildhood, autonomous consent at 18 years of age or sooner if emancipated minor (presumed to have capacity and competence [legal term])
         c) Emancipated minors: minors who are parents, married, pregnant, in the armed forces, or considered mature minor (after evaluation, such as living independently)
         d) Many have criticized defining competence according to age, parenthood, other factors
      4) Models of surrogate decision making
         a) Substituted judgment
         b) Previously competent; application of known values to new situation
         c) Pure autonomy—clear preferences about specific treatment by previously competent patient
         d) Patient's best interests—assessment of risks and benefits; maximizing benefit; unknown values
         e) Model used in pediatrics: parents are surrogate decision makers
      5) *Parens patriae*: common law: government intervention on behalf of incompetent individual, protecting safety and well-being; may challenge surrogate authority under extreme circumstances
      6) Vulnerable populations: people potentially disadvantaged to make decisions or advocate on their own behalf (e.g., neonates, prisoners)
      7) Sanctity of life: intrinsic value to life itself
      8) Quality of life (QOL): balance of benefits and burdens: physical, psychological, social, subjective
         a) Health-related QOL: contribution of health to QOL assessments
         b) Disability paradox: nondisabled individual's difficulty imagining good QOL with disability
         c) Debates
            i. Every life should be lived versus every life of value.
            ii. What is the value of life?
            iii. What tools can measure value in children and infants?
            iv. Should they be subjective or objective?
      9) Futility
         a) Physiologic: scientific evidence shows treatment "doesn't work"
         b) Qualitative: treatment effective but due to patient's condition will not meet desired goals
         c) Quantitative: chance of achieving effect is very low
         d) Ethical debates: for example, futile to whom—patient, physician, family; or to which goals? Texas Advance Directives Act outlines procedures so physicians not obligated to provide futile care
      10) Doctrine of double effect: one action yields both good and bad effects; morally permissible if three conditions are met—action itself is not wrong; good effect is direct result of the action and is the intended effect; benefits of the good effect outweigh harmful consequences

11) Privacy: five types—informational privacy (HIPPA), decisional privacy (choices), physical privacy (person, space), proprietary privacy (genetic information), relational or associational privacy (physician-patient relationship)
12) Confidentiality: pledge not to redisclose private information originally shared in a relationship (e.g., physician giving information to third party without consent of patient)
13) Veracity (truth): comprehensive, accurate, comprehensible, direct, and unbiased transmission of information to the patient; promotes effective treatments, autonomy, and fiduciary promises
    a) In rare circumstances (e.g., HIV in children), many believe there is rationale to forgo telling children the truth; however, in general, it is thought that children benefit from the truth (palliative care).

2. Clinical presentations: see "Ethical Dilemmas," later
   a. Dilemmas arise when principles and values conflict between (among) decision makers.
3. Diagnosis: bioethical consultation, three models
   a. Individual consultant
   b. Committee consultation
   c. Team consultation
4. Evaluation
   a. Ethical theories
      1) Normative ethics (e.g., utilitarianism [consequence-based analyses])
      2) Deontologic and Kantian (duty-based analyses)
      3) Virtue ethics (promote positive virtues and characteristics)
      4) Ethics of care (centered around care and concern)
   b. Ethical approaches used for analysis
      1) Principlism: approach used in North American medical ethical analyses; based on four principles that transcend cultures and religions (Beauchamp and Childress, 2001):
         a) Beneficence: actively promoting the welfare and preventing harm of another
         b) Nonmaleficence: not doing something that would inflict harm
         c) Respect for autonomy: acknowledging others' rights to make their own decisions consistent with their values and beliefs; framework for medical decision making for competent patients
         d) Justice: balancing individual rights with fair allocation of resources and burdens in society
      2) Ethics of care: promotes attachment, care, and concern for relationships in the patient's life; prioritized over impartiality and detachment
      3) Feminist theory: power discrepancies in relationships in medicine (e.g., gender); pregnancy does not compromise capacity; powerlessness: parents trying to gain control of a neonatal intensive care unit (NICU) situation
      4) North American medical systems favor principlism, although not unanimous; approaches more individualistic (e.g., autonomy) versus other countries that are more communitarian
5. Treatment approaches
   a. Bioethical mediation: identify conflict and interests, neutralize power discrepancies, seek common ground, maximize options, ensure consensus, implement follow-up.
      1) Many conflicts in medicine can be solved without bioethical or legal consultation. It is preferable to avoid litigation as legal interpretations evolve (e.g., voting rights for women), and legal actions may not be ethical and vice versa. Providers should be cognizant of their state's regulations because different states reach different conclusions (e.g., regarding physician-assisted suicide)

Ethical and Legal Issues: Specific Bioethical Dilemmas

MATERNAL-FETAL CONFLICT: KNOW THE EVOLVING ISSUES OF MATERNAL VERSUS FETAL RIGHTS

The fetus is:

1. Only accessible through interventions on the mother;
2. Reliant on her for health and well being.

Issues arise as fetal best interests are balanced against maternal autonomy, including legal rights of privacy, self-determination, informed consent, and protection from invasion of bodily integrity. Debates highlight whether a mother's moral obligations to an unborn fetus are legal obligations and when a fetus gains rights similar to those of a child. Currently, professional medical organizations favor respect for maternal autonomy over fetal best interests. They focus on preserving the maternal and physician relationship so high-risk mothers are not deterred from seeking care. However, a few states prioritize fetal beneficence and prosecute women with child endangerment who expose the fetus to harm (e.g., illegal drug use).

Broader implications of fetal rights legislation (Unborn Victims of Violence Act; Unborn Child Pain Awareness Act) have yet to be determined. Fetal rights debates revolve around when the fetus achieves personhood. There is no consensus on when personhood begins. Arguments range from conception to the acquisition of certain developmental milestones (e.g., pain sensation), viability, birth, human characteristics (smiling), or cognitive traits associated with personhood (e.g., capacity to communicate, self-consciousness). This dialogue has been the source of many political, philosophical, legal, religious, and societal debates (e.g., abortion, frozen and discarded embryos, palliative care for very small preterm infants).

Feminist ethicists offer an alternative perspective. They emphasize the relationship between mother and fetus as being complementary, not adversarial, and use terminology such as *maternal fetal conflict,* which contributes to the perception of conflicting fiduciary responsibilities.

Case Law and Legislation

1. Re: AC, 1987, Washington DC: terminal cancer patient at 26 weeks; *parens patriae* invoked; judge approved culture and sensitivity (C&S); overturned by DC Appellate Court; landmark ruling favoring autonomy

2. Whitner v. State Supreme Court of SC, 1997: infant positive for crack and cocaine screen; mother indicted for child endangerment; US Supreme Court did not review
3. US Supreme Court: Fergeson v. City of Charlestown, 2001: women screened for drug use without consent; results to police: violation of Fourth Amendment; illegal search and seizure
4. Child Abuse Protection and Treatment Act (CAPTA): mandates that states have policies to address needs of drug-exposed infants; states differ as to whether illicit drug use is child endangerment
5. Munoz v. John Peter Smith Hospital et al., 2017: 33-year-old woman, brain dead, 14 weeks pregnant; withdrawal of ventilator per patient's former wishes refused by hospital, alleging Texas Advance Directive Act prevents removal of "life-sustaining" treatment from pregnant women; district judge ruled in favor of family based on brain death; no comment on constitutionality of the law

LIMITS OF VIABILITY

Recognize the controversies associated with treating extremely premature infants. Controversies result from prognostic uncertainty, perceptions of sanctity of life and quality of life, beneficence and nonmaleficence, and inability to predict outcomes.

1. Five factors: birth weight, antenatal steroids, gender, multiple and singleton, and gestational age are important predictors of prognosis. Despite American Academy of Pediatrics (AAP) endorsement, criteria using gestational age alone are still sometimes used. Three categories of risk are proposed:
   a. Early death likely, risk of severe morbidity high, intensive care not indicated
   b. Survival likely, risk of severe morbidity low, intensive care indicated
   c. Prognosis uncertain, survival associated with decreased quality of life, parental discretion advised—"grey zone"
2. In the grey zone, the AAP recommends shared decision making, with clear communication of information and options for comfort care and intensive care guided by the infant's best interests. Parental preferences for decision making, how they manage uncertainty, and perceptions of QOL vary from parent to parent. Trends in perinatal counseling have proposed personalizing consultations and individualizing risk with frameworks such as SOB-PIE (***s***ituation, ***o***pinion and options, ***b***asic politeness, ***p***erspectives, ***i***nformation, and ***e***motions).
3. Historically, ethical debates in neonatal care were focused on nontreatment of children with disabling disorders, which coincided with the advent of disability rights movements. More recently, bioethical attention has questioned principles of justice, with research showing inherent biases toward treatment of extremely premature infants, despite similar prognoses to other patients, pessimistic predictions of QOL in premature children surviving with disability compared with parents and the children themselves, and variations in resuscitation practices at extremes of prematurity correlated only with center of birth. This potentially leads to self-fulfilling prophecies that perpetuate discrimination toward extremely premature infants. Treatment debates for infants with trisomy 18 and 13 highlight alternative perspectives on QOL and disability. Other arguments about justice consider cost and resource allocation.
4. Moral distress in neonatal care often questions futility and the balance between beneficence and nonmaleficence. *Parens patriae* is generally reserved for extreme cases when parental decisions cause direct, imminent, and irreversible harm (harm principle) or when decisions are clearly not in the best interests of the infant. Redirection of care toward comfort measures or noninitiation after thoughtful deliberation with parents has been supported by AAP policy. Regardless of gestational age, when survival is very unlikely, and/or when affected survival is not in the interest of the child, interventions are not mandatory, and comfort care and palliative care are generally recommended. In addition, the AAP considers the withdrawal or noninitiation of care ethically equivalent, with withdrawal of fluids and nutrition ethically permissible under circumstances in which redirection is warranted.
5. Recognizing the interdependency of infant and family interests and acknowledging emotions, although controversial, have gained more support as approaches relying on relational autonomy, "family interests," and "good enough interests" have provided alternative ethical perspectives.
6. Finally, research in the neonatal population is an important endeavor that has not been addressed until recent years (see later, "Limits of Technology"). Intense debates focus on informed consent procedures, research oversight, and "reasonable foreseeable risks" when evidence is absent, especially for emergency situations that occur at birth (e.g., intubation).

Important Federal Regulations

1. Rehabilitation Act of 1973, Section 504: medical therapy cannot be withheld on basis of disability (see Maine Medical Center v. Houle)
2. Baby Doe Rules (US Department of Health and Human Services [DHHS])
   a. Two sets, 1982 and 1984; federal funds jeopardized if Section 504 violated; second rule included hotlines, posted announcements, and oversight committees
   b. Prompted by Bloomington "Baby Doe" case (later), Robinson case (infant with spina bifida; surgery refused; infant placed for adoption), and second Jane Doe case (later); rules overturned. Baby Doe Amendment added to CAPTA; if violated would affect federal funding to hospitals
3. 1983: President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research: Deciding to Forgo Life-Sustaining Treatment: Section on Seriously Ill Newborns; parents are surrogate decision makers.
4. CAPTA, 1974; "Baby Doe Amendment," 1984: hospitals could not withhold treatment based on quality of life assessments unless criteria met:

   a. Infant is chronically and irreversibly comatose.
   b. The provision of such treatment would merely prolong dying, would not be effective in ameliorating or correcting all the infant's life-threatening conditions, or would be futile in terms of the infant's survival.
   c. Or, treatment would be virtually futile or inhumane.
5. EMPTALA: 1986, provision to provide emergency care to those presenting to a hospital, regardless of ability to pay in an emergency medical situation (see "Baby K," later)
6. Born Alive Infants Protection Act (BAIPA): 2002, defines alive as product of conception outside of the uterus, regardless of means, with pulsation, heart rate, movement, or breathing; DHHS 2005 memo: investigate claims of nonadherence under CAPTA and EMPTALA; Neonatal Resuscitation Program (NRP) response: no impact on standard care

Case Law

1. Maine Medical Center v. Houle, 1974: infant with multiple anomalies, parents refused repair, hospital petitioned; court ordered treatment; "vitalist," "life at all costs."
2. Baby Doe, Bloomington, IN, 1982: trisomy 21 with tracheoesophageal fistula (TEF) and esophageal atresia (EA); parents refused surgery due to mental disability, court-appointed guardian concurred; infant died of pneumonia; Indiana Supreme Court did not hear the case.
3. Baby Jane Doe: Bowen v. American Hospital Association; New York Supreme Court, 1983; US Supreme Court, 1986: meningomyelocele and hydrocephaly; parents opted against surgical repair; activist sued; New York Supreme Court upheld parents' decision; US Supreme Court concurred: state has no authority to give unsolicited advice.
4. Miller v. HCA, 2003: 23-week-old infant resuscitated, despite parental objections; Texas Supreme Court upheld actions, saying consent not necessary under emergent circumstances.
5. State v. Messenger, 1994: infant resuscitated despite parental refusal; father discontinued ventilator; he was charged with homicide and acquitted.
6. Baby K, 1994: anencephalopathic child presenting multiple times to emergency room for resuscitation; hospital petitioned court to limit treatment; US Fourth Circuit of Appeals upheld EMPTALA.
7. Montalvo v. Borkovec, 1996: 23 weeks' gestation, sued for insufficient disclosure of disability risks; Wisconsin Court of Appeals; parents cannot withhold life sustaining treatment.
8. Preston v. Meritier Hospital, Supreme Court of Wisconsin, 2005: 23-week infant not resuscitated; hospital sued for violation of EMPTALA; ruling: this involved an inpatient, so EMPTALA did not apply.
9. Looney v. Moore, US District Court for the Northern District of Alabama, Southern Division, 2015: litigation focused on "reasonable foreseeable risks," informed consent procedures, and research oversight in the Surfactant, Positive Pressure, and Oxygenation Randomized Trial (SUPPORT) research; charged with negligence, failed informed consent, and breach of fiduciary duty; judge dismissed case because of insufficient measure of causality.

Limits of Technology

Recognize the controversies associated with the introduction of new technologies to treat previously fatal disorders, such as an experimental therapy that may save a life, prolong a life, or prolong death. Innovative or experimental therapies are approaches that deviate from standard evidence-based practices, but they are not necessarily always considered research.

Research occurs under conditions of clinical equipoise, increases generalizable knowledge, and benefits future patients. Innovative therapies help individual patients after standard therapies have failed. Innovation can refer to new therapies or novel applications of existing therapies (e.g., ventilating extremely premature infant).

1. Ethical concerns include consent processes for vulnerable patients under emergent circumstances. Therapeutic misconceptions, erroneous beliefs that research will be therapeutic, could mislead parents. The AAP recommends that physicians be clear about the distinctions among research, innovation, and therapy, including disclosure about why innovative therapies are recommended, deviation from standard of care, any conflicts of interest, previous experiences, or known side effects of the therapy. Oversight committees are encouraged for patient protection, community trust, thoughtful innovation, and monitoring outcomes. Safeguards are recommended until protocols and Institutional Review Board (IRB) approvals have been obtained. It is important to note that few NICU therapies have been formally studied. Respirators, high-frequency ventilators, extracorporeal membrane oxygenation (ECMO), and cardiac surgery were all considered innovative therapies before they became standard of care.
2. Ethical analysis justifies the use of innovative strategies based on principles of justice (sick patients otherwise denied access to experimental therapy due to randomized controlled trial [RCT] ineligibility) and beneficence (small chance of benefit outweighs significant risks of unknown side effects and death). This is also supported by the World Medical Association Declaration of Helsinki and the Belmont Report.

RELEVANT REGULATIONS AND LEGISLATION

1. FDA Expanded Use: access to therapies not yet approved (e.g., medical devices, medications)
2. Best Pharmaceutical Act for Children (BPCA), 2003: facilitates research on drugs currently used off-label, addressing disparity in research on infants and children
3. "Right to try" legislative action to permit dying patients access to therapies prior to US Food and Drug Administration (FDA) approval; does not mandate pharmaceutical companies to provide therapy

Genetic Testing and Gene Therapy

Recognize the controversies associated with the introduction of new genetic tests for rare and common diseases

that present in the neonatal period. Genetic screening is performed to identify individuals at risk in a population. Genetic testing is performed secondary to clinical suspicion, positive screening results, family history, or other reasons seeking a definitive diagnosis for an individual.

1. Newborn genetic screening: conditions selected for the newborn screen are based on best interest standards (taking into consideration potential psychological harm of false-positives) and three Wilson and Junger criteria (natural history of the disorder; available interventions with cost-effective screening [improved with tandem mass spectroscopy]; available confirmatory tests). Currently, 1 in 300 infants screened will have a positive result. Due to variability in the number and type of conditions screened among states, the Recommended Uniform Screening Panel (RUSP) was developed to provide federal guidance. States, however, retain the ultimate decision regarding selection of disorders and are often lobbied by special interest groups.
2. Parental refusal of screening is generally permitted in all states but Nebraska; two states require active consent. Objections to permitting refusals argue that states have interests in healthy children, benefits significantly outweigh risks, and consent leads to time-consuming refusals. Generally, medical exemptions are permitted, but states determine whether to accept religious objections.
3. Genetic testing: there has been a tremendous evolution in genetic testing, from karyotyping to microarray testing to discovery of new mutations causing diseases in neonates to whole-exome sequencing (WES) or whole-genome sequencing (WGS). WGS and WES are currently not widespread but, if implemented, concerns about incidental findings and disclosure procedures (e.g., who should be told and how to safeguard the information) will need to be addressed. The term *genetic exceptionalism* suggests that genetic information is unique because it affects the entire family, with consequences on reproductive decisions. Ethical debates concerning carrier screening and testing for adult- onset disorders in minors challenge boundaries between infant and family interests. Research in this area is evolving faster than policies, and findings have uncertain significance, given variable penetrance. Therefore, protecting a child's open future from an inevitable fate is a major reason why the AAP has recommended delayed testing, until the minor is of age to consent. Earlier testing would be considered if treatment exists to slow disease progression or parents suffer from severe anxiety.

LEGAL CONSIDERATIONS

1. 10th Amendment: states can implement programs for health and well-being of its citizens
2. Common law: *parens patriae*
3. 14th Amendment: protects individuals' rights to refuse care and treatment (includes parental surrogate decision making on behalf of infant's best interests)
4. Newborn Screening Saves Lives Act 2008 and reauthorization, 2014: national newborn screening guidelines; requires informed consent should blood spots be used in research

Recognize Controversies Associated With Development of Gene-Based Therapies to Treat Neonatal Conditions

Certain conditions are fatal in the first year of life. Advances in gene therapy have altered the course of the disease for these fragile patients. However, they rely on virus vectors, which can trigger immunologic responses or predispose to higher rates of malignancy if they are inserted near proto-oncogenes. Other therapies, such as nusinersen for spinal muscular atrophy (SMA), which received accelerated FDA approval, have potential benefits in slowing the progression of disease but carry uncertain long-term effect profiles, require repeated treatments, and are very expensive. Ethical concerns include discussions about justice and informed consent procedures. (e.g., Wiskott-Aldrich syndrome, severe combined immunodeficiency, chronic granulomatous disease [CGD], ornithine transcarbamylase [OTC], adrenoleukodystrophy).

IMPORTANT HISTORICAL CASE

Jesse Gelsinger, an 18-year-old with OTC deficiency, died in an IRB-approved experimental gene therapy trial. The initial study was intended for infants who carried the lethal diagnosis of OTC, but the IRB thought that these patients were too vulnerable, potentially jeopardizing informed consent. Therefore the study was performed with older, less severely affected OTC individuals who could provide active consent. The IRB balanced potential for harm versus adequate consent. Jesse died, and a lawsuit followed.

DEATH AND DYING

Know the components of bereavement counseling prior to, during, and after the death of a newborn infant, including palliative care.

1. The AAP defines pediatric palliative care and pediatric hospice care goals that aim to:
   a. Relieve suffering.
   b. Improve quality of life (including family's adaptation).
   c. Facilitate informed decision making.
   d. Assist with care coordination.

There are two models, integrative (prenatal, postnatal with life-threatening diagnoses, postnatal with worsening conditions) and consultative (primary team identifies patient and then consults palliative care expert). Changes in the patient condition shift goals between curative and palliative pain control and comfort. Perinatal hospice is a strategy for infants with conditions incompatible with life, as an alternative to termination.

2. Prior to death: the AAP recommends sharing one clear consistent message through a single spokesperson. Team collaboration and conflict resolution between members should occur prior to meeting with parents.

Parents should feel supported regardless of their decision and feel secure that they will not be abandoned. Frameworks such as SOBPIE (see earlier), clear, honest, and direct statements about prognosis while providing options for palliative care, time for parents to digest information (permitting silence), and providing anticipatory guidance for the grieving process can help parents. Reframing the decision so parents feel that they are protecting their infants from pain and burden of care and prolonged dying can also be helpful. Increasingly, parents are partners in care.

Research regarding parental participation in decisions and care around the end of life is increasing. Parents cope with the news of impending death differently. Some parents find it helpful to witness resuscitations and codes, whereas others do not. Personalizing conversations about death and dying will help assess and explore with parents whether they believe witnessing resuscitative measures would be beneficial for them, emphasizing support for whichever decision they choose. Although "do not resuscitate" (DNR) orders can be helpful in the palliative route, they are not mandatory to give comfort care for children. Indeed, legally, children can receive comfort medication and palliative care without a DNR order. Asking parents to sign a DNR and "Do Not Intubate" (DNI) is not a prerequisite for comfort care and should not be encouraged. Ethics research has shown that signing a DNR is perceived akin to a death warrant by surrogates of adult patients.

3. During the death: conveying empathy and continued involvement while guiding parents through the dying process is important. Also recommended is allowing time for the infant and other family members in a private setting, limiting disruptions but reassuring parents that a primary care provider will be available, encouraging memories (memory box), and providing symptom management to alleviate pain or other symptoms. Narcotics and sedatives do not shorten time to death and should be given when needed. For example, if a neonate is dying and in pain, it is ethically permissible to provide morphine to relieve pain, even if this results in a decreased respiratory drive. The question is not whether the infant will die, but rather whether he or she will die in pain. At birth, there is increasing evidence demonstrating adverse psychological outcomes when parents have not seen their child and are absent during death. Efforts should be made to encourage parents to see and be with their child in a culturally sensitive manner.
4. After death: debriefing staff and following up with parents (phone calls or meetings) is important. Additional recommendations include a memorial 1 year from the date, supported by the hospital, ensuring that other caregivers are aware and facilitate referrals, as needed. Phases of bereavement include shock and numbness, searching and yearning, disorientation, reorganization, and resolution. The time course of grieving is personal.

Recognize the importance of obtaining an autopsy and understand the proper way to seek consent from and share results with the parents. Rates of autopsy are decreasing. Autopsies provide valuable information to facilitate closure for the family and generalizable knowledge for the scientific community. Evidence obtained can explain effects of treatment, iatrogenic complications, changing of presumed diagnoses, and cause of death and serves as quality control. Declining autopsy rates have been suggested to be due to poor reimbursement, fear of litigation, lack of standards, parental concerns, or physicians not seeking consent (most likely). Obtaining consent should be done in an empathetic manner and is more likely to be obtained when death is sudden or unexplained. Parents often cite concerns for disfigurement as reasons for refusal. In this situation, offering a limited autopsy focusing on the primary organ(s) of interest may help. Providing continuity of care with a consultant is important to answer questions and provide follow up.

Suggested Readings

American Academy of Pediatrics. Committee on Bioethics, Committee on Genetics; American College of Medical Genetics, Social, Ethical, and Legal Issues Committee. Ethical and policy issues in genetic testing and screening of children. *Pediatrics*. 2013;131(3):620–622.

Beauchamp TL, Childress JF. Principles of Biomedical Ethics. 5th ed. New York, NY: Oxford University Press; 2001.

Diekema DS, Botkin JR, the Committee on Bioethics. Clinical report—forgoing medically provided nutrition and hydration in children. *Pediatrics*. 2009;124(2):813–822.

Haward MF, Kirshenbaum NW, Campbell DE. Care at the edge of viability: medical and ethical issues. *Clin Perinatol*. 2011;38(3):471–492.

Rysavy MA, Li L, Bell EF, et al. Between-hospital variation in treatment and outcomes in extremely preterm infants. *N Engl J Med*. 2015;372:1801–1811.

Section on Hospice and Palliative Medicine and Committee on Hospital Care. Pediatric palliative care and hospice care commitments, guidelines, and recommendations. *Pediatrics*. 2013;132(5):966–972.

Questions

1. Decline in autopsy rates are largely due to:
   a. better diagnostic procedures
   b. physicians not asking
   c. disfigurement concerns
   d. litigation

2. For emergency fetal circumstances, culture and sensitivity (C&S) do not require maternal consent, per EMPTALA. Is this true or false?

3. Which of the following factors help(s) refine risk for infants at extremes of prematurity?
   a. Birth weight
   b. Gender
   c. Center of birth
   d. Multiple gestation
   e. All of the above

4. Which of the following is not ethically permissible?
   a. Withdrawing hydration
   b. Providing morphine for suffering at the end of life
   c. Emergency C&S without maternal consent

5. Carrier screening of minors for adult onset disorders is permitted for disabling parental anxiety. Is this true or false?

SECTION 21

Core Knowledge and Scholarly Activities

CARL T. D'ANGIO and EMER FINAN

79 Biostatistics in Research

CARL T. D'ANGIO

Underlying Concepts

- Statistics involves *inference*
  - From a *sample* of the entire *population*, what can we understand about the whole population? (Fig. 79.1)
- Statistics attempt to measure the likelihood that an observed result reflects what is true in the population
- A combination of *large differences* and *large sample* makes a true difference more likely

Understanding Variables

- Types of variables
  - *Continuous* variables can have any value on a scale (for instance 1.0, 1.1, or 1.11)
    - Example: weight
  - *Ordinal* variables are also ordered (for instance 1, 2, 3), but,
    - The variable cannot assume a value between those specified
    - The distance between values is not necessarily constant
    - Example: Apgar score
  - *Categorical* variables (also known as *nominal* variables) describe categories without any implied order of the categories
    - Examples (two categories): yes/no choices, sex
    - Example (>2 categories): hair color
- Dependence
  - *Independent variables* are independent of other factors
    - Example: age
  - *Dependent variables* are expected to be changed by other factors (e.g., disease or intervention)
    - They are typically the outcome variables in a study
    - Example: in a study of vasodilators, pulmonary blood flow would be a dependent variable

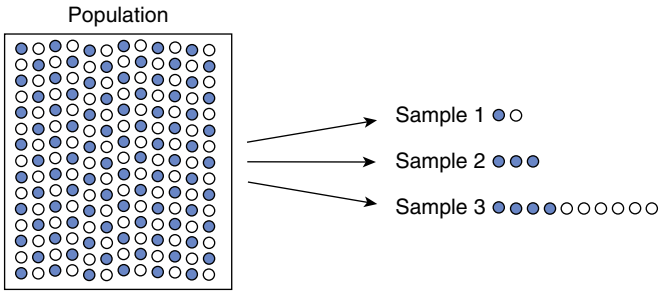


Fig. 79.1 Sampling and inference. Statistics infers the nature of a population from a sample or samples drawn from the population. Larger samples provide more precise estimates of population characteristics.

Distribution of Data

- *Normal distribution* implies that values are evenly distributed around a central value
  - A *skewed* distribution is not evenly distributed around a central value (Fig. 79.2)
- Measures of *central tendency* (i.e., where is the middle of the data?)
  - *Mean* is the average
  - *Median* is the middle value
  - *Mode* is the most common value
  - Example: with values (1, 1, 1, 2, 2, 3, 11)
    - Mean is 3 (= [1 + 1 + 1 + 2 + 2 + 3 + 11]/7)
    - Median is 2 (1, 1, 1, *2*, 2, 3, 11)
    - Mode is 1 (*1, 1, 1,* 2, 2, 3, 11)

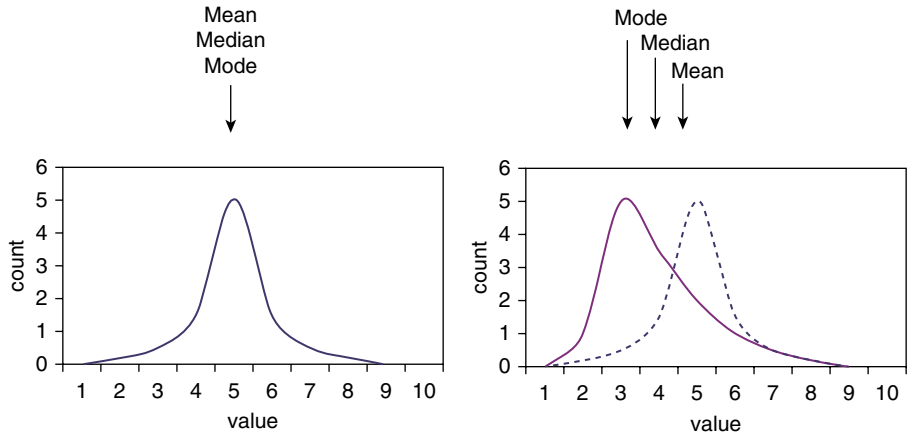


Fig. 79.2 Normal and skewed populations. The mean, median, and mode of a normally distributed population (left-hand panel) are the same. If the population is skewed (right-hand panel), the mode and median of the sample fall to one side of the mean value.

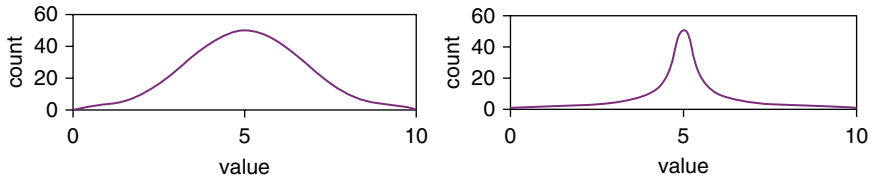


Fig. 79.3 Distribution widths. The data on the left have a wider standard deviation (and less certainty about the central value) than the data on the right.

- *Standard deviation* is a measure of the spread of the data (Fig. 79.3)
- *Standard error* is a measure of the precision of an estimate of the mean of a population
  - The larger the population sampled, the smaller the standard error; you are more likely to be sure that your estimate of the mean of 100 values is more accurate than if you only have 10 values
- The *confidence interval* is the range within which a certain proportion of estimates of a value would fall
  - For instance, the 95% confidence interval (CI) is the range containing 95% of the estimates of a value
    - If we made multiple estimates of the mean value of a measure using the same population, 95% of them would fall within the 95% CI
  - Typically expressed as "1.5 (95% CI 1.3, 1.7)" or "1.5 (95% CI 1.3–1.7)"

Hypothesis Testing

- Statistical hypothesis testing starts with an assumption of no difference
  - The *null hypothesis* (H_0) is that there is no difference between groups tested
  - The *alternative hypothesis* (H_a) is that there is a difference between groups tested
- The measure of statistical significance, usually the *p value*, is the likelihood that the observed differences within the *sample* reflect random chance rather than a true difference in the *population*
  - Specifically, the likelihood that the observed results or results that are "more extreme" (larger difference) would be seen in the sample if the null hypothesis (no true difference in the population) were true
    - A *high* p value (e.g., 0.80) reflects a *high* probability that any difference is due to chance
    - A *low* p value (e.g., 0.01) reflects a *low* probability that the difference is due to chance; that is, the difference is likely to be due to a *true* population difference (Fig. 79.4)
  - In the biomedical literature, a p value <0.05 (<1 in 20 chance that the observed results or more extreme results are due to chance) is generally considered to be *statistically significant*, or a low enough likelihood of error to accept the result
- Types of error in statistical comparisons
  - A *type I* (or α) error is concluding that there is a true difference in the population when there is, in fact, no difference
    - This error is minimized by choosing a restrictive p value (also known as *α statistic*)

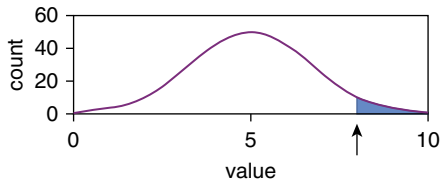


Fig. 79.4 Graphic representation of p value. Five percent of values in this distribution fall at or beyond the arrow, and a new observed value in the shaded range would have a 5% or lower likelihood of truly falling within this population.

  - A *type II* (or β) error is concluding that there is no difference in the population when there is, in fact, a difference
    - This error is minimized by using a large enough sample of the population (which increases the *power* of a study to find differences)
- Multiple comparisons
  - When multiple comparisons are made (e.g., among multiple groups of test subjects), the likelihood of an erroneous conclusion also rises
    - For instance, if 10 independent comparisons are made using a p value of 0.05 to define significance, the likelihood that none of the comparisons is due to chance is only 0.60 (0.95^{10})
      - Technically, the likelihood that at least one result would be due to chance is $1–(1 – 0.05)^{10}$, or 0.40
    - The most common method for correcting for multiple comparisons (the *Bonferroni method*) is to divide the p value that will be used to determine statistical significance by the number of comparisons
    - For 10 comparisons, a significant p value would be 0.05/10 = 0.005

Statistical Tests

- Common statistical tests for varying data types
  - Tests that measure differences in central tendencies (e.g., means, medians) based on the central value and the spread of data are used on continuous or ordinal variables. In general:
    - A *t test* is used when the data are continuous
      - The t test performs well when data are normally distributed
      - Even if the data are not normally distributed, it still performs well if the number of observations is relatively large (over about 25)
      - The t test can be used only when two groups are being compared (not 3 or more groups; see ANOVA, later)

- A *nonparametric* test (e.g., *Mann-Whitney U* test, also called *Wilcoxon rank-sum test*) is used when data do not meet the "parameters" (e.g., normal distribution) for the t test
  - Nonparametric tests are also used when the data are ordinal
- *Analysis of variance* (ANOVA) testing is used when three or more groups are being compared
  - Tests whether the means are the same among all groups (null hypothesis)
  - If the null hypothesis is rejected, further testing is needed (with correction for multiple comparisons) to describe where differences exist
- Tests that compare number of values in a category (e.g., number of males vs. number of females) are used with categorical variables
  - *Chi square* (χ^2) test in most cases
  - *Fisher exact* test with very small samples

- Test statistics
  - Statistical tests generate a *test statistic* (e.g., the *t statistic* or the χ^2 *statistic*) that can be translated into a p value
    - Computerized statistics programs often report the test statistic, but display the p value as well
- Paired data
  - If the two continuous data points being compared are linked to one another (e.g., same patient before and after an intervention), a *paired* t test is used
    - Compares the mean change in variable pairs, rather than change in means
  - The *McNemar* test is used to compare paired categorical data
- One- and two-tailed tests
  - A *one-tailed* test is used if one mean varies from another in only one direction (greater or less)
    - Will detect smaller differences in the hypothesized direction, but cannot be interpreted if the difference is in the opposite direction
  - A *two-tailed* test evaluates differences in both directions
  - Most clinical questions should be evaluated by a two-tailed test

Comparing Risks

- Risk reduction
  - *Absolute risk reduction* is the *absolute* change in the risk of an event between one group and another
    - If a certain treatment reduces the incidence of myocardial infarction in a population from 3/1000 to 2/1000, the absolute risk reduction is 1/1000, or 0.1%
  - *Relative risk reduction* is the *proportional* change in risk of an event between one group and another
    - If a certain treatment reduces the incidence of myocardial infarction in a population from 3/1000 to 2/1000, the relative risk reduction is 1/1000 ÷ 3/1000, or 33%
  - Note that these are two descriptions of the same result
- *Relative risk* or *risk ratio (RR)* is the ratio of the risk of an outcome in one group (typically a treated or comparison group) to the risk in another group (typically a control group) (Fig 79.5)
  - Risk of an outcome is the number with the outcome divided by the total population

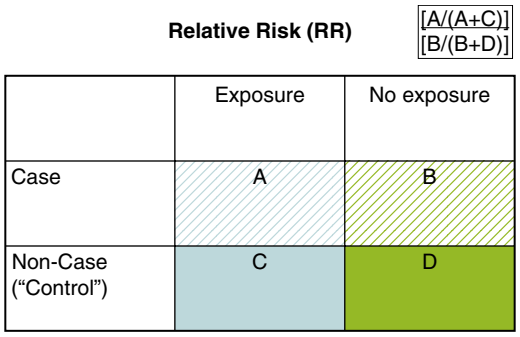


Fig. 79.5 Relative risk. The relative risk of being a case with a particular exposure (as opposed to a case with no exposure) is the ratio of hatched blue/total blue (left column) to hatched green/total green (right column).

    - If one person out of a population of four people has an outcome, the risk is 1/4 = 0.25
- *Odds ratio (OR)* is the ratio of the odds of an outcome in one group to the odds in another group
  - Odds of an outcome is the number with an outcome compared to the number without the outcome
    - If one person out of a population of four people has an outcome (i.e., one does and three do not), the odds are 1:3, also expressed as 1/3 or 0.33
  - When prevalence of an outcome is rare, odds ratio and relative risk are similar
  - When prevalence of an outcome is common, odds ratio gives a bigger estimate of effect than relative risk
  - Why use an odds ratio?
    - Because of the characteristics of the math, odds ratios are not affected by the oversampling of disease that happens in *case-control* studies (see Chapter 80), making it possible to estimate the effect of an exposure on a disease from these studies (despite the fact that they start by finding people with diseases rather than assessing exposure) (Fig. 79.6)

Measuring Correlation

- When comparing two continuous variables, we can measure the *correlation* between them
  - The *correlation coefficient* (usually expressed as *Pearson product moment correlation, or r*) puts a number on this (Fig. 79.7)
    - A correlation coefficient of 1 (r = 1) indicates a perfect correlation; the variables line up on a straight line, and a change in one variable is directly correlated to a change in the other
    - A correlation coefficient of 0 (r = 0) indicates no correlation between the two variables
    - Correlations can be positive (slope of line is up) or negative (slope of line is down); the sign only indicates direction, not strength
  - Ordinal or skewed variables can be compared using *Spearman rank order correlation* (also known as *Spearman rho*)
- Interpreting the r value
  - Definitions of levels of correlation are strictly descriptive
    - Above 0.70–0.75 = "strong"
    - Below 0.25–0.30 = "weak"
    - Everything in between is fair-to-moderate (sometimes split as below 0.50 = fair and above 0.50 = moderate)

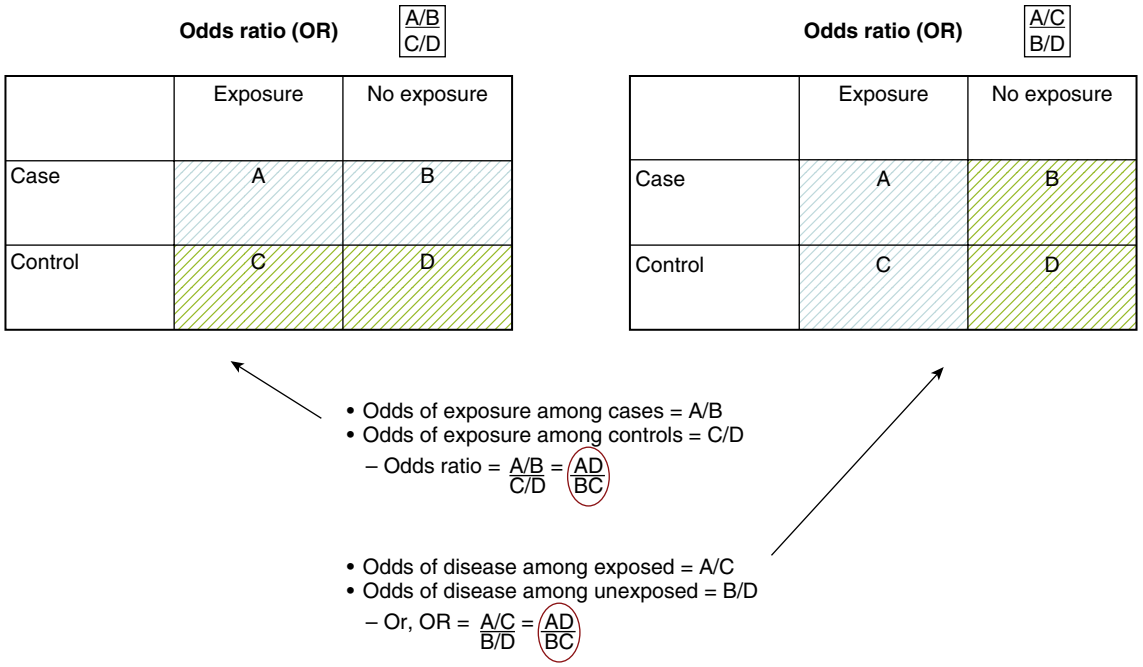


Fig. 79.6 Odds ratio. Odds ratio can be calculated in two ways, which yield equivalent results regardless of the frequency of cases in a sample.

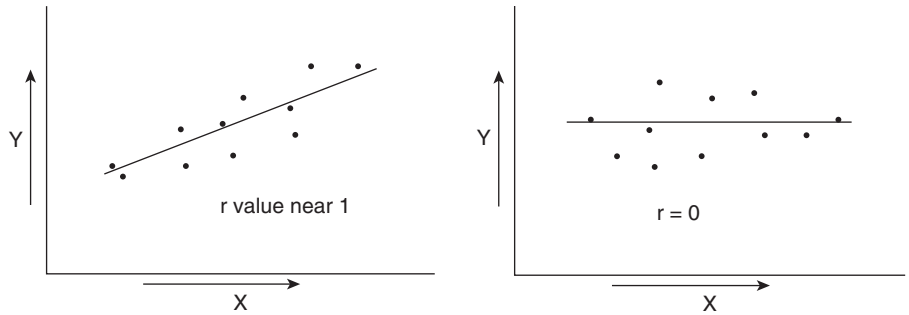


Fig. 79.7 Correlation coefficient (r value). A group of observations that closely approximate a linear relationship between X and Y (left) has r close to 1 (perfect correlation), while a group of observations in which one variable has no correlation to the other (right) has r = 0.

- P values can be assigned to correlations, but even weak correlations will be "statistically significant" if the number of observations is large
  - The strength of the correlation is often a better indicator of correlation than a p value
- The *coefficient of determination* describes how much of the variance in one variable is determined by the value of the other
  - Calculated by the square of r *(r^2)*
  - For an r of 0.60 (a moderate correlation), 36% of the variance in one variable is described by the other ($r^2 = 0.60^2 = 0.36$)
    - And, 64% of the variance is described by something else

Regression Analysis

- Regression analysis applies statistical testing to correlations
- *Linear* regression is used to assess the effect of a continuous *independent* variable (or variables) on a continuous *dependent* variable
  - The results are typically expressed as correlation coefficient (r), 95% CI, and p value
- *Logistic* regression is used when the *dependent* variable is categorical
  - The results are typically expressed as an odds ratio, 95% CI, and p value
- Both linear and logistic regressions can incorporate multiple *independent* variables = *multiple regression*
  - The analyses measure the effect of each independent variable on the outcome when the effect of all other independent variables is controlled

Survival Analysis

- *Survival analysis* is used to compare the time to an event in two or more groups

- Typically used to measure survival following a therapy in patients
- The *Kaplan-Meier* analysis (Fig. 79.8) is the most commonly used survival analysis and accounts for the fact that different patients may have been observed for differing periods of time since treatment, *censoring* a patient's data at the time that patient has been observed since treatment
- Survival curves may be compared using median time to an event or by calculating a *hazard ratio*: a specialized version of relative risk comparing outcome rates

Diagnostic Tests

- Diagnostic tests are used to predict the presence of a disease, and seldom do so perfectly

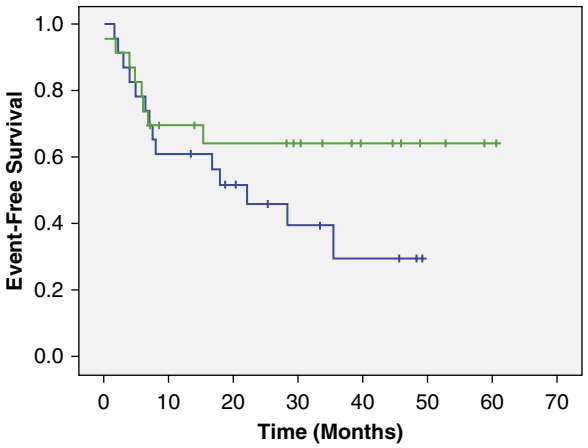


Fig. 79.8 Kaplan-Meier survival curve. Each step downward represents an event and each tick mark represents a censored observation (subject has not yet had an event, but has only been observed for that length of time). (Courtesy Craig Mullen.)

- When assessing the effectiveness of a diagnostic test, it should be compared to an independent *gold standard* known to correlate highly with disease
  - Example: an imaging modality used to detect lymph nodes containing tumors might be compared to lymph node biopsy
- Tests can result in four possible outcomes (Fig. 79.9)
  - Test positive and disease present = *True-positive*
  - Test positive but disease absent = *False-positive*
  - Test negative and disease absent = *True-negative*
  - Test negative but disease present = *False-negative*
- Test performance
  - *Sensitivity* is the ability of a test to detect those with disease (true-positives/all patients with disease)
    - A highly sensitive test has few false-negatives
  - *Specificity* is the ability of a test to correctly identify patients without disease (true-negatives/all patients without disease)
    - A highly specific test has a few false-positives
  - *Positive predictive value (PPV)* is the likelihood that a positive test means that a patient truly has disease
    - A test with a high PPV has many true-positives
    - PPV is highly affected by disease prevalence in the population; if disease prevalence is very low, even the best test will have a lot of false-positives (Fig 79.10)
  - *Negative predictive value (NPV)* is the likelihood that a negative test means that a patient truly does not have disease
    - A test with a high NPV has many true-negatives
    - NPV is also highly affected by disease prevalence in the population; if disease prevalence is high, even the best test will miss disease (Fig. 79.10)

		Bacterial infection present: Yes	Bacterial infection present: No	
Laboratory test result	Positive	True positives (a)	False positives (b)	***Positive predictive value*** *(a)/(a+b)*
	Negative	False negatives (c)	True negatives (d)	***Negative predictive value*** *(d)/(c+d)*
		Sensitivity *(a)/(a+c)*	***Specificity*** *(d)/(b+d)*	

Likelihood ratio, positive *Sensitivity/(1-specificity)*

Likelihood ratio, negative *(1-sensitivity)/specificity*

Prevalence *(a+c)/(a+b+c+d)*

Fig. 79.9 Diagnostic test characteristics. Example uses a laboratory test's ability to predict bacterial infection. Sensitivity, specificity, positive predictive value, and negative predictive value are commonly expressed as percentages or proportions; likelihood ratios represent fold increases or decreases in odds. Prevalence is not relevant in case-control (see Chapter 80). (From Weinberg GA, D'Angio CT. Laboratory aids for diagnosis of neonatal sepsis. In: Remington JS, Klein JO, Wilson CB, Nizet V, Maldonado YA, eds. *Infectious Diseases of the Fetus and Newborn Infant.* 8th ed. Philadelphia: Elsevier; 2015:1132–1146). (Modified from Feinstein AR. Clinical biostatistics: XXXI. On the sensitivity, specificity, and discrimination of diagnostic tests. *Clin Pharmacol Ther.* 1975;17:104–116. From Jaeschke R, Guyatt GH, Sackett DL. Users' guides to the medical literature. III. How to use an article about a diagnostic test. B. What are the results and will they help me in caring for my patients? *JAMA.* 1994;271:703–707). (From Radetsky M. The laboratory evaluation of newborn sepsis, *Curr Opin Infect Dis.* 1995;8:191–199.)

Prevalence	Sensitivity	Specificity	PPV	NPV
21%	60%	92%	66%	89%
9%	60%	92%	41%	96%
6%	60%	92%	30%	98%

Fig. 79.10 Effect of changing prevalence of disease on positive and negative predictive values. In a test with constant sensitivity (disease producing positive test) and specificity (no disease producing negative test), as the prevalence of disease in a population increases, PPV (positive test implying disease) increases and NPV (negative test implying health) decreases.

Assessing Diagnostic Tests

- *Likelihood ratios* are a measure of the change in likelihood of a disease based on results of a test (Fig. 79.11)
  - Ratios vary with sensitivity and specificity of a test
    - *Likelihood ratio (positive)* is the change in disease likelihood if a test is positive
      - = Sensitivity/(1 – specificity)
        - Example: a test with a sensitivity of 0.90 and a specificity of 0.80 would have a likelihood ratio (positive) of 0.9/0.2 = 4.5
      - A highly predictive test has a likelihood ratio (positive) of about 10
    - *Likelihood ratio (negative)* is change in disease likelihood if a test is negative
      - = (1 – sensitivity)/specificity
        - Example: a test with a sensitivity of 0.90 and a specificity of 0.80 would have a likelihood ratio (negative) of 0.1/0.8 = 0.125
      - A highly predictive test has a likelihood ratio (negative) of about 0.1
  - The likelihood ratio tells you how much the odds (not risk) of an outcome are changed if a test is positive or negative (see Chapter 81)
- *Receiver operating characteristic (ROC) curves* compare the sensitivity and specificity of multiple cutoff values (to define a "positive" test) of a diagnostic test (Fig. 79.12)
  - The ROC curve plots 1 – specificity versus sensitivity
    - Example: a test of fetal lung maturity would become more specific (include fewer false-positives), but less sensitive (include fewer true-positives) as the surfactant cutoff value rose
  - Curves with high "shoulders" (nearer to the left upper corner) imply better test performance
  - Performance can also be described by the *area under the ROC curve (AUC)*
    - An AUC of 1 describes a perfect test
    - An AUC of 0.50 describes a test that performs no better than chance
- *Clinical prediction rules* are methods that combine the results of a number of different parameters (e.g., patient characteristics, test results) to predict the likelihood of an outcome

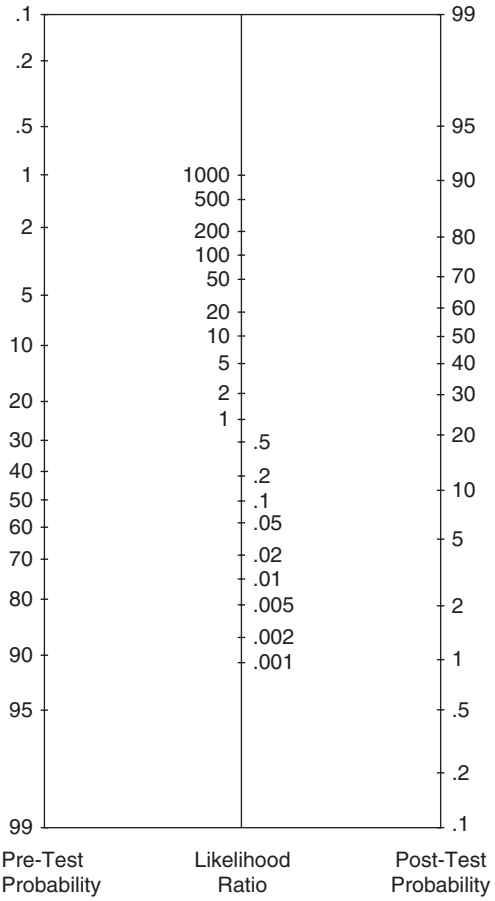


Fig. 79.11 Likelihood ratio nomogram. This nomogram uses a line drawn through pretest probability of disease and a known likelihood ratio to determine posttest probability of disease. The nomogram does the math of converting probabilities to odds and back again automatically. (From Evidence Based Emergency Medicine <ebem.org/definitions.html>, accessed 10/27/2018.)

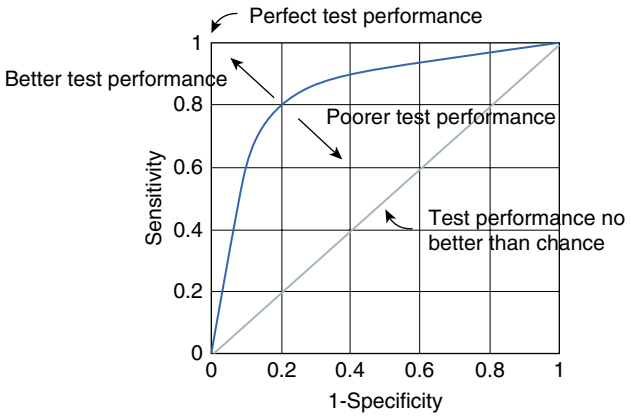


Fig. 79.12 Receiver operating characteristic (ROC) curve. This idealized curve shows a test with a sensitivity of 0.80 and specificity of 0.80 at the left "shoulder" of the curve. A perfect test would fill the entire graph (area under the curve [AUC] of 1.0), and a test without predictive value would describe a straight upward diagonal line (AUC of 0.50).

  - Examples: Score of Acute Neonatal Physiology (SNAP and its modifications) and NICHD Neonatal Research Network outcome calculator (Fig. 79.13) use patient characteristics and/or physiologic parameters to predict neonatal morbidity and mortality

- Outcomes are usually listed as percentages of patients in similar situations that will have a particular outcome; these percentages are seldom 0% or 100%
  - Characteristics not measured by the rule will also affect outcomes, and the data used to generate the model may not apply to the specific patient (e.g., may be old or derived from a different population)
  - Application of results to an individual patient requires understanding of patient's overall situation

Systematic Reviews and Meta-Analysis

- *Systematic reviews* assess existing literature, taking advantage of electronic literature databases to identify all articles that meet reviewers' criteria and to avoid inclusion bias in articles reviewed
  - Systematic reviews are limited by several factors: search strategies used, publication bias that affects the articles available, and inherent subjective decisions regarding how to treat data
- *Meta-analysis* is a statistical method of combining results of multiple trials to increase power of comparisons and to further decrease the bias in systematic reviews of therapies
  - Studies to be included are sought systematically and must meet predetermined inclusion criteria
  - Outcomes of individual studies and an overall weighted combination of the studies are expressed as a comparison between study groups (e.g., OR, RR, or mean difference) and 95% CIs, and displayed as a *Forest plot* (Fig. 79.14)
    - Studies are typically weighted according to effect size
    - 95% CIs that do not cross the line of identity (1 for OR and RR, 0 for mean difference) are statistically significant
  - Meta-analyses are limited by search strategy and publication bias, as well as by undetected differences between studies that may make them inappropriate to combine
    - Although potentially superior to small clinical trials (see Chapter 80), meta-analyses may not be as definitive of a large trial containing the same total number of patients included in the meta-analysis

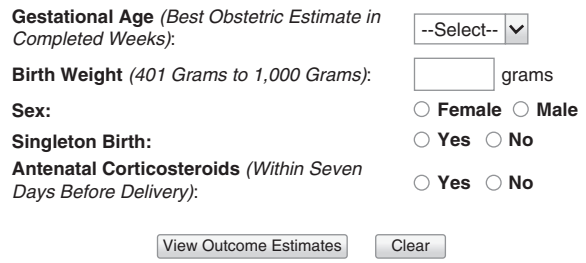


Fig. 79.13 Clinical prediction rule applied to neonatal survival and morbidity. Eunice K. Shriver National Institutes of Child Health and Human Development neonatal outcome estimator uses clinical factors combined in a multivariate regression derived from a large data set to estimate survival and neurodevelopmental impairment. (From *Eunice Kennedy Shriver* National Institute of Child Health and Human Development <https://www.nichd.nih.gov/about/org/der/branches/ppb/programs/epbo/Pages/epbo_case.aspx>, accessed 10/27/2018)

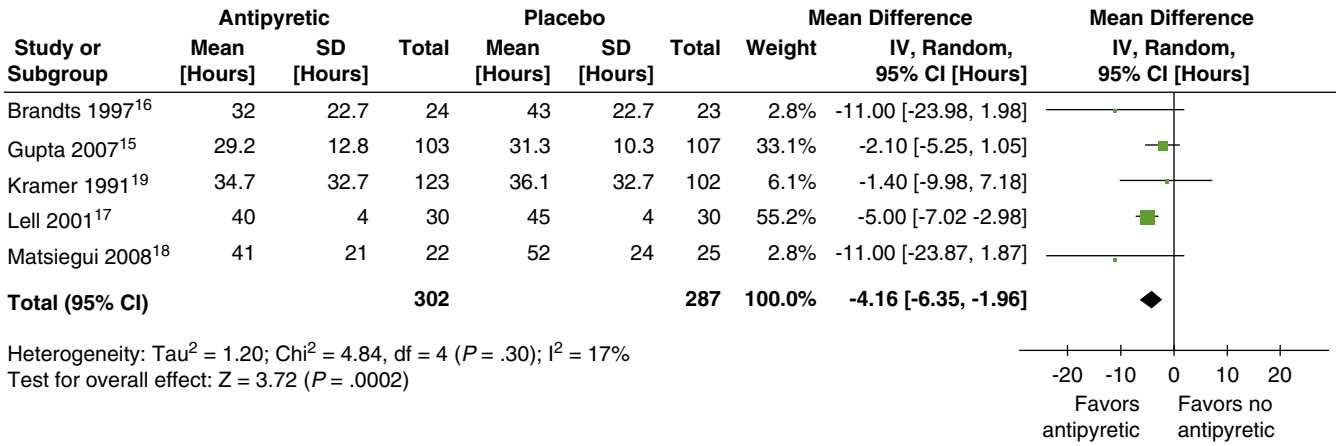


Fig. 79.14 Forest plot from a meta-analysis. Data are from studies showing effect of antipyretics on duration of febrile illness. Plot shows results from each individual study (green boxes and whiskers) and the weighted combination of studies (black diamond) and displays a mean difference in illness duration favoring antipyretics. (From Purssell E, While AE. Does the use of antipyretics in children who have acute infections prolong febrile illness? A systematic review and meta-analysis. *J Pediatr*. 2013;163(3):822–827.)

Suggested Readings

Adams ST, Leveson SH. Clinical prediction rules. *BMJ*. 2012;344:d8312.
Dawson B, Trapp RG, eds. *Basic & Clinical Biostatistics*. 4th ed. New York: McGraw-Hill; 2004. <http://accessmedicine.mhmedical.com/content.aspx?bookid=356&sectionid=40086278>.

Questions

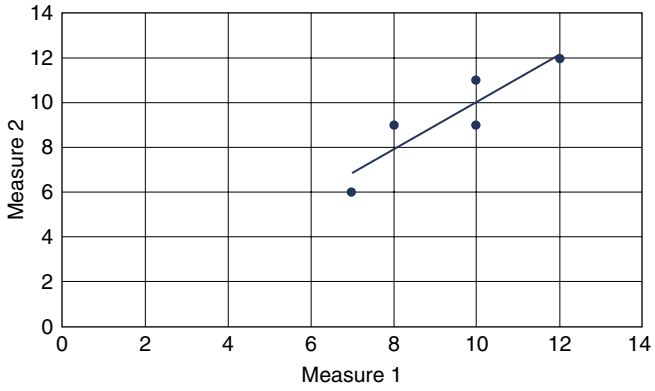
1. Investigators are studying two methods ("new" and "old") of preventing intraventricular hemorrhage (IVH). The new method reduces the proportion of infants with IVH, compared to the old method. The p value on a chi square test is 0.04. The clearest interpretation of the results would be:
   a. There is a 4% chance that the groups are different.
   b. The probability of finding a difference of this magnitude or more extreme, if there were truly no difference between groups, is 4%.
   c. There is a 4% chance that the old method works.
   d. There is a 96% chance that the new method works.

2. A nonparametric test (e.g., Mann-Whitney U test) might be the most appropriate statistical test to compare two groups of numerical values with each of the following characteristics except:
   a. five observations per group
   b. skewed distribution
   c. normal distribution
   d. ordinal data

3. The following groups of infants with hypoxic respiratory failure are treated with a selective pulmonary vasodilator: (1) infants with meconium aspiration syndrome, (2) infants with idiopathic pulmonary hypertension, (3) infants with congenital pneumonia, (4) infants with congenital diaphragmatic hernia. Mean changes in right ventricular pressure are measured and compared using analysis of variance (ANOVA), which generates a p value of 0.01. The most appropriate interpretation of the result is:
   a. The null hypothesis of no difference among groups can be rejected.
   b. Each of the groups differs from each of the others.
   c. No statistically significant differences among groups are present.
   d. One of the first two groups differs from one of the second two groups.

4. In a preclinical test of a new surgical dressing, 7 out of 10 dressings in one group and 3 out of 10 dressings in the other fail after 30 minutes of water exposure, with a p value of 0.07 by chi square. The investigators are concerned about a type II error. The most appropriate response would be to:
   a. Repeat the analysis using a more stringent p value.
   b. Repeat the experiment using a larger N.
   c. Repeat the analysis using a Fisher exact test.
   d. Repeat the experiment using different surgical dressings.

5. An echocardiographic study compares two measures of left ventricular end diastolic volume. The two measures are compared in eFig. 79.15. The correlation coefficient (r) is 0.90. We can conclude that:



eFig. 79.15

Table 79.1

	NEC Present	NEC Absent
Test Positive	15	10
Test Negative	5	40

   a. 90% of the variance in one measure is described by the other measure.
   b. The two measures are strongly correlated.
   c. 95% of the variance in one measure is described by the other measure.
   d. Measure one is a better reflection of left ventricular end diastolic volume than Measure 2.

6. Investigators are testing a new serum cytokine panel to predict the development of necrotizing enterocolitis (NEC) among infants with feeding intolerance. The performance of the test in predicting Bell Stage II or above NEC is shown in Table 79.1. The sensitivity of the test is:
   a. 75%
   b. 60%
   c. 80%
   d. 89%

7. The specificity of the test in Table 79.1 is:
   a. 75%
   b. 60%
   c. 80%
   d. 89%

8. The positive predictive value (PPV) of the test in Table 79.1 is:
   a. 75%
   b. 60%
   c. 80%
   d. 89%

9. The negative predictive value (NPV) of the test in Table 79.1 is:
   a. 75%
   b. 60%
   c. 80%
   d. 89%

10. A proposed diagnostic test to predict the occurrence of a positive blood culture among infants with clinical signs consistent with sepsis is evaluated using a receiver operating characteristic (ROC) curve. The area under the ROC curve (AUC) is 0.60. We can conclude:
    a. Infants with a positive test have a 60% chance of having a positive blood culture.
    b. At a cutoff for positive that provides a sensitivity of 100%, the test specificity will be 60%.
    c. This is not likely to be a very useful test.
    d. At a cutoff for positive that provides a specificity of 100%, the test sensitivity will be 60%.

80 Epidemiology and Clinical Research Design

CARL T. D'ANGIO

Study Types

- Timing of data collection
  - *Retrospective* studies collect data after study events have occurred
    - Have drawback of being unable to decide which data will be available
    - Preclude being able to perturb the system; they are, by nature, *observational* rather than *experimental*
  - *Prospective* studies collect data while study events are occurring
    - Data collection can be planned up front
    - These studies can be either observational or experimental
- Types of observational studies (observe, rather than cause, outcomes) (Fig. 80.1)
  - *Case reports* are descriptions of individual cases
    - Advantages: useful for education and generating hypotheses
    - Disadvantages: may not be *generalizable* (one may not be able to draw conclusions about other cases from them)
  - *Case series* are a collection of cases, usually at least partially retrospective
    - Advantages: potentially generalizable
    - Disadvantages: lack a *control* group of unaffected patients
  - *Cross-sectional* studies are evaluations of the state of a population at a particular point in time
    - Advantages: can assess number of people with a disease or condition (*prevalence*), often in a large population
    - Disadvantages: provide no information about frequency of onset (*incidence*) or progression of disease (Fig. 80.2)
  - *Case-control* studies identify *cases* and compare them to *controls* without disease
    - Typically look retrospectively to evaluate previous exposures or conditions that may have preceded disease (and thus would be more common in cases)
    - Controls are often *matched* to cases (e.g., age or sex) to make the groups as similar as possible, other than the factors of interest
    - Advantages
      - Allow for oversampling of cases, which is particularly useful with rare conditions
      - Example: rather than following 1000 subjects to find 10 who develop a disease with an incidence of 1% over 10 years, one can find 100 cases and 100 healthy controls
    - Disadvantages
      - Retrospective by nature
      - Regardless of matching, cases and controls are likely to differ in ways other than an exposure of interest, making conclusions difficult
  - *Longitudinal studies* follow patients or test subjects over time (Fig. 80.3)
    - Many, but not all, longitudinal studies are observational
    - The simplest longitudinal studies follow a group of interest over time, an expanded version of a case series
  - *Cohort studies* follow cohorts of subjects, typically at least one group with an exposure or condition of interest and a control group without that characteristic
    - Can be solely retrospective, identifying exposures in the past and assessing outcome in the present
      - Example: follow-up of a cohort with a known perinatal exposure and a control group without it
    - Can be prospective (identifying exposed and control cohorts now and following for outcomes)
    - Can also have *before-after* or *sequential* design (identifying cohorts before and after the addition or removal of an exposure)
    - Example: incidence of necrotizing enterocolitis before and after a change from formula to donor milk feedings
    - Advantages
      - All types of cohort studies are likely to yield more complete longitudinal data than case-control studies
      - Prospective and before-after cohort studies are more likely to have complete information about exposure
    - Disadvantages
      - Difficult to study rare conditions
      - Uncontrolled differences between cohorts beyond exposure of interest may cloud results
    - Before-after studies may also be particularly affected by changes in other factors over time (known as *secular trends*)
- *Experimental* studies involve the investigator altering the conditions of study subjects—typically by administering a drug or an intervention (Fig. 80.4)
  - *Randomized controlled trials (RCTs)*, also called *clinical trials*, are the classic experimental study
    - Investigators assign participants *randomly* to an intervention or control (not receiving intervention) group and follow for outcomes of interest
    - Control circumstance may be a *placebo* (inactive compound) or the best current therapy

- Often *blinded* (participants and/or investigators do not know which subjects are receiving which intervention), as well
- Advantages
  - Random assignment distributes unknown baseline differences evenly between groups
  - Allow controlled investigation of a single factor on outcome, with a concurrent control group
  - Prospective nature allows investigators to collect research-quality data from outset of trial
- Disadvantages
  - Expensive
  - Lengthy
  - Investigators are manipulating conditions, potentially directly exposing participants to risks
- In crossover studies, investigators assign subjects to a condition (e.g., intervention) and then cross them over to another condition (e.g., no intervention), observing the results of both conditions. Can also cross over two groups (Fig. 80.5)
  - Advantages: all participants experience both conditions
  - Disadvantages
    - Sequence of conditions may *confound* (complicate interpretation of) results
    - Secular trends over time may confound results
- *Open-label* studies typically expose all subjects to an intervention
  - Sometimes it also refers to a controlled, but nonblinded, trial
  - Advantages: all subjects experience intervention
  - Disadvantages
    - Lack of control group
    - When subjects know they are receiving an intervention, they may experience changes not truly due to the intervention (*placebo effect*)
- Experimental studies can also be described by the *phase* of investigation (Table 80.1)

- Additional analyses of planned trials
  - *Post-hoc* analyses explore questions not initially planned for study
    - Advantages: allow investigators to adjust analyses based on findings
    - Disadvantages: findings may not be due to initial intervention
  - *Subgroup* analyses explore outcomes in parts of the study groups

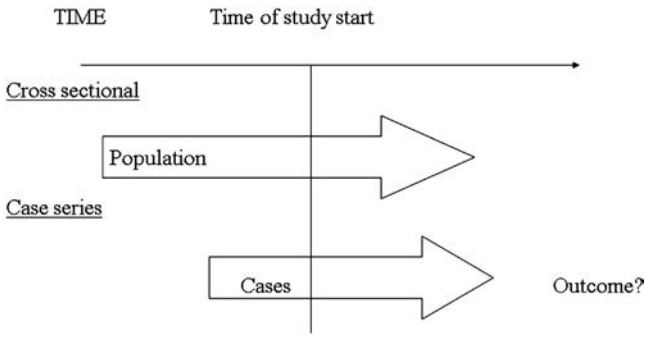


Fig. 80.1 Observational studies I. A case series reports accumulated cases of an illness. A cross-sectional study evaluates a condition in the population at one point in time (allowing estimates of *prevalence* (see Prevalence and Incidence, later).

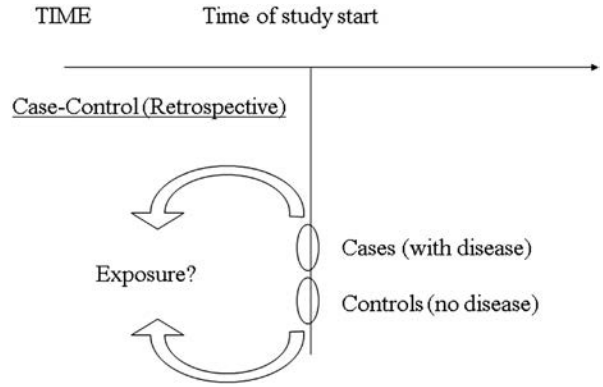


Fig. 80.2 Observational studies II: case-control study. A case-control study chooses cases (with disease) and controls (without disease) and looks retrospectively for exposures.

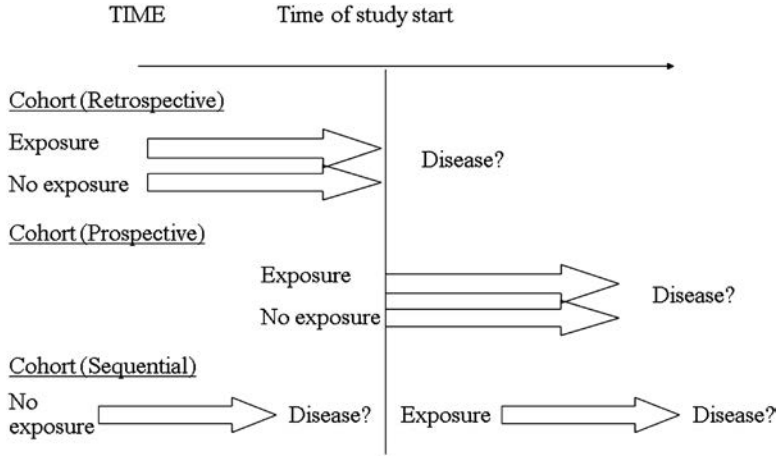


Fig. 80.3 Observational studies III: cohort studies. Cohort studies follow two (or more) cohorts of patients, with and without exposure, and assess the frequency of an outcome of interest. Cohort studies can be retrospective (cohorts chosen for known past exposure, which is relatively uncommon), prospective, or sequential ("before-after").

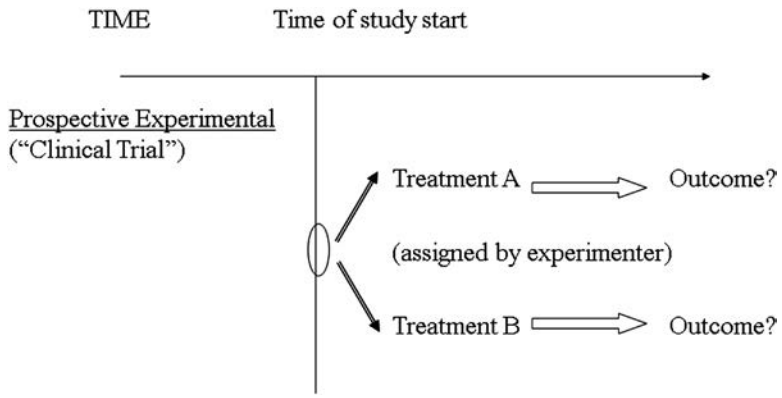


Fig. 80.4 Experimental study: randomized controlled trial. In an experimental trial, the investigator assigns participants to an intervention. Characteristics of randomized controlled trials can include random assignment to groups, control conditions (sometimes with a placebo), and double-blinding of investigators and participants to who is exposed to the intervention condition (see text in Study Types for description).

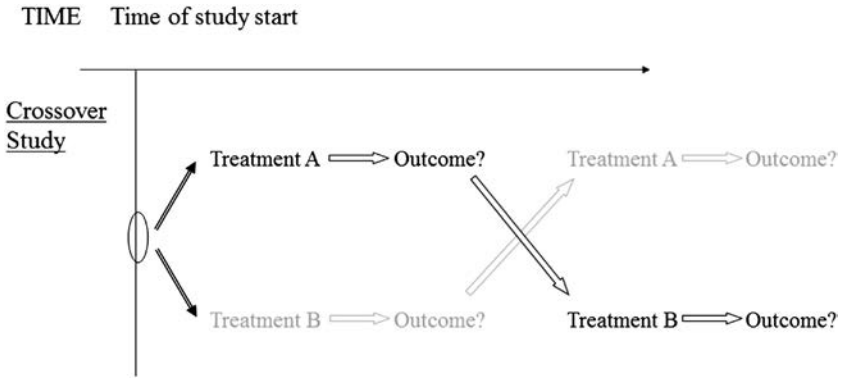


Fig. 80.5 Crossover study. Study participants are first exposed to one condition, followed by the other condition (e.g., control followed by intervention). Frequently, a second group (in gray) is exposed in the opposite order to control for the effect of sequence.

Table 80.1 Regulatory Terminology Describing Experimental (Particularly Drug) Studies

Phase I	Small safety trial, usually uncontrolled; does the drug do immediate harm?
Phase II	Larger, controlled safety and initial *efficacy* (effect in a research setting) trial
Phase III	Definitive, large, randomized controlled trial; studies drug efficacy
Phase IV	Postmarketing safety and *effectiveness* (effect in real world) surveillance

  - Advantages: allow investigators to explore effects in specific groups
  - Disadvantages: lower numbers raise risk of type II error, multiple comparisons raise risk of type I error
- Additional analyses are often best viewed as *hypothesis-generating*, rather than hypothesis-testing

Sources of Error in Clinical Studies

- Random error (e.g., type I or type II error, random misclassification of subjects)
- *Bias*: systematic, nonrandom error that leads to an erroneous conclusion about data
  - Example: in a cohort study evaluating intensive monitoring to prevent preterm birth, women at risk for preterm birth are incidentally more likely to be included in intensive monitoring arm, which leads to incorrect conclusion that intensive monitoring increases preterm birth
  - Can occur at any step in research process
  - Bias can be minimized by strict enrollment criteria, randomization, matching, blinding, clear outcome definitions
- *Confounding*: inappropriate attribution of effect to an independent variable, when, in fact, another variable, related both to the independent and dependent variables is responsible
  - Example: paroxysmal atrial tachycardia among neonatologists attributed to sleep deprivation, when, in fact, caffeine is the cause (Fig. 80.6)
  - Confounding can be minimized by
    - Distributing confounding variable equally between groups (e.g., randomization, *restriction* [choosing all subjects to have the confounding variable], or matching subjects on that variable, if it is suspected to be a confounder)
    - Using multivariate models (e.g., regressions) to identify effects of multiple independent variables
- *Effect modification*: another variable modifies the effect of an independent variable

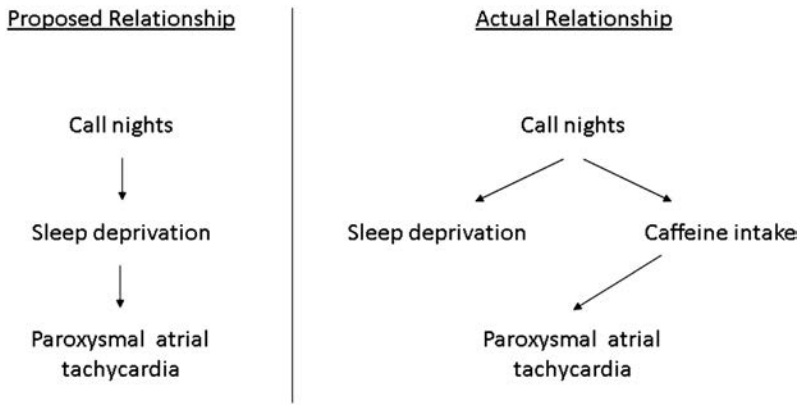


Fig. 80.6 Example of confounding. Although the initial hypothesis was that sleep deprivation during call nights caused paroxysmal atrial tachycardia, the actual causal pathway was through caffeine intake, which is related to sleep deprivation through call nights.

- Example: differing metabolism rates for a drug could modify drug toxicity in groups with differing enzyme alleles (slow metabolizers have more toxicity, regardless of dose, the independent variable being evaluated)

Causation Versus Association

- One variable is *associated* with another variable if the two vary in tandem
  - Association implies neither *causation* (A causes B) nor, if there is causation, the *direction* of causation (A causes B vs. B causes A)
- *Causation* is best tested in experimental studies; if one adds an intervention and an outcome changes, causation is likely
  - In observational studies, one can infer causation if certain things are true (e.g., temporal sequence, dose response, repetition in a different population, consistency with other studies, biologic plausibility), but it is harder to be certain (Box 80.1)

Incidence Versus Prevalence

- *Incidence* is a rate: events over a certain period of time in a defined population
  - Example: premature births per 1000 women per year
- *Prevalence* is number of cases in a population at a given time (i.e., a cross-sectional measure)
  - Example: Former premature infants currently alive in the US population

Screening

- In general, screening for a disease is most easily justified when the following are true (Box 80.2)
  - The combination of the test *accuracy* and disease prevalence will identify a suitable portion of people with the disease (*sensitivity*) with an acceptably low number of false-positives (*positive predictive value*)
  - With low disease prevalence, even an excellent test will produce far more false-positives than true-positives
- The burden caused by disease is high

Box 80.1 Factors Suggesting a Causative Relationship Between an Independent and Dependent Variable

1. Shown in experimental studies
2. Temporal sequence
3. Dose response
4. Repetition in a different population
5. Consistency with other studies
6. Biologic plausibility

Box 80.2 World Health Organization Criteria for Optimal Usefulness of Screening

1. The condition should be an important health problem
2. There should be a recognizable latent or early symptomatic stage
3. The natural history of the condition, including development from latent to declared disease, should be adequately understood
4. There should be an accepted treatment for patients with recognized disease
5. There should be a suitable test or examination that has a high level of accuracy
6. The test should be acceptable to the population
7. There should be an agreed policy on whom to treat as patients
8. Facilities for diagnosis and treatment should be available
9. The cost of screening (including diagnosis and treatment of patients diagnosed) should be economically balanced in relation to possible expenditure on medical care as a whole
10. Screening should be a continuing process and not a "once and for all" project

From Wilson JMG, Jungner G. *Principles and practices of screening for disease.* Geneva, Switzerland: World Health Organization; 1968. Report No.: Public Health Papers No. 34. Available from: <http://whqlibdoc.who.int/php/WHO_PHP_34.pdf>, accessed 10/28/2018.

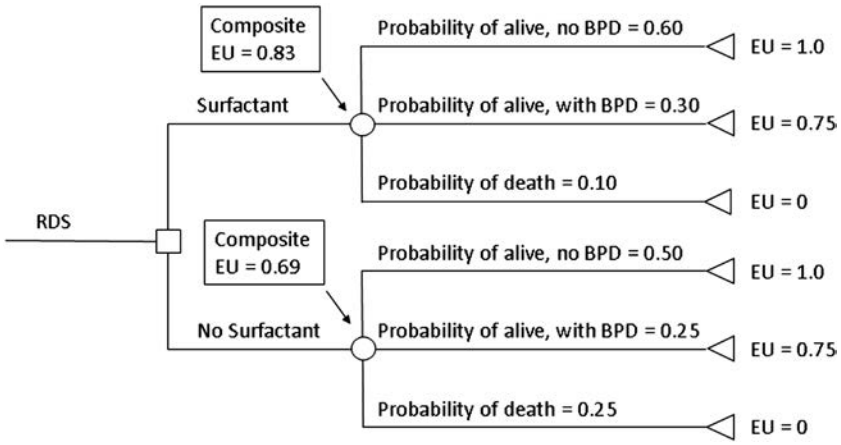


Fig. 80.7 Example of a decision tree for an imaginary population with respiratory distress syndrome (RDS). The tree attempts to quantify the values of outcomes when surfactant increases both survival and bronchopulmonary dysplasia (BPD). Based on the assumptions (which would be drawn from the literature and subjective judgments about value), the composite expected utility (EU) of surfactant use would be the sum of the probability of each outcome times the EU for each outcome, in this case (0.60 × 1.0) + (0.30 × 0.75) + (0.10 × 0) = 0.83, while the composite EU of no surfactant would be (0.50 × 1.0) + (0.25 × 0.75) + (0.25 × 0) = 0.69, implying that surfactant would be the preferred choice. See text for limitations of this analysis.

- The burden of the testing is low
- There is a *presymptomatic* state during which the application of an intervention will prevent the onset of symptoms or ameliorate the disease process
- The screen can be performed for a reasonable *cost*

- These factors form a *risk-benefit* analysis for a proposed screen
  - Example: as diagnostic accuracy of cystic fibrosis screening in the newborn improved with the addition of genetic techniques, and evidence accumulated that screening improves nutritional outcomes, the risk-benefit balance improved (lower risk, more benefit)

Decision Analysis

- A formalized method for evaluating the factors involved in clinical decision making
  - Attempts to identify the probability of each outcome, based on diagnostic or therapeutic decisions, and assign a value (*expected utility [EU]*) to that outcome
    - Example: assuming that life without disability would be the best outcome and death would be the worst, EU (life without disability) would be 1.0 and EU (death) would be 0 on a 0–1 scale
  - By combining outcome probabilities and EUs, a best decision is suggested
  - EU is most commonly depicted as *decision trees* with branch points for each decision (Fig. 80.7)
  - Advantage: quantifies and clarifies assumptions about probabilities and value of outcomes
  - Disadvantages:
    - Decision trees tend to be complex, limiting clinical utility
    - Even complex decision analysis uses only a limited number of variables, potentially omitting important factors
  - If assumptions for analysis are inaccurate, analysis may yield misleading results
  - Expected utilities are often subjective
    - Example: is alive with disability = 0.75 or 0.5, and who decides?

Cost Analyses

- Cost analyses are a form of decision analysis, measuring outcomes in terms of monetary cost
  - A *cost-benefit* analysis assigns a monetary value to each outcome and often seeks the outcome with the lowest costs
  - A *cost-effectiveness* analysis seeks to evaluate the cost to achieve an outcome
- Outcomes that involve survival are often measured in years of life gained or in *quality-adjusted* life years (*QALY*), which assign a numerical estimate of quality of life (much like EU, above)
- Costs can be estimated from multiple perspectives—the patient, payors, society, etc.—and the conclusions may differ depending on perspective

Sensitivity Analysis

- *Sensitivity analysis* measures the effect of alterations in assumptions on the outcome of an analysis; what if the data were different than the observed or projected values?
  - Example: in Fig. 80.7, a higher assigned EU of bronchopulmonary dysplasia (BPD) would increase the composite EU of surfactant use, while a smaller improvement in death would decrease the composite EU of surfactant use. Try varying the values to understand this
  - Like the initial data analysis itself, sensitivity analysis is limited by the validity of the assumptions (which may be entirely theoretical)

Qualities of Measurement

- Types of validity in measurement (i.e., does the test work?)
  - *Face* validity is a subjective impression of whether a tool is likely to measure what it is intended to measure
  - *Content* validity is the ability of a tool to measure all aspects of what it purports to measure

- *Criterion* validity is the ability of a tool to predict other characteristics associated with the measured characteristic, either at the same time (*concurrent* validity) or in the future (*predictive* validity)
- *Construct* validity implies a high correlation with other measures of the same characteristic
- *Internal* validity is the confidence that any proposed causal relationship is valid (a measure of experimental quality)
- *External* validity is the ability of the outcome of a study to be *generalized* to other similar populations

- *Reliability* refers to the reproducibility of the data (i.e., can the test be applied?)
  - *Interobserver* or *interrater* reliability is the degree of agreement between observers measuring the same thing
    - Interrater reliability is typically measured using the *kappa* (κ) statistic (which varies from 0 to 1); a high κ means high agreement between observers
  - *Internal consistency* is the degree of relationship among items on a test that purport to measure the same thing (e.g., among three items measuring depression)
    - Internal consistency is typically measured by *Cronbach alpha* (α), which can vary from 0 to 1; a high α means high internal consistency
  - *Test-retest* reliability is the ability of a tool to get the same result on a repeat measurement

- *Accuracy* is the ability of a tool to measure the true value of a quantity
- *Precision* is the ability of a tool to produce consistent results
  - Accuracy and precision are separate characteristics (Fig. 80.8)

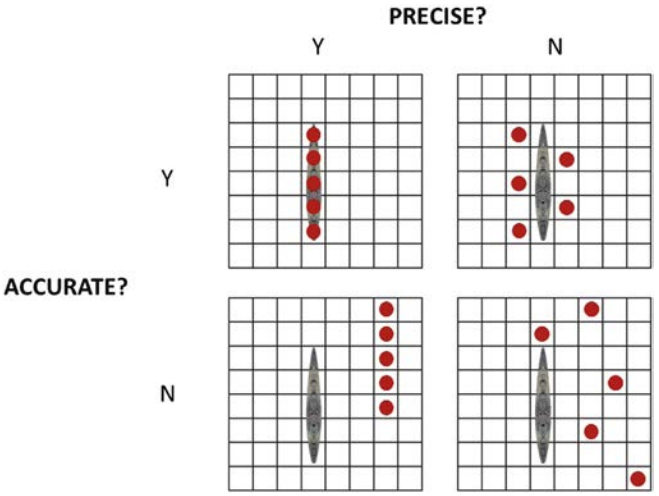


Fig. 80.8 Accuracy and precision. Accuracy is the ability of a measure (on average) to correctly reflect a true value. Precision is the reproducibility of the measure.

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Questions

1. An advantage of case-control over cohort studies is that they
   a. Can more accurately predict causation
   b. Are more likely to yield accurate exposure data
   c. Can oversample for rare outcomes
   d. Allow better assessment of relative risk

2. Investigators are considering a study to assess the effect of diuretic administration on the development of bronchopulmonary dysplasia. Compared to a case-control study, a randomized controlled trial would
   a. More strongly infer causation of any observed effect
   b. Be less resource intensive
   c. Involve fewer additional risks to subjects
   d. Be completed more quickly

3. Investigators studying the effect of a new, oral angiogenesis inhibitor on diabetic retinopathy in a randomized controlled trial are concerned about bias in participant-reported side effects. Methods to avoid this might include:
   a. developing a table of side-effect severity
   b. concealing treatment allocation from study participants and investigators
   c. using no treatment, rather than placebo, in the control group
   d. asking about side effects weekly rather than monthly

4. Investigators are concerned about confounding factors in a study of the effect of a new breast milk fortifier on feeding intolerance. They could best minimize the chances of missing confounding by
   a. Avoiding matching of control to case subjects
   b. Performing multivariate outcome analysis
   c. Performing an observational study
   d. Minimizing data collection about feeding-intolerance–related factors

5. Factors that make it more likely that an association between variables A and B in an observational study reflects A causing B include all of the following, EXCEPT
   a. Patients with higher exposure to A are more likely to develop B
   b. A affects an enzyme pathway known to produce B
   c. B always precedes A
   d. Several previous studies in different populations have shown an association between A and B

6. The most appropriate way to report the incidence of postneonatal sepsis in a pediatric population would be
   a. 0.05%
   b. Five cases per 10,000 children
   c. Five cases per year
   d. Five cases per 10,000 children per year

7. A factor that improves the suitability of a screening test includes:
   a. low sensitivity of the test
   b. presence of a presymptomatic period
   c. low prevalence of disease
   d. lack of effective treatment

8. Factors that increase the advisability of a course of action in decision analysis include:
   a. low likelihood of desired outcome
   b. unclear data about probability of outcome
   c. high expected utility of the likely outcome
   d. low agreement on value of expected utility of outcome

9. A neuroimaging scoring system to predict later neurodevelopmental impairment has been shown in previous studies to have good sensitivity and specificity, but is complicated to derive from the images. A second neuroradiologist is being added to the study team. An appropriate approach to ensuring that the data that will be generated are reliable would be to
   a. Assess the face validity of the scoring system
   b. Assess the internal consistency (Cronbach α) of the scoring system
   c. Assess the interrater reliability (κ) of the scoring system
   d. Assess the predictive validity of the scoring system

10. Which of the following tests is accurate, but not precise?
    a. Pulmonary arterial pressure is 50 mm Hg and echocardiographic estimates yield 48, 50, and 52 mm Hg
    b. Pulmonary arterial pressure is 50 mm Hg and echocardiographic estimates yield 58, 60, and 62 mm Hg
    c. Pulmonary arterial pressure is 50 mm Hg and echocardiographic estimates yield 23, 42, and 58 mm Hg
    d. Pulmonary arterial pressure is 50 mm Hg and echocardiographic estimates yield 42, 51, and 56 mm Hg

81 Applying Research to Clinical Practice

CARL T. D'ANGIO

Assessment of Study Design, Performance, and Analysis

- Assessing the details of design, performance, and analysis allow a clinician to determine the *internal validity* of a study (see Chapter 80)
- Selecting control groups
  - Control groups for case-control studies (Fig. 81.1)
    - Think of cases and controls as belonging to the same cohort (i.e., similar in all ways other than the presence of the disease or condition of interest)
    - Criteria for choosing controls
      - Representative of population from which cases are drawn
      - Should be sampled independent of exposure of interest (i.e., should not have any known factor that would make exposure more or less likely)
        - Example: in a study of risks for intraventricular hemorrhage, choosing a control group from another neonatal intensive care unit (NICU) with a differing rate of indomethacin prophylaxis would bias the exposure
      - The same exposure information as used for cases should be available
    - Methods to choose appropriate controls
      - Drawing from the same database or population as cases
      - Matching on important, potentially biasing or confounding factors, without "overmatching" in a way that inadvertently equalizes exposures
        - Example: matching on early respiratory support would equalize that exposure in a case-control study of bronchopulmonary dysplasia (BPD)
  - Control groups for cohort studies (Fig. 81.2)
    - Like controls in a case-control study, unexposed controls (also known as the *comparison group*) in a cohort study should be as similar to the exposed cohort as possible
      - Specifically, as similar as possible on possible confounding factors
      - Similar data about exposure and outcome should be available
    - Sources of comparison groups
      - An *internal* comparison group is drawn from the same population, but differs in exposure
        - Example: in a study of necrotizing enterocolitis (NEC), a group of premature infants from the same NICU differed only in exposure to human donor milk
      - An *external* comparison group is drawn from another group that is similar, other than the exposure
        - Example: in a study of NEC, a group of premature infants from another, similar NICU, differing only in the second NICU's use of human donor milk
      - The general population
- Surrogate endpoints (Fig. 81.3)
  - A *surrogate endpoint* is a study outcome that stands in for another, more definitive endpoint
    - Example: change in systolic blood pressure as a surrogate for lowering risk of stroke

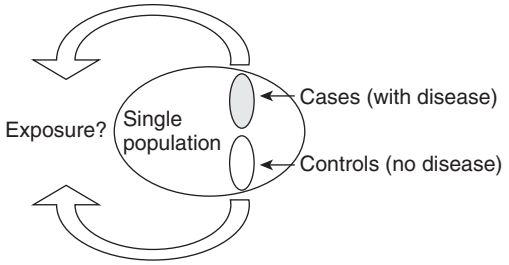


Fig. 81.1. Choosing controls in case-control studies. Controls drawn from the same population, differing only on presence of disease or condition of interest, are least likely to have other, confounding exposures. Matching helps to choose controls who are similar.

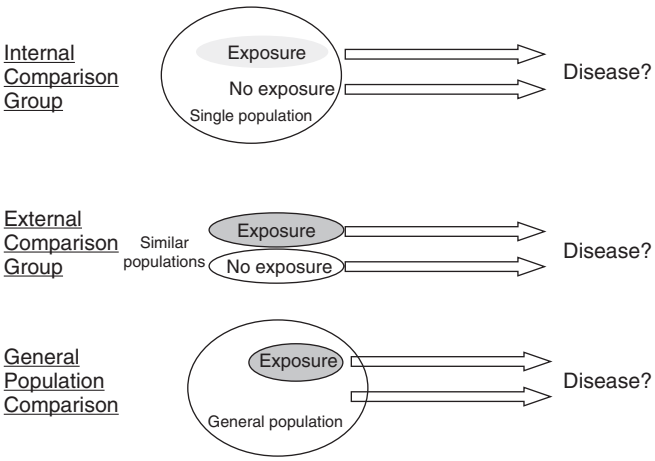


Fig. 81.2. Choosing controls for cohort studies. The control or "comparison" cohort should be as similar as possible to the exposed cohort and have the same information available. Internal (same population, differing only on exposure), external (similar population, differing only on exposure), and general population comparison groups are illustrated.

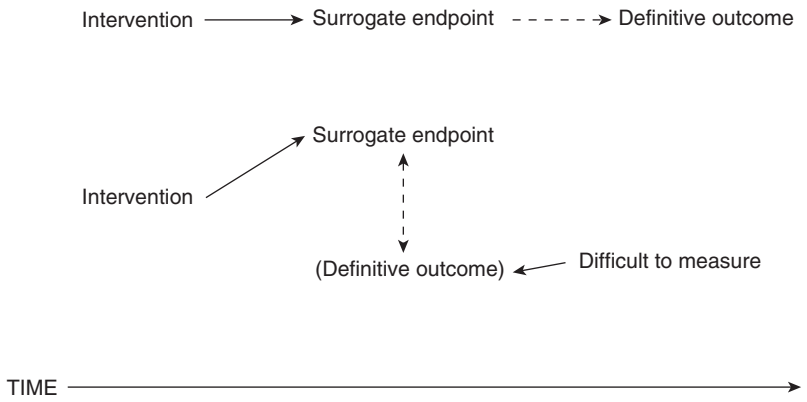


Fig. 81.3. Types of surrogate endpoints. An intermediate surrogate endpoint ("intermediate outcome") occurs before the definitive outcome and reliably (but nearly never perfectly) predicts the outcome *(top)*. Surrogate endpoints can also be outcomes that are highly correlated to a definitive outcome, measured at the same time, when the definitive outcome is difficult to measure *(bottom)*.

- *Biomarkers* (physical or other biological outcomes that are correlated with clinical outcomes) are a form of surrogate endpoints
- Why use surrogate endpoints?
  - A definitive clinical endpoint may only occur a long time after the intervention, making the waiting period for a definitive outcome prohibitive
  - The definitive clinical outcome may be prohibitively expensive
  - The definitive outcome may not be possible to measure
    - Example: in clinical studies aimed at improving intrapulmonary inflammation, it may not be safe to sample lung tissue
- What are the characteristics of a good surrogate endpoint?
  - The relationship of the surrogate should be stronger than mere correlation
    - A change in a good surrogate endpoint should predict a change in clinical outcome
    - Surrogates shown in clinical trials to predict clinical outcomes are called validated surrogate outcomes (Table 81.1)
  - Surrogate endpoints are ideally more timely, less expensive, and/or less risky than the definitive endpoint
- Disadvantages:
  - The relationship between surrogates and definitive outcomes is seldom guaranteed
  - Even some clinical endpoints usually considered definitive are actually surrogates for later outcomes, and may themselves be imperfect
    - Examples: BPD does not always predict longer term pulmonary outcome; 5-year cancer survival does not always predict cure

Table 81.1 Validated Surrogate Endpoints. A Partial List of Surrogate Endpoints That Have Been Shown in Clinical Trials to Predict Definitive Outcomes

Validated Surrogate Endpoint	Correlated Clinical Outcome
Systolic blood pressure (SBP)	Occurrence of stroke
Low density lipoprotein (LDL) cholesterol level	Occurrence of heart attack
Forced expiratory volume in 1 second (FEV1); *the amount of air that a person can blow out of his or her lungs in 1 second*	Improved breathing after taking medication for chronic lung disease such as asthma
Human immunodeficiency virus (HIV) viral load; *the amount of the human immunodeficiency virus that is present in the blood*	Development of an acquired immunodeficiency syndrome (AIDS) diagnosis

From US Food and Drug Administration <https://www.fda.gov/aboutfda/innovation/ucm512503.htm>, accessed 8/4/2017.

- *Intention-to-treat* analysis
  - In a randomized, controlled trial, some participants will not begin or complete treatment
  - The temptation is to include those participants in the control group (if never treated) or exclude them
    - However, participants who do not receive the full course of treatment are likely to differ systematically from fully treated participants (i.e., be biased) and will skew results if moved or eliminated
    - Solution: keep all participants in the treatment group in that group for analysis = intention-to-treat analysis
      - Less likely to result in skewed results than any amount of attempting to control for incomplete treatment
- Sample size
  - The larger the sample size, the less likely a study is to have a type II error (i.e., the less likely it is to miss a true difference between conditions)
    - Likelihood of type II error is known as the *β (beta) error*
    - Resistance to type II error is called study *power*
      - Study power is $1 - \beta$
        - Example: in a typical study, where a β error of 0.20 would be tolerated, the power would be $1 - 0.20 = 0.80 = 80\%$
    - So, larger sample size = better power
  - Power to detect adverse events also varies with sample size
    - Because some adverse events may be rare, even a well-powered randomized controlled trial may miss them (i.e., type II error in detecting adverse events)
    - Extremely large, postmarketing, *Phase IV* observational studies may be necessary to detect rare adverse events (see Chapter 80)

Table 81.2 Calculated Sample Size Given Differing Values for Difference, Standard Deviation, Type I Error, and Power

Difference					
Value Group 1	Value Group 2	Standard Deviation	Type I Error (α)	Power (1 – β)	Sample Size (Per Group)
20	30	15	0.05	0.80	36
20	*25*	15	0.05	0.80	142[a]
20	30	*30*	0.05	0.80	142[a]
20	30	15	*0.01*	0.80	53
20	30	15	0.05	*0.90*	48

The quantity varying in each row is in *italics*.
[a]Note that the effect size is the same for these two calculations (effect size = difference/standard deviation = 0.33)

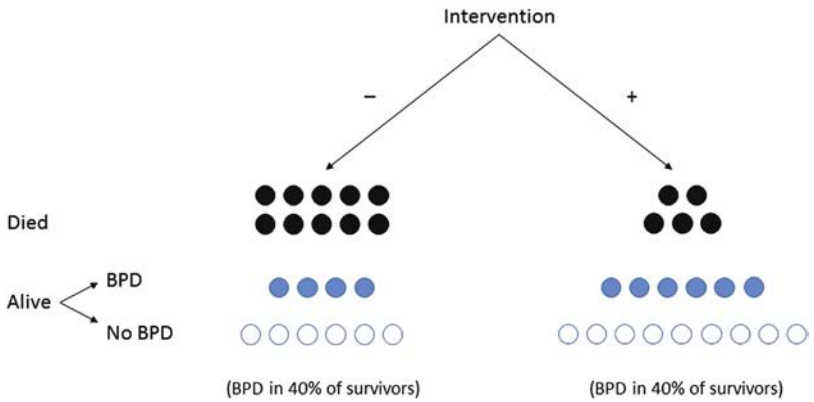
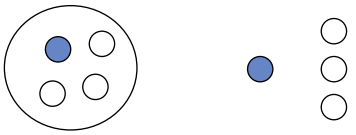


Fig. 81.4. Survival bias caused by competing outcomes. An imaginary intervention applied to extremely premature infants does not affect bronchopulmonary dysplasia (BPD) among survivors, but results in a marked drop in early death (which precludes development of BPD) from 50% to 25%. Although the absolute incidence of BPD is higher in the intervention group (30% vs. 20%), the incidence of the composite outcome of death or BPD is lower (55% vs. 70%).

- Calculating sample size for a study
  - Four parameters drive sample size
    - What difference would be *clinically meaningful*?
      - Choosing a small, meaningless difference (e.g., a 1% difference in respiratory distress syndrome (RDS) rates) inflates the sample size needlessly
      - Choosing too large of a difference (e.g., a 50% difference in RDS rates) raises the likelihood of type II error and missing a clinically meaningful difference
    - What is the spread of the data (variability in measurement)?
      - The wider the spread (e.g., standard deviation), the larger the sample size needed to detect the same difference
      - The relationship of difference between the group means to the standard deviation is known as *effect size*
        - Effect size = difference/standard deviation
          - If difference = standard deviation, effect size is 1
          - If difference = one-half standard deviation, effect size is 0.5, etc.
        - Smaller effect size needs a larger sample size
    - What level of type I error is acceptable?
      - Type I or α error typically set at 0.05
    - What level of type II error is acceptable?
      - Type II or β error typically set at 0.10–0.20
        - This gives a power of 80%–90%
    - Sample size calculators use these parameters to calculate necessary sample size (Table 81.2)

Assessment of Generalizability

- Assessing the details of generalizability allows a clinician to determine the *external validity* of the study (see Chapter 80)
- Even a well-performed study, with excellent internal validity, may not reflect what is happening in the general population
- Bias in enrollment or in who completes the study can imperil generalizability
  - *Selection* or *enrollment* bias involves choosing enrollees or cases that do not actually reflect the general population
  - *Survival* bias in who completes the study may result in outcomes that do not reflect the overall result of a therapy or condition
    - *Competing outcomes* can cause survival bias; for instance, early death would prevent evaluation of BPD at a later time (Fig. 81.4)
      - This is often handled with the *composite* outcome of "death or condition X"



Risk
1 out of 4
with disease
1/4 = 0.25

Odds
1 with disease to
3 without disease
1:3 = 0.33

Fig. 81.5. Risk versus odds. Risk is the likelihood that a member of the population will have a condition = $(n_{condition})/(N_{population})$. Odds are the likelihood that a population member will have a condition versus the likelihood that he/she will not = $(n_{condition}):(N_{no\ condition})$. In both examples, one out of every four members of the population will have the condition.

- *Ascertainment* or *information* bias, with less information available about one group, may prevent accurate assessment of outcomes
- Clinical trials have a tension between being *standardized* enough for the population, intervention, and outcome to be interpretable, but *practical* enough to represent the "real world" of clinical medicine, where these categories are not homogeneous
  - Overstandardization can limit generalizability
  - Practicality can limit interpretation
- The data source used to collect results can also influence external validity
  - Example: billing data (aimed at revenue) and a government database may yield differing estimates of disease prevalence
  - *Subjective* measures like diaries may be susceptible to the *Hawthorne* effect: the tendency of a group that knows it is being observed to act differently than if unobserved

Application of Information for Patient Care

- Likelihood ratios
  - Likelihood ratios are an application of *Bayesian* statistics, based on *Bayes theorem*
    - Rather than asking the question, "What is the evidence that this difference is not due to chance?" of traditional *frequentist* statistics, Bayesian statistics ask how new information changes one's prior impression of the probability of an event
  - To review, the likelihood ratio measures the change in the odds from pretest to posttest (see Chapter 79)
  - Clinicians usually think in terms of risk, not odds (Fig. 81.5)
    - Example: if the risk of a disease is 1/4 (0.25), the odds of having the disease is 1 yes to 3 no, or 1:3 (0.33)
    - To convert:
      - Odds = $(numerator_{risk})/(denominator_{risk} - numerator_{risk})$
        - If risk = 1/4, then odds = 1:(4–1) = 1:3 = 0.33
      - Risk = $(numerator_{odds})/(denominator_{odds} + numerator_{odds})$
        - If odds = 1:3, then risk = 1/(3 + 1) = 1/4 = 0.25

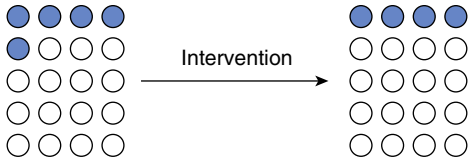


Fig. 81.6. Number needed to treat. In this example, if the intervention changes the likelihood of an outcome from 25% (5 out of 20) to 20% (4 out of 20)—20 people must be treated for one to experience a different outcome.

  - Likelihood ratios use odds because they are not bound by 1, while risk must be
    - Odds of 99:1 are still a risk of 0.99 (99%); risk is never >1 (100%)
  - Example of applying likelihood ratio
    - If the pretest probability of a diagnosis is 20% (0.20) and the likelihood ratio of a positive test (LR[+]) is 8, then posttest probability is
      - Pretest risk 0.20 → pretest odds 1:(5–1) = 1:4 = 0.25
      - Times LR(+) of 8 = 0.25 × 8 = posttest odds 2:1 →
      - Posttest risk 2/(1+2) = 2/3 = 0.67
      - Note: Posttest probability is not 0.20 × 8 = 1.6; that would be an impossibility
    - Or you can use a likelihood ratio nomogram, introduced in Chapter 79
- Risk reduction
  - To review, absolute risk reduction is the change in the raw numbers
    - A drop from 3/1000 to 2/1000 is an absolute risk reduction of 1/1000
  - Relative risk reduction is the percent change
    - A drop from 3/1000 to 2/1000 is a relative risk reduction of 33%
- Number needed to treat (NNT)
  - Calculates the number of patients who would need to be treated with a therapy for one patient to experience a positive effect
    - = 1/(absolute risk reduction)
  - Example: if a therapy reduces death from 25% to 20%, an absolute risk reduction of 5% or 0.05, then NNT = 1/0.05 = 20 (Fig. 81.6)
- Statistical significance versus *clinical importance*
  - If large numbers of subjects are treated, very small absolute risk reductions can be statistically significant, but may not be of any clinical relevance (or importance)
    - For instance, with about 1100 subjects per group, a study could expect to detect a drop in preeclampsia from 95% to 92% with a particular treatment, which is not likely to be very useful clinically

Using the Medical Literature

- Constructing a literature search
  - Specific, targeted questions will yield more specific and useful results
  - One approach is to construct a search question the way one constructs a research hypothesis, with the PICO format
    - **P**opulation (in this case, patients): in which patient group is the question being asked?

- **I**ntervention: what is the therapy?
- **C**omparator: compared to what? (another therapy? no treatment?)
- **O**utcome: what is the outcome of interest?
  - Example: among infants born at 23–24 weeks gestation does the use of caffeine in the first 14 days, compared to no caffeine therapy, change the incidence of death before discharge?
- For a nontherapeutic question, a modified format using **P**atients, **P**rognostic factors and **O**utcomes ("PPO") can be useful
- A refined question also simplifies the sorting of articles that return from a search
- Different literature databases cover different portions of the literature
  - Most offer the ability to refine a search, but ease of use varies

- Choosing a study type to answer specific sorts of questions
  - Accuracy of diagnostic tests
    - A cross-sectional study comparing a test to a gold standard
  - Benefits or harms of an intervention
    - Randomized controlled trial is the gold standard
    - Observational cohort studies are another possibility, but more subject to bias
    - For rare outcomes, a phase IV, postmarketing, extremely large registry study may be the best source of information
  - Prognosis of a condition
    - Longitudinal, long-term, observational study, either single group or traditional (with affected and comparison groups) cohort study
    - Administrative databases (insurance, state, or other large databases) may also provide long-term outcome data

Suggested Readings

Dawson B, Trapp RG, eds. *Basic & Clinical Biostatistics*. 4th ed. New York: McGraw-Hill; 2004. <http://accessmedicine.mhmedical.com/content.aspx?bookid=356&sectionid=40086278>.

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Questions

1. Neonatologists are interested in evaluating the effect of a new therapy on the development of hearing loss among infants with congenital cytomegalovirus (CMV). Which of the following would be the most appropriate surrogate endpoint for the effect of therapy on hearing loss diagnosed by behavioral audiometry at age 3 years?
   a. Brainstem auditory evoked response at birth
   b. Brainstem auditory evoked response at 6 months of age
   c. Death from CMV
   d. Cholestatic jaundice

2. Which of the following would allow a smaller sample size, but maintain the power of a study?
   a. Larger expected difference between groups
   b. Smaller acceptable alpha (α) error
   c. Larger variability within groups
   d. Smaller acceptable beta (β) error

3. A test to predict NEC among infants with feeding intolerance is determined to have a likelihood ratio (negative) of 0.5. Knowing that the prior probability of NEC in this population is 33%, this can be interpreted as meaning:
   a. The risk of having NEC drops by 50% among infants with a negative test.
   b. The odds of NEC among infants with a negative test are 0.5 times the prior odds.
   c. The likelihood of NEC among infants with a negative test is 50%.
   d. The odds of having NEC among infants with a negative test are 0.5 times those with a positive test.

4. A new preventive therapy for bronchopulmonary dysplasia (BPD) among high-risk infants reduces the need for supplemental oxygen at 36 weeks postmenstrual age from 70% to 50%. The relative risk reduction in this study is closest to:
   a. 20%
   b. 29%
   c. 1.4
   d. 0.7

5. A new intervention to prevent retinopathy of prematurity reduces the likelihood of disease from 40% to 33% in a group of infants. Which value is closest to the number needed to treat?
   a. 15
   b. 7
   c. 7%
   d. 3

6. A therapy for upper respiratory infection is tested in a large trial. It shortens the duration of cough in upper respiratory infection from (mean ± standard deviation) 48 ± 12 hours to 46 ± 15 hours, with $p = 0.02$. The result is
   a. Clinically important and statistically significant
   b. Not clinically important and not statistically significant
   c. Clinically important, but not statistically significant
   d. Not clinically important, but statistically significant

7. A cross-sectional study with comparison to a gold standard would be most appropriate for a study of the:
   a. Association of a rare disease with an earlier exposure
   b. Benefits and harms of an intervention
   c. Accuracy of a diagnostic test
   d. Prognosis of a condition

8. A case-control study would be most appropriate for a study of the:
   a. Association of a rare disease with an earlier exposure
   b. Benefits and harms of an intervention
   c. Accuracy of a diagnostic test
   d. Prognosis of a condition

9. A longitudinal cohort observational study, either with or without a comparison group, would be most appropriate for the study of the:
   a. Association of a rare disease with an earlier exposure
   b. Benefits and harms of an intervention
   c. Accuracy of a diagnostic test
   d. Prognosis of a condition

10. A randomized controlled trial would be most appropriate for a study of the:
    a. Association of a rare disease with an earlier exposure
    b. Benefits and harms of an intervention
    c. Accuracy of a diagnostic test
    d. Prognosis of a condition

82 Principles of Teaching and Learning

RITA DADIZ and EMER FINAN

Educational Theory

Adult learning theory: Knowles' theory of "andragogy" (the science of adult learning) is based on certain assumptions regarding adult learners (Table 82.1). These characteristics have implications for the learning environment and the teaching methods that educators incorporate.

MOTIVATIONAL STRATEGIES

- Intrinsic motivation: an internal drive to pursue learning
- Extrinsic motivators: external influences that impact pursuit of learning (e.g., grades)
- Adult learners are self-directed and learn best when intrinsically motivated
- Deci and Ryan note three needs that drive intrinsic motivation:
  - *Competence*: the need to gain skill or expertise in an area
  - *Relatedness*: the need to connect and share experience with others
  - *Autonomy*: the need to take responsibility for one's own learning
- Extrinsic motivators may negatively impact intrinsic motivation by reducing learner autonomy
- Strategies educators may use to motivate learners include:
  - Making learning "problem-centered" and relevant to learners' roles
  - Developing clear, focused objectives (learners often have many competing interests)
  - Engaging learners in developing their own learning plans and experiences
  - Creating a "safe" environment where learners can share their experiences and insights

Reflective practice: the process of continual development and modification of practice through ongoing reflection on learning

- The "reflective practitioner," as described by Schön, reflects "in action" during an event to draw on past experience and aid decision making. After the event, the practitioner reflects "on action" to deconstruct and analyze management and to refine approaches to future scenarios. Strategies to promote lifelong self-assessment and learning are encouraged (e.g., case-based reflections within a portfolio and group activities such as debriefing)
- Educators have a role in fostering learners' critical and analytical thinking through reflection. The educator should also model reflective practice within the clinical context

Effective learning environments: a comfortable physical space conducive to learning, plus

- A safe environment created with mutual respect between teachers and learners. Learners must feel personally and professionally safe to share opinions and ideas without negative consequences
- Learners' experiences and their contributions are valued and appreciated
- Learners are given autonomy and responsibility for their own learning
- Teaching is relevant with educational goals reflecting individual learner goals
- Educators engage learners through interactive approaches to learning that meet practical needs
- Educators recognize different learning styles and adapt their teaching to meet these needs

Hidden curriculum: the unspoken institutional culture and views of educators that are learned through observed behaviors and actions. While the formal curriculum is clearly outlined, the hidden curriculum may be experienced and modeled on a daily basis

- Medical educators and practitioners need to be aware of a hidden curriculum as it may conflict with formal curriculum (e.g., learners may be taught core elements of professionalism yet observe unprofessional team behaviors within the clinical environment)
- Role modeling and case discussions may have an important role in analyzing and addressing the hidden curriculum within medical training

ASSESSMENTS

- Educators assess learners' competence using different methods (Table 82.2). Progressing from levels one to four of Miller's triangle tests cognition (levels one and two) and application of knowledge and behavior (levels three and four)
- Assessments should be multimodal, reflect identified learning objectives, and appropriately target learners' level of training
- *Evaluations and feedback* are both forms of assessments given for different purposes:
  - Evaluation: assignment of a grade or the comparison of a learner's performance to others (summative)
  - Feedback: constructive appraisal of learner performance to reinforce effective behaviors and help improve ineffective behaviors (formative)

- Characteristics of effective feedback
  - *Timely*: limits recall bias and helps learners make performance improvements in real time
  - *Nonjudgmental*: provides objective descriptions of learner behaviors to avoid the association of the educator's opinion with the learner's value or worth, which could demoralize and deactivate learning
  - *Focused on changeable behaviors or attainable goals*: imparts constructive feedback on behaviors or goals that learners can target for improvement, rather than on the person
  - *Specific and based on observed behaviors*: uses concrete examples evidenced in the learner's own practice to help the learner recognize and understand what is being discussed
  - *Focused on positive consequences of change*: balances positive and negative feedback to reinforce desirable behaviors and opportunities for change to target improvements in behavior
- Types of feedback
  - Formative feedback aims to provide learners with ongoing input while learning is occurring to help them identify areas for improvement in their knowledge or skills
    - Opportunities for providing formative feedback: periodic meetings between a learner and an educator, a review of learner's reflective journals/portfolio, homework exercises that are reviewed during class discussions
  - Summative feedback is a final evaluation that aims to measure how well learners have achieved a goal or competency in knowledge and skills and some endpoint
    - Common summative evaluations: end-of-rotation clinical evaluations, specialty board certification exams, dissertations, peer-reviewed manuscripts, and grants

Table 82.1 Adult Learning Theory

Characteristics of Adult Learners	Implications for Educators
Self-directed, independent	▪ Educators need to engage learners in identifying their own needs; provide autonomy and responsibility
Adults come with a vast array of previous experience	▪ Educators and learners need to appreciate the experience that each learner brings to create a respectful learning environment ▪ Educators and learners should recognize how opinions may be influenced by prior experiences ▪ Diversity in past experiences creates a rich environment for learning, but educators may need to target teaching at different levels
Readiness to learn linked to "social roles"	▪ Learning objectives need to be relevant to learners' needs, practical and applicable to their current roles and responsibilities
Knowledge acquired is generally applied more rapidly	▪ Adults often have a need for problem-centered, goal-oriented approach to learning
Motivation to learn	▪ Educators need to respect adults' internal motivation and provide learners with autonomy and responsibility for their learning

TEACHING METHODS

- A variety of teaching methods can be adopted by medical educators, depending on teaching context and content to be covered (Table 82.3). All teaching sessions should incorporate:
  - Effective planning
  - Knowledge of learners and their needs
  - Clear, predetermined learning objectives
  - Content relevant for learners
  - Interactive learning
- Individuals have different preferred learning styles. Fleming's VARK model describes the main learning styles: visual, auditory, reading/writing, and kinesthetic.
- Educators should try to understand and accommodate different learning styles (e.g., visual learners appreciate visuals such as diagrams, pictures, and video, while kinesthetic learners appreciate "hands-on" teaching, etc.).
- Learners should be encouraged to reflect on their individual learning style and integrate complementary study aids to optimize learning.

Table 82.2 Miller's Triangle Describing Levels of Learner Assessment

What Is Being Assessed?	Assessment Methods	Strengths	Weaknesses
Knows (level 1) What is the learner's knowledge?	▪ Multiple-choice exams	▪ Represents the foundation of developing competence ▪ Assessments are not labor intensive	▪ Does not assess application of knowledge in the clinical environment
Knows How (level 2) Does the learner know how to use the knowledge?	▪ Case presentations ▪ Short answer questions ▪ Oral exams	▪ Measures learners' theoretical approach to patient care	▪ Does not assess application of knowledge in the clinical environment
Shows How (level 3) How well does the learner perform the skill?	▪ Simulations ▪ Objective structured clinical exams (OSCEs)	▪ Shows how new knowledge and skills are used in an artificial environment	▪ Measures behaviors, but not how well concepts and theories were learned ▪ The reliability, validity, and feasibility of high-stakes assessment tools need testing
Does (level 4) How well does the learner apply knowledge and perform skills in practice?	▪ Clinical practice	▪ Assesses learners in the "real world" setting	▪ Assessments can be time intensive ▪ May need 360 evaluations to perform a comprehensive assessment

Teaching Preparation and Planning

- Needs assessment: process of determining core requirements along with gaps in learners' knowledge, skills, and attitudes. This process facilitates the formulation of individualized learning plans, curricula, or learning collaboratives
  - Methods: surveys, focus groups, exams, performance in clinical rotations, critical clinical incident reviews, etc.
- Goals: long-term outcomes that learners work toward achieving in their continuing professional development
- Learning objectives: short-term, concrete steps taken to achieve a goal
  - Well-formulated learning objectives are *specific*, *measurable*, and *outcome-based*, stating what the learner should be able to do after a learning activity

Table 82.3 Strengths and Challenges of Teaching Methods

Teaching Method	Strengths	Challenges
Lecture	▪ Can expose large group of learners to information ▪ Efficient in the delivery of core theory/content, especially after learners are able to think through concepts beforehand	▪ Passive learning with limited interaction between educator and learner ▪ Difficult to assess learners' understanding of content ▪ Cannot cater to individual learner needs ▪ Unable to draw on learner experience
Small Group Discussion	▪ Allows for more opportunity for interactive discussion and learner engagement ▪ Can draw on learner experiences ▪ Allows for exploration of learners' critical thinking, application of knowledge ▪ May be more conducive to "problem-centered" approach	▪ Enhances understanding of core concepts through discussion ▪ May require many facilitators and a higher teacher:learner ratio
Bedside Teaching	▪ Highly relevant, "problem-centered" ▪ Allows for the opportunity to explore critical thinking and application of knowledge ▪ Experiential learning (i.e., opportunity to learn through reflecting on practical experience) ▪ Engages patients and families	▪ Time pressures; need to adopt focused teaching methods (e.g., "one-minute preceptor") ▪ Engages patients and families ▪ Learners may be intimidated by the presence of families or other health care professionals
Simulation and Debriefing	▪ Experiential learning ▪ Engaging and interactive learning environment ▪ Opportunity to apply knowledge and practice behaviors, both individual and team-based ▪ No patient safety concerns: learners encouraged to make errors in simulation setting ▪ Explicitly includes reflection on experience and behaviors to facilitate learning ▪ Can control "clinical" exposure and learning environment	▪ May be costly and require trained facilitators, instructors, technical operators ▪ May require many facilitators and a higher teacher:learner ratio

Table 82.4 Kirkpatrick's Model for Evaluating the Effectiveness of Training

What Is Being Evaluated?	Evaluation Methods	Strengths	Weaknesses
Reaction (level 1) How did learners react to the educational activity?	▪ Surveys ▪ Focus groups ▪ Verbal feedback ▪ Learner evaluations	▪ Educators can use feedback to modify training so that learners are more motivated to participate again ▪ It is quick and easy to obtain this data	▪ Activities that are reviewed unfavorably are not necessarily ineffective educational sessions ▪ There may be reporting bias if evaluations are completed on a voluntary basis
Learning (level 2) What knowledge and skills did learners learn from the educational activity?	▪ Pre- and posttraining tests ▪ Oral exams	▪ Measures knowledge acquisition and learners' theoretical approach to patient care	▪ It is easier to measure knowledge than skill acquisition ▪ Improved knowledge does not equate improved patient care ▪ Knowledge attrition can occur over time; immediate assessment after an educational activity may not predict future knowledge retention
Behavior (level 3) How did learners change their behaviors in the learning or clinical environment after the educational activity?	▪ Simulated patient events ▪ Observed behaviors during patient care ▪ Peer and 360-degree evaluations	▪ Shows how new knowledge and skills are used in the work environment	▪ Learners must be intrinsically motivated to apply new knowledge and skills in the learning or clinical environment ▪ Outcomes depend on environmental conditions that must be conducive to change (e.g., collaboration from others, etc.)
Results (level 4) What are the patient care and/or organizational outcomes that resulted from the educational activity?	▪ Quality assurance reviews ▪ Chart audits ▪ Patient satisfaction ▪ Staff retention	▪ This is the "bottom line" outcome ▪ Positive outcomes can foster organizational change	▪ Outcomes depend on environmental conditions that must be conducive to change ▪ Improvements in patient care and at the organizational level are harder to measure

  - Serve as an educational guide for both learners and educators
  - Help learners and educators choose the most appropriate educational methods to accomplish the learning objectives
  - Provide educators with a guide for evaluating the effectiveness of educational methods Use *measurable* verbs to convey the educational action item:
    - Measurable verbs: identify, demonstrate, calculate, develop, assess, etc.
    - Nonmeasurable verbs: know, understand, improve, appreciate, etc.
- Assessments: educators acquire different types of information to determine: (1) how learners will be assessed, and (2) the effectiveness and impact of their training programs (Table 82.4)

Suggested Readings

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Questions

1. You have been supervising a medical student in the newborn nursery and observed him speaking to a mother about her daughter's jaundice. After the encounter, you decide to provide him with formative feedback. Which of the following statements are consistent with the principles of providing effective feedback?
   a. "You did a great job talking to the mother about jaundice."
   b. "When the mother asked how long her daughter needed to stay in the hospital, you estimated 1–2 days. I also suggest letting her know what her baby should accomplish before going home so that she understands the discharge criteria, just in case her baby does not respond to phototherapy as anticipated."
   c. "Before we speak to the next mother, please practice these communication skills with another person."
   d. b and c only.
   e. All of the above.

2. You are preparing a workshop on developing a quality improvement project for a small group of pediatric residents. As you think about what you would like the residents to learn, you remember that learning objectives should have all of the following characteristics *except*:
   a. Be specific in content, such as, "To list three ways statistical process control charts may be used in quality improvement initiatives."
   b. Identify the goals of learning, such as, "To understand the principles of quality improvement."
   c. Detail how learning would be measured, such as, "To describe the pros and cons of using different quality improvement models such as PDSA, Six Sigma, and CQI."
   d. Provide an outcome measure, such as, "To develop a quality improvement project using the PDSA cycle."
   e. None of the above; all are characteristic of learning objectives.

3. You want to make this workshop an effective learning opportunity. As you are developing the plan for the session, you remember there are some key concepts in creating an effective learning environment for adults. An effective learning environment comprises:
   a. A very bright room so that learners stay alert and engaged.
   b. Clear learning objectives, relevant to learners needs.
   c. A safe, interactive environment where learner input is encouraged.
   d. b and c only.
   e. All of the above.

4. As a neonatal fellow, you are responsible for teaching residents in a number of settings from lectures to simulation-based training. One of the pediatric residents is interested in learning more about various teaching strategies and asks about the benefits and challenges of each method. All of the following are true *except*:
   a. Lectures allow the delivery of large amounts of teaching material in an efficient manner.
   b. Small group discussions create a more interactive learning environment.
   c. Bedside teaching enables the facilitator to explore application of learners' knowledge.
   d. Simulation-based training enables standardization of learner exposure.
   e. Small group discussions require a lower facilitator: learner ratio than lectures.

83 Ethics in Research

CARL T. D'ANGIO

Background

- Three landmarks:
  - *The Nuremburg Code* (Box 83.1) promulgated in 1949 during the trial of Nazi physicians and scientists for war crimes committed against concentration camp prisoners.
    - Enunciated 10 components of ethical human subjects research.
  - *The Belmont Report* (Table 83.1) issued in response to continued failings of the US research community in obligation to protect research participants, including the *Tuskegee syphilis study*, which followed African-American men with untreated syphilis long after treatment became available.
    - Laid out three ethical *principles* and their application to research
      - *Respect for persons:* an individual's *autonomy* to make decisions independently, applied in appropriate use of *informed consent*
      - *Beneficence* (and some add its twin, *nonmaleficence*): doing what is good for other people, applied through *assessment of risks and benefits*, minimizing risks
      - *Justice:* treating people in equal situations equally, applied by the equitable *selection of subject*, avoiding having one group of people bear risks in finding information on or treatment for a disease that affects many groups
  - *The "Common Rule"* (45 CFR 46) issued by the US Department of Health and Human Services (DHHS) in 1991, governs human subjects research across nearly all federal agencies.
    - Has been updated several times since, recent major revision in 2018

Box 83.1 Ten Components of the Nuremberg Code, 1949

1. Voluntary consent
2. Fruitful results for good of society, not otherwise obtainable
3. Well designed
4. Avoid suffering and injury
5. No intended death
6. Benefit should outweigh risk
7. Proper preparation for ill effects
8. Conducted by scientists
9. Voluntary withdrawal
10. Ability of investigators to terminate for harm

National Institutes of Health. Trials of War Criminals before the Nuremberg Military Tribunals Under Control Council Law: The Nuremberg Code. Washington, D.C.: US Government Printing Office; 1949:10(2):181–182. Available at <https://history.nih.gov/research/downloads/nuremberg.pdf>.

- Animal research is also governed by a wide variety of federal regulations.
  - The Department of Agriculture, as well as other agencies, enforces these regulations.
- Research misconduct is policed by several federal agencies, including the DHHS's Office of Research Integrity (ORI) and Office of Human Research Protection (OHRP).

Conflicts of Interest and Commitment

- *Conflicts of interest* can either consciously or subconsciously influence the way a researcher views, analyzes, and presents data.
  - One definition: "A divergence between an individual's private interests and his or her professional obligations" (American Thoracic Society) (Fig. 83.1)
  - Can be difficult to identify and depends heavily on individuals identifying and self-reporting them
  - Some commonly identified conflicts of interest
    - Financial conflict
    - Intellectual conflict
    - Personal/relationship conflict
    - Physician-researchers also have an inherent conflict of "fiduciary" (responsibility for the welfare of others) roles between individuals as patients and research subjects
- Methods for managing conflicts of interest
  - Avoiding them
  - Disclosure: allows reviewers, funders, scientific community to decide conflict
  - Management
    - Reducing, modifying, or eliminating one's interest to decrease/remove conflict
    - Modifying one's role in research
    - Third-party oversight of the program to manage conflicting interests
  - When in doubt, recusal from discussion or study performance
- Conflict of commitment

Table 83.1 Components of the Belmont Report, 1979

Ethical Principle	Application to Research
Respect for persons (autonomy)	Informed consent
Beneficence	Assessment of risk and benefits
Justice	Selection of subjects

Summarized from: *The National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research.* Ethical Principles and Guidelines for the Protection of Human Subjects of Research (The Belmont Report). April 18, 1979.

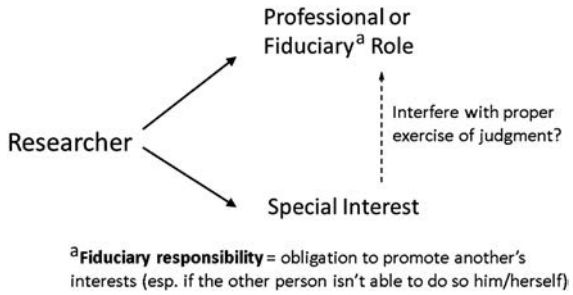

Fig. 83.1 Conflict of interest. A conflict of interest occurs when a personal or special interest interferes with the ability of a person to exercise a professional or fiduciary duty. As noted in the chapter text, special interests can be monetary or nonmonetary.

- Researcher is dedicating time to personal or other activities (either for pay or not) that may detract from his or her primary responsibility to an institution

Misconduct and Professionalism in Research

- According to the US ORI, "Research misconduct means fabrication, falsification, or plagiarism in proposing, performing, or reviewing research, or in reporting research results" (definitions below modified from ORI).
  - *Fabrication* is manufacturing data or results that do not exist.
  - *Falsification* is the manipulation of materials, equipment, processes, or data to alter the representation of research results.
  - *Plagiarism* is representing another's words, images, or ideas as one's own, without giving appropriate credit.
- Research misconduct "does not include honest error or differences of opinion" (ORI)
- Authorship on scientific publications
  - The International Committee of Medical Journal Editors (ICMJE) suggests four criteria that all authors must meet to be listed on a publication.
    - "Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work."
    - "Drafting the work or revising it critically for important intellectual content."
    - "Final approval of the version to be published."
    - "Agreement to be accountable for all aspects of the work."

Definitions of Research With Human Subjects

- Under US federal research regulations, *research* is considered "a systematic investigation … designed to develop or contribute to generalizable knowledge" (45 CFR 46.102).
- *Human subjects research* is research conducted on "a living individual about whom an investigator … obtains (1) data through intervention or interaction with the individual, or (2) identifiable private information" (45 CFR 46.102).
- Humans taking part in research are interchangeably called *subjects* or *participants.*

The Role and Responsibilities of an Institutional Review Board

- An *Institutional Review Board (IRB)* is a group, established according to federal rules and regulations, that is charged with reviewing and monitoring human subjects research
  - Can approve, require modifications of, or disapprove proposed research
- Certain research activities are *exempt* from IRB review (i.e., do not have to be reviewed, but the decision of whether this is true still rests with IRB)
  - Some educational, interview, and survey research
  - Use of existing records or specimens, provided that subjects are not identifiable
  - Some consumer preference testing
  - 2018 updates to exemptions include:
    - Scholarly (e.g., historical) research, oral history, public health surveillance, benign behavioral interventions, law enforcement/intelligence activities
    - Identifiable survey research and use of identifiable biospecimens, with a new level of "limited" IRB review
- Analysis of risks and benefits
  - IRBs are charged with evaluating risk and determining that:
    - Risks to subjects are minimized
    - Risks are reasonable in relation to anticipated benefits to the subjects or society
  - Risks can be thought of in terms of both *probability* and *magnitude*
  - *Minimal risk* applies to a specific category of research involving research-specific risks that are "not greater … than those ordinarily encountered in daily life …" (45 CFR 46.102)

Further Application of Research Ethics to Human Subjects

- *Clinical equipoise* describes a state of uncertainty in the medical profession about the balance of benefits and harms of a proposed therapy.
- The *therapeutic misconception* or *therapeutic fallacy* is a belief on the part of a patient (and sometimes his/her provider) that an experimental treatment being applied as part of research is for the direct benefit of the patient.
- Ethical considerations in study design
  - "Scientifically unsound research on human subjects is *ipso facto* unethical in that it may expose subjects to risks or inconvenience to no purpose." (Council for International Organizations of Medical Sciences)
  - *Placebo* controls are often necessary to measure the *placebo effect* of a research subject knowing he/she is receiving an agent.
  - *Deception* is sometimes permissible, usually in psychology research, when the value of the research is high, there are no alternatives, and subjects are *debriefed* (have deception revealed) afterward.

- As is clear from the formative documents of research ethics, minimization of harms is a necessary prerequisite for ethical research.
- *Privacy* (right to be left alone) and *confidentiality* (right not to have your information shared) are protected by both federal research rules and the Health Insurance Portability and Accountability Act (HIPAA).
  - Privacy concerns generally prevent researchers without a bona fide relationship to a patient from contacting the patient directly for recruitment.
  - Confidentiality concerns generally prevent the dissemination of identifiable data without a person's consent.
- *Data and safety monitoring boards* are independent groups of experts (usually in the condition being studied and in statistics and trial design) charged with monitoring the conduct of a study.
  - Monitor data integrity, safety, and accumulating efficacy information
  - Often have access to group-specific data during the trial in blinded trials
  - Can make recommendations to the study investigators or sponsor to alter, suspend, or terminate a study, based on findings

Consent, Assent, and Permission

- Definitions
  - *Consent* is an autonomous, voluntary decision made by someone with *decisional capacity* (i.e., possesses the understanding necessary to make a decision) to receive a treatment or participate in research.
  - *Assent* is the agreement of a person without full decisional capacity (e.g., a child or an elder who has lost capacity) to a decision made by someone else to have the person receive a treatment or participate in research.
    - Infants and people with advanced dementia cannot assent.
  - *Permission* is what someone with a legal responsibility for someone else (e.g., parent, guardian) gives for that person to receive a treatment or participate in research.
    - Has many characteristics of consent but is more limited than consent
- Consent (and assent and permission) for research is expected to be *informed.*
  - Ethically, the person needs all the information necessary to make a decision.
  - Practically, the person needs to understand the purpose, procedures, risks and potential benefits, and context of the research.
  - Consent is a process, rather than merely a form, but regulations specify the information that should be present in a consent form (Box 83.2).
- The voluntary nature of consent can be undermined by inappropriate consent practices.
  - *Undue influence* or *undue inducement* is the application of positive enticements to participate in research.
  - *Coercion* is the actual or implied threat of harm if a potential subject does not participate.

Research in Vulnerable Populations

- Populations can be *vulnerable* due to lack of capacity (e.g., children, the mentally disabled, the elderly), lack of voluntariness (e.g., prisoners), risk of undue influence (e.g., economically or educational disadvantaged or desperately ill), or other factors (Fig. 83.2).
- Federal regulations provide extra protections for vulnerable groups
  - Pregnant women, fetuses, and nonviable newborns (45 CFR 46 Subpart B)

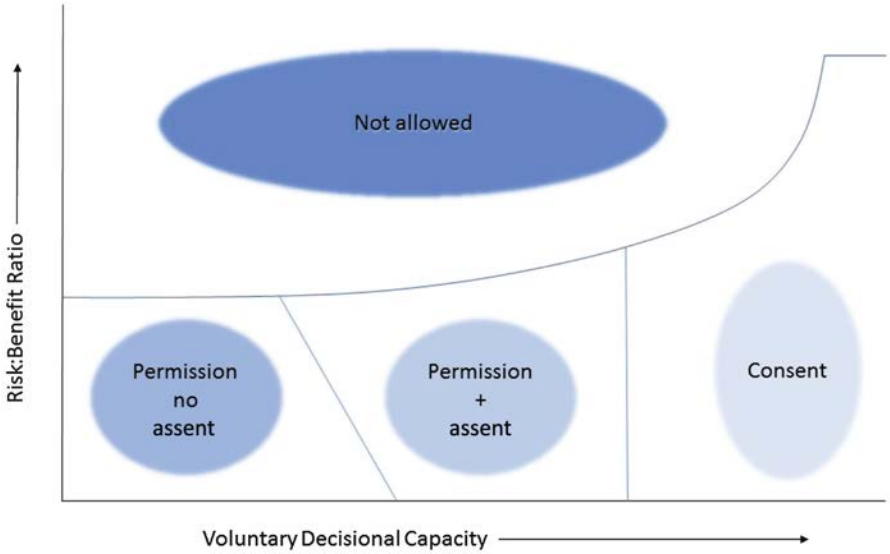

Fig. 83.2 Relationship among risk, benefit, and decisional capacity in research consent/permission. A person with full, voluntary, decisional capacity may consent to nearly any research (although note that research with very high risk and no benefit is not approvable). As the capacity to make voluntary, fully informed decisions diminishes (e.g., prisoners), some types of research are not allowed. People with limited or no decisional capacity (e.g., children or infants) depend on permission from others, with or without assent. Note that in some cases with a high chance of benefit to the individual, permission may override assent among persons who would otherwise be asked to assent.

Box 83.2 Required Components of Consent Forms

1. Identification as research
2. Purpose of study
3. Study procedures
4. Risks
5. Potential personal benefits
6. Alternatives to participation in research
7. Confidentiality
8. Compensation for injury
9. Contact information for investigators
10. Voluntary nature of participation

2018 changes to the Common Rule require more specific information in consent forms about reuse or dissemination of private information and biospecimens, and information about whether results will be shared with the research subject.

Summarized from 45 CFR 46.116, Federal Policy for the Protection of Human Subjects, US Department of Health and Human Services.

- Prisoners (45 CFR 46 Subpart C)
- Children (45 CFR 46 Subpart D); see next section

Research in Children

- Children are vulnerable due to their inability to provide informed consent for research.
  - As noted, parents instead provide permission—as in therapy, the overall criterion in deciding to provide permission is the *best interests* of the child, generally understood as minimizing risks and maximizing benefits.
  - When appropriate, children must give assent.
- Although *child* generally refers to someone below the age of majority (18 years old), specific definitions are dependent laws of the locality and specifics of proposed intervention.
- Allowable research in children (Table 83.2)
  - Children may generally participate in research that is of minimal risk (same definition as with adults) or has the prospect of direct benefit for the child, even if the risk is high (e.g., cancer chemotherapy trials).
  - Children may also participate in research that represents a "minor increase over minimal risk" and does not hold the prospect of direct benefit, but review and permission requirements are stricter.
  - Children are generally not allowed to participate in research that poses significant risks but does not offer a reasonable prospect of direct benefit to the child (see "best interests," above).

Table 83.2 Categories of Research in Children

Category	Description	Special Conditions
§46.404	Research not involving greater than minimal risk	None
§46.405	Research involving greater than minimal risk but presenting the prospect of direct benefit to the individual subjects	Risks no greater than alternative approaches
§46.406	Research involving greater than minimal risk and no prospect of direct benefit to individual subjects, but likely to yield generalizable knowledge about the subject's disorder or condition	Risk must be only a "minor increase over minimal risk" Two-parent consent required
§46.407	Research not otherwise approvable which presents an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of children	Permission of Secretary of Health and Human Services required

Descriptions are drawn verbatim from 45 CFR 46, Federal Policy for the Protection of Human Subjects, US Department of Health and Human Services.

Suggested Readings

Code of Federal Regulations Title 45, Part 46 (45 CFR 46, "The Common Rule"), Protection of Human Subjects. Subpart D – Additional Protections for Children Involved as Subjects in Research. https://www.hhs.gov/ohrp/regulations-and-policy/regulations/45-cfr-46/index.html#subpartd.

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Questions

1. The Belmont Report outlined three principles that are applied to clinical research. Each of the following represents an application except:
   a. Informed consent
   b. Subject selection
   c. Data analysis
   d. Assessment of risks and benefits

2. An investigator is the inventor of a drug delivery system and the owner of the company that makes the system. The investigator wishes to conduct a clinical study using the system as a step toward marketing it. What would be the most appropriate resolution of the investigator's conflict of interest?
   a. Divesting all financial and patent interests in the system
   b. Turning day-to-day management of the company over to a colleague while maintaining stock ownership
   c. Choosing a subordinate at the company to conduct the clinical study
   d. Conflict of interest? What conflict of interest?

3. You are reviewing a manuscript detailing the development of a new drug treatment. You notice the figures depicted in Fig. 83.3 and mention the similarities between them in your review. The author returns the manuscript with no changes to the figures and no comment. This is a case of:
   a. Falsification
   b. Fabrication
   c. Plagiarism
   d. Honest difference of opinion

4. You have been an investigator on a project since its inception. You were instrumental in designing and analyzing one of the assays in the manuscript. You drafted that portion of the manuscript and provided comments on the remainder of the manuscript. You have reviewed and understand the other components of the manuscript. You receive an email notifying you that the manuscript has been submitted. You open the attached file and notice that your discussion of your assays has been altered in a manner that changes the interpretation of the results. Which requirement for authorship do you not meet?
   a. Approving the manuscript in its final form
   b. Performing all assays
   c. Drafting the entire manuscript
   d. Reviewing the primary data from all assays

5. Investigators plan to study a new drug to reduce the risk of preeclampsia in pregnant women in a large randomized trial. They propose to screen women for preeclampsia risk but not share the results of the screen with the women. All women will be started on drug or placebo. High-risk women will be randomized to the drug or placebo. Low-risk women will all be treated with placebo. Since the safety of the drug in pregnancy is incompletely studied, all women will be followed for adverse pregnancy outcomes, with the low-risk group serving as a concurrent comparison group to establish the baseline rate of complications in the population. Which of the following is most likely true of this study?
   a. Risks have not been minimized, and potential benefits have not been maximized
   b. Risks have been minimized, but potential benefits have not been maximized
   c. Risks have not been minimized, but potential benefits have been maximized
   d. Risks have been minimized, and potential benefits have been maximized

6. A clinical practice group is considering participating in a large randomized trial of an already available drug now being tested for amelioration of osteopenia of prematurity. One large observational trial suggested the drug might be effective and did not report new side effects. Small uncontrolled trials have yielded mixed results. One small controlled trial suggested efficacy but did not reach statistical significance. A meta-analysis concluded that there were insufficient data to combine to measure efficacy. In the practice group, some members routinely use the drug, while others avoid it. Which statement best describes the situation?

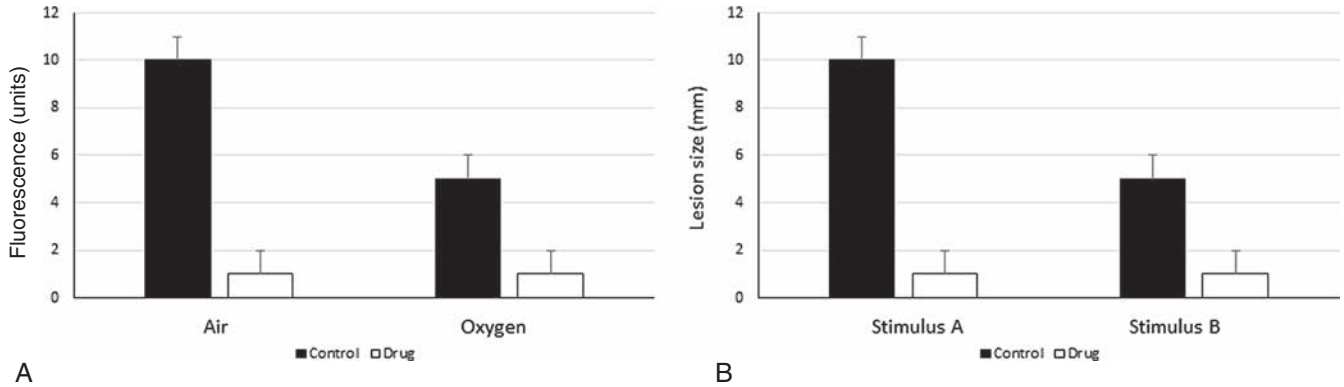

Fig. 83.3 – Figures from an imaginary manuscript.

a. The data suggest efficacy, the group should not join the trial
b. There is clinical equipoise, it would be reasonable to join the trial
c. Since members of the group disagree, there is no clinical equipoise
d. In the absence of firm evidence of efficacy, the group should not join the trial

7. A newborn with severe sepsis and shock is eligible for a phase I, first-in-human trial of a new biological agent that decreases systemic inflammatory response in animal studies. The parents are eager to enroll their infant in the trial, stating that they are sure that the new treatment recommended by the doctors will help their baby. This is an example of which of the following?
   a. Appropriate informed consent
   b. Need for assent
   c. Deception in research
   d. The therapeutic misconception

8. A 12-year-old with leukemia is eligible for a study involving several additional blood draws and assays on 1 mL additional marrow samples at the time of clinical bone marrow aspirates. The aim of the study is improved understanding of tumor biology. Which is best describes the consent process for this study?
   a. The child can provide informed consent
   b. Due to the serious nature of the illness, parental permission without assent from the child is most appropriate
   c. Due to the risks, this research is not approvable
   d. Parental permission with assent from the child is most appropriate

9. Given the existence of special protections of pregnant women and fetuses, which of the following would you expect is NOT likely to be approvable under federal regulations?
   a. Research with the prospect of direct benefit to the mother and fetus, and risk of significant harm to the fetus
   b. Research with the prospect of direct benefit to the mother, and risk of significant harm to the fetus
   c. Research with no prospect of direct benefit to the mother or fetus, and risk of significant harm to the fetus
   d. Research with the prospect of direct benefit to the fetus, and risk of significant harm to the fetus

10. Investigators wish to learn more about modifier gene effects on osteogenesis imperfecta (OI) phenotypes. They propose to perform open bone biopsies on unaffected school-age siblings of children with OI. Which of the following is true?
    a. This would be considered minimal risk research
    b. This would be considered greater than minimal risk research with the prospect of direct benefit
    c. This would be considered research with a minor increase over minimal risk
    d. This research would not be considered approvable without permission of the Secretary of Health and Human Services

Answers Section

Chapter 2

1. **a.** Increased cardiovascular demand may cause or worsen cardiac dysfunction in women with cardiac diseases. Echocardiography is recommended in each trimester or with new cardiac symptoms. Peak flow monitoring should be used because expiratory respiratory indices are unchanged in pregnancy. Systemic vascular resistance decreases in pregnancy; thus, antihypertensive doses often can be lowered or eliminated. Insulin dose increases are common because of progressive insulin resistance in pregnancy. Although total T_4 and T_3 increase in pregnancy, steroid-binding globulin also increases, so free levels are unchanged.
2. **d.** An interpregnancy interval of at least 18 months is advised. Folic acid supplementation is recommended for all women to prevent neural tube defects. Lisinopril use is contraindicated in pregnancy; transition to a preferred medication should be carried out. Gamete donation can prevent genetic disease in the offspring if parents are known carriers. Expanded carrier screening is offered to all patients of Eastern and Central European Jewish descent. Although this couple may be presumed to be Tay-Sachs carriers, mutation analysis will confirm recurrence risk and screen for other at-risk conditions.
3. **d.** Alloimmunization may have caused demise if the fetus was Kell-positive. Absence of bleeding does not rule out Kell sensitization; anemia develops from transplacental passage of maternal antibodies. Sensitized patients may have uncomplicated pregnancies if a fetus is antigen-negative. Paternal antigen testing will show if a pregnancy is at risk—no fetal risk if the father is Kell-negative, but possibly so if the father is Kell-positive (may be heterozygous or homozygous).
4. **e.** Stillbirth risk is increased with DM; fetal surveillance is recommended from 32 weeks. If glycemic control is poor, then 37- to 38-week delivery is considered. Delivery is delayed until 39 weeks in well-controlled patients to allow time for fetal maturity. Nutrition consultation is recommended in all diabetic pregnancies. Fetal echocardiography is advised due to the increased risk of anomalies. Frequent blood glucose checks are necessary to guide dosing of medications. Metformin, glyburide, and insulin may all be used to achieve glycemic control.
5. **c.** This patient has HELLP syndrome. If maternal and fetal statuses are reassuring, delivery should take place after completion of a steroid course. Severe features of a preeclampsia syndrome (HELLP syndrome and severe hypertension) are present; thus, a and b are incorrect. If the only severe feature is controllable hypertension, then expectant management detailed in (e) is appropriate. Fetal lung maturity testing is not advised because delivery is indicated regardless of fetal maturity.
6. **c.** Many, but not all, fetuses with trisomy 21 have structural anomalies or soft marker ultrasound findings. The lack of anomalies or markers does not rule out a trisomy 21 diagnosis. Maternal serum quad testing is a screening test for aneuploidy; a positive screening result should not be considered diagnostic. Although the detection rate of the serum quad test is high (75%), the false-positive rate is also high.

Chapter 3

1. **c.** Umbilical artery Doppler velocimetry defines a group of fetuses that is at high risk of adverse perinatal outcomes. Reversed end-diastolic flow should prompt delivery after 32 weeks. An EFW < 10th percentile defines growth restriction, but fetal tests of well-being are used to make delivery decisions. Oligohydramnios does not prompt delivery until term. Intermittent variable decelerations on a reactive NST do not portend imminent compromise.
2. **c.** This fetus receives 2 points each for amniotic fluid volume, movement, tone, and breathing (total of 8 points). No points are received for the NST because the fetus is not reactive (15 beat accelerations are required at 34 weeks). A BPP score of 8 or 10 is predictive of normal fetal oxygenation, and no further testing is required. A BPP score of 6 is an equivocal test and requires follow-up testing (BPP at 8 and 24 hours) to determine if delivery is required.

Chapter 4

1. **d.** Large fetal masses are at risk of rupture or dystocia during attempted vaginal deliver; thus, cesarean delivery is recommended. Hydrops is an indication for delivery near term. Women with two or less low-transverse cesareans may consider a trial of labor. Cesarean delivery is not required for fetal gastroschisis. Labor and vaginal delivery are well tolerated by fetuses with congenital heart disease; cesarean delivery is considered only in extreme cases. Most women with cardiac disease can have safe vaginal deliveries.
2. **a.** History and sonographic features are suggestive of placenta accreta. Management involves planned cesarean hysterectomy at 34–36 weeks due to ongoing risk of massive hemorrhage. Because this patient presented with heavy bleeding, prompt delivery is indicated. Repeat steroid courses are not given after 34 weeks of gestation; thus, (b) and (c) are incorrect. Also, (c) does not call for cesarean hysterectomy, which is the definitive management of placenta accreta. Expectant management is not appropriate,

given active hemorrhage. Testing for fetal lung maturity is not recommended because delivery is indicated by the maternal condition.

Chapter 5

1. **c.** This patient is likely in secondary apnea. The appropriate next step is to provide effective positive-pressure ventilation. Continuous stimulation is unlikely to induce spontaneous respirations and improvement in heart rate in this infant. Deep suctioning may further exacerbate bradycardia by inducing a vagal nerve stimulatory response. If the patient does not respond to effective bag-mask ventilation, obtaining a more secure airway and administration of epinephrine may become necessary, but not before a period of effective positive-pressure ventilation and chest compressions has been attempted.
2. **c.** The infant in choice c presents with signs of moderate encephalopathy after a known perinatal hypoxic event and is most likely to have a neurologic benefit from whole-body cooling. The infant in (b) has also experienced a significant hypoxic event at birth but shows signs of only mild encephalopathy on examination and therefore does not meet the criteria for whole-body cooling. The infant in (a) is preterm; cooling in this population has not yet been established to be beneficial. The infant in (d) had an unwitnessed hypoxic event 12 hours after birth; whole-body cooling for neonates who experience this type of arrest is not the standard of care.
3. **c.** This is the preferred dosage and route of administration for epinephrine during a neonatal resuscitation.
4. **a.** Of the most commonly used devices used in neonatal resuscitation, the self-inflating bag is the only device that can deliver positive-pressure breaths without being attached to a source of compressed air or flow. A self-inflating bag cannot deliver PEEP unless additional valves or mechanisms are attached to the device, whereas a T-piece resuscitator can. Additionally, the benefit of a T-piece resuscitator is that it will deliver consistent PIP and PEEP to the patient, provided that a good seal is made between the mask and the patient's face and/or the ETT remains in place. Both devices can deliver PPV with an increased Fio_2 concentration if attached to an oxygen source.
5. **c.** The hypercapnia, hypoxemia and acidosis that result from asphyxia will initially cause a redistribution of blood flow to the most vital organs, the heart, brain and adrenal glands.
6. **b.** Necrotic cell death occurs after primary energy failure due to depletion of cerebral ATP stores and inactivation of the Na/K membrane pumps. Secondary energy failure occurs 6–48 hours after the initial hypoxic injury and results in decreased glutamate reuptake, which leads to the induction of apoptosis.

Chapter 6

1. **a.** Truncus arteriosus results from failure of the conotruncus to separate.
2. **a.**

Chapter 7

1. **b.**

Chapter 8

1. **d.** The infant is this scenario is having a hypercyanotic spell caused by an acute decrease in pulmonary blood flow. These are commonly triggered by medical procedures such as blood draws. Morphine and phenylephrine are first-line agents to counteract the hypercyanotic spell.
2. **d.** Both type B interrupted arch and truncus arteriosus are associated with 22q11 deletion syndrome. Infants with 22q11 deletion syndrome frequently have hypocalcemia and an absent thymus.

Chapter 9

1. **c.** Numerous cardiac tumors found in a neonate are almost always rhabdomyomas, which are strongly associated with tuberous sclerosis.

Chapter 10

1. **c.** This infant has complete heart block related to transplacental transfer of SSA and/or SSB antibodies related to maternal lupus. Although the heart rate is low, the infant has adequate cardiac output, as evidenced by good capillary refill and blood pressure. Monitoring is all that is required in this situation.
2. **b.** This infant had an episode of atrial flutter, which is very unlikely to recur and thus does not warrant prophylaxis.

Chapter 11

1. **b.** Atrioventricular block is a well-described result of digoxin toxicity. Digoxin toxicity is more likely to occur in the setting of hypokalemia.
2. **d.**

Chapter 13

1. **a.** Increase surfactant spreading at air liquid interface. Surfactant proteins are categorized as either hydrophobic (SP-B and SP-C) or hydrophilic (SP-A and SP-D). The hydrophobic proteins are secreted with surfactant in lamellar bodies and are required for production of lamellar bodies and for the normal spreading of surfactant phospholipids into a monolayer at the alveolar air-liquid interface. SP-B and SP-C are developmentally regulated. SP-A and SP-D are collectins that bind to carbohydrates on the surfaces of bacteria, fungi and viruses. They are developmentally regulated and are important components of the lung host defense system.

2. **d.** All of the above. The 2010 AAP policy statement on use of glucocorticoids to mitigate BPD does not recommend high dose dexamethasone because of the potential for adverse neurologic outcome. No subsequent policy has been issued. Both low dose dexamethasone and low dose hydrocortisone need more randomized controlled trials, particularly focusing on neurodevelopmental outcome, before they can be recommended. Short courses of low dose glucocorticoids are commonly used to treat BPD in ventilator- dependent patients. Their use should balance the potential benefits of these agents with potential harm they may cause. The decision to use these drugs should be individualized for selected patients.

Chapter 14

1. **b.** Lung lavage with dilute surfactant does not have clear evidence to support its routine use. MAS is associated with inactivation of surfactant and use of surfactant has been associated with less use of ECMO. Use of high ventilator rates can increase air-trapping and increase the risk for pneumothorax. Further, hypocarbia can be detrimental to cerebral circulation. Muscle relaxants may be useful to improve oxygenation in severe MAS with PPHN, but routine use of muscle relaxants is not recommended.
2. **c.** CMV transmission and disease is rare in term infants as mother will likely have transferred passive immunity to the infant during pregnancy. In preterm infants, passive transmission of immunity is incomplete and cannot be relied upon. In a prospective cohort study of very low birth weight infants born to CMV seropositive mothers, the cumulative incidence of CMV infection at 12 weeks was 6.9%. About 17% of the infected infants developed disease. Sepsis-like syndrome, interstitial pneumonia, hepatitis, and necrotizing enterocolitis are important clinical presentation of CMV disease in preterm infants. Holder pasteurization (62.5°C [144.5°F] for 30 minutes) and short-term pasteurization (72°C [161.6°F] for 5 seconds) of expressed breast milk can inactivate CMV. It is likely the short-term pasteurization will preserve more nutrients than the Holder method. Freezing of expressed milk does not reliably eliminate CMV.

Chapter 15

1. **a.** Unilateral vocal cord paralysis is the second most cause of stridor in infants. This is more common on the left side following damage to the recurrent laryngeal nerve. Surgery in the neck or the chest is the most common cause of the palsy, but trauma around birth, especially with the use of forceps, is also an important cause. Subglottic stenosis is usually acquired and is not present at birth while laryngomalacia tends to present after the first few days of life with the symptoms peaking at around 4–6 weeks of age. Similarly, hemangioma also presents after first few weeks once the tumor enters the proliferative phase.
2. **d.** Infant likely has Noonan syndrome with chylothorax. Noonan syndrome is associated with lymphatic abnormalities and is a common cause of congenital chylothorax. Fluid in congenital chylothorax is serosanguinous prior to initiation of feeds and may turn milky with onset of feeding. Diagnosis of chyle includes demonstration of lymphocyte preponderance (contributes to milky color), chylomicrons in the fluid, fluid triglycerides >110 mg/dL and pleural fluid/serum cholesterol <1. Cardiac failure associated with anemia (immune and nonimmune) and cardiomyopathy can also present with fetal hydrops and serosanguinous fluid, but usually do not have lymphocyte preponderance of cell count. Empyema has high neutrophil count and protein in the fluid and can be caused by intra-amniotic shunt placements.

Chapter 16

1. **d.** Fetal breathing is essential for lung development. Fetal breathing movements begin in the first trimester and are initially "tonic" with irregular tonic contraction of diaphragm and prolonged periods of apnea. The breathing becomes phasic in the third trimester but is still associated with apneic periods. Lack of fetal breathing due to neuromuscular diseases or ineffective fetal breathing movements (e.g., when the anterior chest wall is experimentally replaced with a silicone membrane) are associated with pulmonary hypoplasia. The fetus in the question is likely to have significant pulmonary hypoplasia which will complicate the postnatal ventilatory management and may not be compatible with prolonged life.
2. **c.** Biphasic response to hypoxia is characteristically noted in preterm infants, especially in those with apnea of prematurity. Adults normally respond to hypoxia with sustained increase in rate and depth of breathing. In preterm infants, there is an initial increase in the rate of breathing which is thought to be the result of peripheral chemoreceptor stimulation. After 1–2 minutes, though, a period of respiratory depression follows. This is primarily due to reduced rate rather than reduced tidal volume and is thought to be due to hypoxia mediated central ventilatory depression. The mediators for such ventilatory depression include adenosine, GABA, and endorphins. Such inhibition of ventilation is noticed in the fetus too, leading to the hypothesis that the purpose of the inhibition is to reduce the metabolic rate, which, in a fetus dependent on placental oxygen delivery, will lead to reduce oxygen demand.

Chapter 17

1. **a** and **b.** ECMO is used for reversible conditions unresponsive to less invasive treatment options. Given the need to anticoagulate and the technical limitations related to cannulation, it is not standard of care to attempt ECMO in infants < 34 weeks and < 1800–2000 g. It is also important to assess if a condition is reversible before initiating ECMO. Case (d) describes an infant with pulmonary hypertension related to severe pulmonary hypoplasia which developed as a result of prolonged anhydramnios during an important stage of pulmonary

development early in pregnancy. The pulmonary hypertension is related to structural maldevelopment of the pulmonary capillary bed, resulting in a poor prognosis.

2. **e.** Infants of diabetic mothers can have delayed maturation of the surfactant, resulting in increased incidence of RDS at an older gestational age. Cardiac ECHO is indicated to rule out cardiac defect and confirm diagnosis of pulmonary hypertension. CXR assesses lung expansion and possible presence of pneumothorax. Surfactant replacement is indicated before iNO when treating RDS. Steroid therapy has not been shown to benefit infants with RDS, with or without pulmonary hypertension.

Chapter 18

1. **c.** Uniparental disomy in the region of chromosome 15q11-13. PWS is caused by lack of the paternally inherited genes in the 15q11-13 region. PWS can occur secondary to deletion of the 15q11-13 region on the paternally inherited chromosome. Alternatively, PWS can be due to inheritance of both copies of 15q11-13 from the mother (uniparental disomy).
2. **d.** Mitochondria are organelles that have their own chromosome which encodes several genes essential for mitochondrial function. Mitochondrial DNA is inherited almost exclusively from the mother.
3. **a.** Anticipation occurs in trinucleotide repeat diseases. Trinucleotide repeats tend to be unstable, with their size increasing with each subsequent generation, resulting in a more severe phenotype.
4. **b.** Of the choices listed, FISH for 22q11 is the most appropriate test to evaluate for suspected DiGeorge syndrome. Although not listed, aCGH would also have been an appropriate choice. A karyotype does not have sufficient resolution to reliably detect the 22q11 microdeletion. A small fraction (<5%) of patients with DiGeorge syndrome will have normal cytogenetic studies. In those patients, targeted evaluation of DiGeorge locus genes, such as TBX1, may be indicated. WES is not indicated in the evaluation for DiGeorge syndrome.
5. **a.** Preterm or critically ill term infants are more likely to have false positive newborn screening results. Most newborn screening programs utilize tandem mass spectrometry, which can analyze multiple metabolites, simultaneously enabling screening for many disorders with a single blood sample. Newborn screening panels do vary from state to state but all states screen for sickle cell disease and cystic fibrosis.

Chapter 19

1. **c.** Trisomy 13 (Patau syndrome), incidence is 1 in 5,000–10,000 live births, with 95% of trisomy 13 conceptions resulting in spontaneous abortion; 90% born live die within the first year of life. Abnormalities include: cleft lip and palate, polydactyly, narrow hyperconvex fingernails, colobomas, umbilical or inguinal hernia, cryptorchidism, microcephaly, holoprosencephaly, seizures, cardiac defects (VSD), and apnea.
2. **b.** 20% of cases of Beckwith-Wiedemann syndrome is caused by paternal uniparental disomy (UPD). (https://ghr.nlm.nih.gov/condition/beckwith-wiedemann-syndrome#genes)

Chapter 20

1. **e.** Diagnosis of partial fetal alcohol syndrome (PFAS) requires evidenced of prenatal alcohol exposure.

(Hoyme HE, Kalberg WO, Elliott AJ, et al. Updated clinical guidelines for diagnosing fetal alcohol spectrum disorders. *Pediatrics.* 2016;138(2):e20154256.)

Chapter 21

1. **c.** Current evidence suggest an association between ART and small but definite (more than 1.3 times than in spontaneous conception) incidence of congenital malformations. This includes: congenital heart defects, neural tube defects, facial cleft, gastrointestinal malformations, genitourinary malformations, and imprinting disorders. The rates of congenital malformations are similar for each type of ART, except for increased urogenital abnormalities with ICSI. The cause for the increase in malformations with ART are yet to be determined.

(Williams C et al. Congenital malformations after assisted reproduction: risks and implications for prenatal diagnosis and fetal medicine. *Ultrasound Obstet Gynecol.* 2010;35:255-259.)

2. **b.** Amniotic band sequence is an example of disruption. Disruption defects are due to destruction or interruption of a normal developmental process. It usually affects a body part, rather than a specific organ

(Haldeman-Englert CR, Saitta SC, Zackai EH. Evaluation of the dysmorphic infant. In: Gleason CA, Devashar SU, eds. *Avery's Disease of the Newborn*, 9th ed. Philadelphia: Elsevier Saunders; 2012:186-195.)

3. **d.** Deformations are defects caused by abnormal mechanical forces on morphologically normal tissue in utero. They are associated with multiple gestations, uterine malformations, and oligohydramnios.

TYPES OF CONGENITAL ANOMALIES

Malformations	Disruptions	Deformations	Dysplasias
Morphologic defects resulting from intrinsically abnormal developmental processes	Breakdown of, or interference with, an originally normal developmental process	Abnormalities of form or position of a part of the body caused by non-disruptive mechanical forces	Abnormal structure because the tissues, from which individual structures are formed, are abnormal

Continued

TYPES OF CONGENITAL ANOMALIES—cont'd

Malformations	Disruptions	Deformations	Dysplasias
Occur early in embryogenesis	May occur at any time during gestation	Usually develop during the second half of pregnancy	Often due to single abnormal genes

Adapted from Moh W, Graham Jr JM, Wadhawan I, Sanchez-Lara PA. Extrinsic factors influencing fetal deformations and intrauterine growth restriction. *J Pregnancy*. 2012; https://doi.org/10.1155/2012/750485.

4. **d.** Deformations result when normal tissue is exposed to abnormal mechanical forces in utero.

(Haldeman-Englert CR, Saitta SC, Zackai EH. Evaluation of the dysmorphic infant. In: Gleason CA, Devashar SU, eds. *Avery's Disease of the Newborn*, 9th ed. Philadelphia: Elsevier Saunders; 2012:186–195.)

Chapter 22

1. **c.** Infants with urea cycle defects usually become symptomatic in the first days to months of life. Clinical presentation includes: lethargy, hypothermia, poor feeding, tachynea, irritability, vomiting, coma. Differential diagnosis includes sepsis or an organic acidemia. Hyperventilation due to cerebral edema causes respiratory alkalosis.

(Summar M. Current strategies for the management of neonatal urea cycle disorders. *J Peds*. 2001:138(1):S30–S39.)

2. **a.** Zellweger spectrum disorder (ZSD), is a disorder of peroxisomal biogenesis caused by a defect in the PEX gene. A newborn with ZSD presents with dysmorphic features which includes; flattened face, epicanthal folds, upslanting palpebral fissures, broad nasal bridge. and hypoplastic supraorbital ridges with severe hypotonia and hepatic dysfunction.

(Femke C et al. The. Zellweger spectrum disorders: clinical overview and management approach. *Orphanet Journal of Rare Diseases*. 2015;10:151.)

3. **d.**
4. **e.** Uncontrolled maternal phenylketonuria leads to complications in the offspring. These complications include microcephaly, intellectual disabilities, congenital heart disease, and intrauterine growth restriction. Dietary management prior to conception and during pregnancy is important to decrease complication risks in the offspring.

(Waisbren SE et al. Maternal phenylketonuria: long-term outcomes in offspring and post-pregnancy maternal characteristics. *JIMD Reports*. DOI 10.1007/8904_2014_365.)

Chapter 23

1. **d.** True. Lean body mass, including structural components of cells that have been proliferating, muscle, and bone account for the largest fractional increase in body weight, indicating the large nutritional requirements for protein during this period of growth.
2. **e.**
3. **b.** False. The critical amount of amino acid or protein nitrogen for preventing growth faltering in very preterm infants <30-32 weeks is less than 1.5 g/kg/day. This is false, as numerous studies have shown that growth cannot occur until at least 1.5 g/kg/day of amino acids is provided.

Chapter 24

1. **d.** True. Risk factors in preterm infants for calcium and phosphorus deficiency and subsequent rickets include: gestational age <27 weeks or birth weight <1000 grams, long-term parenteral nutrition (<4-5 weeks), severe BPD requiring diuretics and fluid restriction, long-term steroid treatment, a history of necrotizing enterocolitis (NEC), and intolerance to enteral formula or human milk. All of these are true and self-explanatory. Calcium and phosphorus nutrition of very preterm infants is deficient for all of these reasons.
2. **b.** Mn supplementation should be stopped with any signs of hepatic dysfunction or cholestasis. This is true, as excess Mn damages the liver.

Chapter 25

1. **a.** True, for term infants. Human milk provides sufficient energy, protein, fat, carbohydrate, micronutrients, and water for normal metabolism, growth, and development in term infants. Human milk has been the result of several million years of evolutionary development to produce the optimal nutrition of human newborn infants.
2. **a.** Varying degrees of nutrient loss many occur with long term storage, particularly in frozen conditions. This is true, especially when there are multiple freeze-thaw cycles, and is one reason why fresh mother's milk is superior.
3. **c.** Total lipid generally is increased (as much as by 60%), but free fatty acids are reduced, which might increase their nutritive potential. This is False. Total lipids are generally reduced, by up to 60%, but Free Fatty Acids (FFAs) will increase.

Chapter 26

1. **a.** Normal fetal metabolic and growth rates and nutritional requirements stop with birth, precluding routine use of IV nutrition. This is False. There is no reduction in metabolism or potential for growth with birth, and thus the infant will require the same amount of nutrients. If the infant is very small, there will be insufficient nutrient stores to maintain normal metabolism or growth, requiring early IV nutrition and early and continued enteral nutrition.
2. **a.** The amino acid composition of current neonatal parenteral amino acid solutions are based on providing plasma concentrations similar to those of term, fully breast fed infants, which is appropriate for preterm infants who are growing at much faster rates than term infants. This is False. Term infants do not have as high a fractional protein synthetic rate or growth rate as the earlier gestation fetus does and thus the preterm infant of the same gestational age should. Fetal amino acid concentrations are

generally higher than those of term infants fed mature mother's milk, an indication of their need for more amino acid and protein intake to meet their greater requirements.

Chapter 27

1. **c.** The baby is intubated and receiving 100% humidified air which will reduce/ eliminate its insensible losses (15%–30%) from respiration. Sedation also decreases the insensible fluid loss by an additional 5%–25%. Being under a radiant warmer; however, will increase insensible loss by 50%–100%. Combining these factors will lead to a net increase of 15%–45% above the baseline value (-15 plus -5 plus 50 = 25 to -30 plus -25 + 100 = 45). Therefore total fluids would be 115–145 mL/kg/day as a rough estimate. Because this is only an estimate, electrolytes, particularly sodium, ins/outs, and weights should be followed closely.
2. **d.** SIADH can be triggered by birth asphyxia. To make this diagnosis, renal, thyroid, and adrenal function tests must be normal. Confirmation of the diagnosis is made by the finding of urine osmolality higher than serum osmolality and urine sodium should be greater than 20. A finding of urine sodium less than 20 would be suspicious for intravascular volume depletion leading to an increase in urine sodium reabsorption. In such cases, ADH release is appropriate to preserve volume even at the expense of plasma osmolality. A creatinine of 0.7 in a 3-day-old infant would be in the normal range, making AKI unlikely to be the cause of the hyponatremia. Bartter syndrome is a tubular disorder leading to salt wasting, polyuria, and dehydration. Infants typically do not need sodium supplementation until day of life 3. Pseudohypoaldosteronism presents with low sodium and high potassium levels.
3. **c.** The baby's FENa is calculated as $[(U_{Na} \times S_{Cr})/(U_{Cr} \times S_{Na})] \times 100 = (80 \times 0.8)/(10 \times 126) = 0.05 \times 100 = 5\%$. While term babies conserve sodium well with FENa < 1 and often closer to 0.5%, preterm infants' immature tubules lead to sodium wasting and high FENa. A creatinine of 0.8 in an 11-day old ex-25 week infant would fall in the normal range so AKI is unlikely.
4. **e.** Alkalosis stimulates the Na-K ATPase on the basolateral membrane. This will increase intracellular potassium levels and stimulate potassium exit to the urine space. Alkalosis also increases the amount of time the luminal potassium channels are open further encouraging urine potassium secretion and leading to hypokalemia. Avid sodium reabsorption in the proximal tubules as seen in volume depleted states leads to less sodium delivery to the distal tubule. The reabsorption of sodium by ENaC in this segment leaves the lumen electronegative which allows for secretion of potassium. Neonates do initially lack the potassium Maxi-K channels (although these are stimulated by high urine flow which would not be present in the baby in the scenario). The potassium channel ROMK is inhibited by acidosis which would lead to less potassium secretion to the urine. Although aldosterone levels are high in infants, they exhibit less of a response to it.
5. **d.** In a state of volume depletion, alkalosis will persist by the following three mechanisms: (1) a decrease in GFR leads to less filtered bicarbonate; (2) the proximal tubule avidly reabsorbs Na which leads to increased bicarbonate reabsorption; and (3) the volume depletion stimulates RAS which leads to an increase in aldosterone. The aldosterone leads to increased activity of the epithelial Na channel (ENaC), making the lumen more electronegative. This favors both H^+ and K^+ secretion. Typically in alkalosis, H^+ would shift out of the cell in exchange for K^+. Hypokalemia inhibits this process.
6. **a.** The baby has pseudohypoaldosteronism type 1, autosomal dominant type. PHA type 1 presents with vomiting, FTT, hyponatremia, hyperkalemia, and acidosis with high urine sodium. Renin and aldosterone levels are high. It can be inherited as an autosomal recessive or dominant trait. The dominant form is clinically outgrown, usually by age 2. It is limited to renal findings. In contrast, the recessive form is a life-long, systemic illness involving the skin, lungs, and kidney predominantly.
7. **b.** A weight loss of up to 15% is normal in premature infants. Studies have shown that not allowing this weight loss to occur is associated with increased rates of PDA, NEC, and CLD. Potassium should be withheld from the TPN until urine output is established. The baby in the above scenario is urinating normally and has a normal creatinine, so standard of care would be to add potassium to his TPN. His TF should be increased to allow more nutrition, not because of the expected and normal weight loss.
8. **e.** Term infants increase both respiratory rate and tidal volume, but preterm infants increase only their respiratory rate. Bicarbonate is not helpful to treat respiratory acidosis because it decreases respiratory rate. Preterm infants have a decreased ability to reabsorb filtered bicarbonate.
9. **d.** Proximal RTA is most commonly seen in children as part of the renal Fanconi syndrome with wasting of glucose, amino acids, and phosphorus. However, rare genetic causes have been reported. With proximal RTA the defect lies in the reabsorption of the filtered bicarbonate. The distal acidification mechanism is intact. When the serum bicarbonate is low, the distal acidification results in a low urine pH. When alkali therapy is started, the filtered bicarbonate load increases which raises the urine pH. Therapy of proximal RTA requires large amounts of alkali, often 10–15 mEq/kg/day. Distal RTA is due to an acidification defect. It is suggested by a normal AG acidosis with urine pH > 6.5. Hypercalciuria is often present. Type IV RTA presents with mild acidosis (bicarbonate levels in high teens) and hyperkalemia. Technical difficulties obtaining blood samples can lead to factitiously low bicarbonate levels but hyperkalemia and hyperphosphatemia should also be seen in that case. Pseudohypoaldosteronism can have a mild metabolic acidosis but hyperkalemia and hyponatremia are major features of the disease.
10. **b.** Renal prostaglandins play a crucial role in maintaining GFR when the kidney is not receiving normal blood flow due to volume depletion, hemorrhage, etc., or when angiotensin II levels are high. NSAIDs disrupt the production of prostaglandins and can lead to AKI. ANP is released by stretch of the atrium. It acts on the kidney to increase GFR by dilating the afferent arteriole

and constricting the efferent arteriole. Angiotensin II constricts both the afferent and efferent arterioles. If the PDA closed, blood would stop shunting away from the kidneys. Dopamine is natriuretic by decreasing the activity of Na-K ATPase which provides the driving force for Na reabsorption.

Chapter 28

1. **d.** The normal size of fetal kidneys at 20 weeks is 2.7 cm. The bladder can be seen by 15 weeks. The combination of large, bright kidneys with presumably no urine (can't visualize the bladder because it is empty) is very suggestive of ARPKD. ADPKD can present in neonates but a severe presentation such as this with anuria is very rare. More often there is just large kidneys or cysts seen with normal renal function. The lack of family history argues more for ARPKD than ADPKD, although new mutations comprise 10% of people affected by ADPKD. Bilateral MCDK would be associated with anuria but large cysts should be seen in the kidneys. Dysplastic kidneys are usually (but not always) small. The kidneys in Beckwith-Wiedemann can be large but severe impairment of function in utero would be atypical.
2. **a.** MCDK has a characteristic ultrasound picture of multiple cysts of similar size giving an appearance of a "cluster of grapes." They have no function. Often the contralateral kidney will show compensatory hypertrophy in utero as this has. With the normal kidney on the right, you would expect normal amniotic fluid levels. ADPKD is possible but rarely presents in neonates with ultrasound findings. ARPKD rarely presents with visible cysts and affects both kidneys. A UPJ obstruction leads to hydronephrosis while a UVJ obstruction would lead to hydroureter.
3. **c.** Intervention of suspected fetal bladder outlet obstruction has not definitely been shown to improve long-term function of lungs or kidneys. When an intervention is done, the vesicoamniotic shunt is the most common procedure. Serial bladder taps are preferred to obtain fresh urine to analyze the urine electrolytes. Urine Na < 100 and Urine Osm > 200 are predictive of preserved renal function. Other tests predictive of good renal function are: urine Ca < 8 mg/dL, urine protein < 40 mg/dL, urine Beta-2 microglobulin < 4 mg/L.
4. **d.** The baby likely has a renal artery clot due to the UAC. Clots are thought to form due to disruption of the endothelium during line placement. A low-lying UAC is more likely to have a renal artery clot as compared to a high lying UAC. The findings of decreased LE perfusion, hypertension, and hematuria without oliguria, congestive heart failure, or multi-organ failure suggest a "minor" clot. The treatment would be removal of the catheter and symptomatic therapy. Hypertension is common following a renal artery clot. The hypertension should resolve but this may take months or years. ESRD is seen with bilateral renal artery clots. Loss of toes or bowel ischemia would be expected with a more severe clot involving the aorta.
5. **d.** The baby has several risk factors for renal vein thrombosis: sepsis, prematurity, presence of UVC. The classic clinical findings suggestive of RVT are: flank mass, low platelets, and hypertension. The presence of all three findings is actually rare. While preterm kidneys are more likely to have stones or nephrocalcinosis, the affected kidney would not be small. Dysplastic kidneys are often small but should not have calcifications. Kidneys affected by ARPKD are large and diffusely echogenic.
6. **c.** A rise in serum creatinine between 2 and 2.9 times the lowest creatinine obtained in the prior 7 days or UOP > 0.3 and ≤ 0.5 mL/kg/hour defines stage 2 AKI by KDIGO definition.
7. **e.** You have assessed him as euvolemic so further fluid boluses are unlikely to help. If his hydration was in question though, a NS bolus could be trialed. Renal dose dopamine has not been shown to hasten renal recovery. Since there is no hydronephrosis or abnormal bladder on U/S, placement of a bladder catheter would not improve his renal function. Kidney biopsies are rarely required in neonates to make a diagnosis of AKI. The baby likely has ATN from prolonged renal hypoperfusion. There is no specific treatment for this other than ensuring good hydration, avoiding further renal insults, and managing any electrolytes issues or hypertension. ATN should resolve over days/weeks depending on its severity.
8. **e.** PD has several advantages in the NICU; it is comparatively technically simple compared to HD or CRRT. It is performed with manual exchanges of fluid done by NICU nurses. The baby is not anticoagulated with PD. It may be easier to get a PD catheter inserted than obtain reliable vascular access for HD or CRRT. PD's disadvantages include the removal of beneficial proteins like immunoglobulins, its slow efficiency at solute and fluid removal, and risk of peritonitis. It is contraindicated in babies with abdominal wall defects or VP shunts. HD can quickly remove solutes but rapid fluid removal is usually not tolerated well. One of CRRT's principal advantages is slow, hourly removal of fluid that can be adjusted each hour.
9. **d.** Preterm infants have slower metabolism of furosemide so should not be dosed multiple times per day. Spironolactone is a weak diuretic used mostly as a potassium sparing agent in the NICU. The baby is likely not responding as well to the Lasix because the tubule segments past the loop of Henle are avidly reabsorbing the sodium due to a state of volume depletion. The distal nephron's Na-Cl cotransporter can be blocked by a thiazide diuretic, which should increase diuresis. Care must be taken though to not induce AKI from intravascular depletion. Close attention to electrolytes is also necessary.
10. **c.** Thiazides can cause increased reabsorption of calcium from the urine. In contrast, loop diuretics are associated with hypercalciuria, kidney stones, and nephrocalcinosis. They are also associated with an increased risk of bone fractures and with hearing loss. Spironolactone is a potassium-sparing diuretic used most often in the NICU in conjunction with a thiazide to mitigate potassium loss in the urine.

Chapter 29

1. **c.** The majority of palpable undescended testes will descend spontaneously after the testosterone surge that accompanies the mini-puberty of infancy which occurs within the first few months of age. Spontaneous descent is unlikely after 4 months of age. There is an increased risk of germ cell malignancy in undescended testes, but malignancy is uncommon in patients who had orchiopexy prior to 2 years of age. Endocrine evaluation for DSD should be performed in patients with BL nonpalpable testes or those with undescended testes and hypospadias or micropenis.
2. **b.** There is a high suspicion that micropenis in a patient with multiple congenital midline anomalies is due to deficient pituitary secretion of LH (leading to testosterone deficiency) or growth hormone. Central hypothyroidism is also possible but does not cause micropenis. Most infants with 17-beta hydroxysteroid deficiency or 5α-reductase deficiency will have a more severe phenotype with ambiguous external genitalia or external genitalia that appear female. Neither condition is commonly associated with other midline defects.
3. **a.** XY males with 5alpha-reductase may have severe undervirilization at birth owing to lack of 5-DHT production, the androgen responsible for the majority of external genitalia in the male virilization fetus. At puberty, testosterone levels increase dramatically and because the androgen receptor is present will cause virilization. There is no function androgen receptor in complete androgen insensitivity, so increased testosterone has no effect. Individuals with partial AI will likely undergo some virilization at puberty. Virilization in an XX female is due to excess androgen production in setting of cortisol deficiency and will not be appreciably affected by female puberty. XY males with 17β-HSD CAH lack an enzyme necessary to produce testosterone so will not have significant virilization at puberty.
4. **d.** Gender assignment remains complex and there usually is not a "right" or "wrong" decision. It is essential that families are involved in the discussion and make the ultimate decision. Some people with DSDs have argued that gender assignment and surgical intervention should be put off until the patient is old enough to decide and provide consent. This is currently not standard practice owing to the perceived difficulty in raising a child with an indeterminate gender and because in some cases surgical outcomes may be better when performed earlier. Although given the changing cultural perceptions on gender it is likely that counseling will evolve to allow for delaying gender assignment as a reasonable possibility.
5. **a.** Estrogen plays no known role in fetal sexual differentiation, the Wolffian ducts (primordial male internal structures) regress spontaneously in the absence of testosterone. Normal male virilization requires the coordinated production of several different hormones as described in answers b–d.
6. **c.** Adrenal insufficiency should be suspected and urgently evaluated in any case of ambiguous genitalia with nonpalpable gonads. This presentation is commonly seen in patients with mutations in adrenal hormone biosynthesis resulting in congenital adrenal hyperplasia. In XX females with CAH causing adrenal insufficiency and ambiguous genitalia, there will be no testes; virilization is due to excessive androgen production. In XY males with CAH causing adrenal insufficiency and ambiguous genitalia, undervirilization will be due to absent/impaired testosterone production and testes will have not descended. Micropenis (a) and hypospadias (b) in the setting of descended testes are most likely due to structural developmental defects, though the former can be the result of growth hormone deficiency and the infant should be monitored for hypoglycemia. Unilateral cryptorchidism (d) with otherwise normal genitalia is relatively common and unlikely to be associated with CAH.
7. **c.** Laboratory workup confirms isolated testosterone deficiency (normal AMH shows that testes/Sertoli cells are present), the absence of elevated androgen hormone precursors rules out CAH. 17β-HSD deficiency (a) would show elevated androstenedione and DHEA, AIS (b) and 5AR (d) would show normal/elevated testosterone levels. Patients with Leydig cell hypoplasia can be treated with a short course of testosterone in infancy for penile enlargement and will develop normal secondary sexual characteristics with testosterone hormone replacement starting at time of puberty.
8. **d.** Presence of virilization in an XX female with absence of laboratory findings of CAH suggests possibility of exposure to maternal endogenous/exogenous androgens or presence of an ovotesticular DSD. Maternal use of androgens as athletically performance enhancing drugs early in pregnancy (in some case before pregnancy was recognized) can cause virilization. Development of maternal hirsutism during pregnancy suggests possibility of placental aromatase deficiency resulting in accumulation of excess androgens in both maternal and fetal circulation. Ovotesticular DSD is a condition associated with both ovarian and testicular tissue; degree of virilization depends upon amount of testicular tissue and testosterone production. In many cases these patients are mosaics for chromosomes (possessing both XX and XY) which can be missed on initial karyotype but will be detected with DNA testing for *SRY*. In the absence of *SRY*, pursuit of other genetic abnormalities (such as *RSPO-1*) with tests such as WES can be considered, but that would not be the next step in the case here owing to expense/delay in results.
9. **b.** Patients with dysgenetic gonads, including XY gonadal dysgenesis, are at increased risk of gonadoblastoma and germ cell malignancy; therefore dysgenetic gonads should be identified and removed. Presence of XY karyotype dose not rule out gonadal dysgenesis; mutations of *SRY* and other genes involved in early sexual differentiation can be responsible for the clinical phenotype. There is wide clinical phenotype in XY gonadal dysgenesis ranging from completely feminized internal and external genitalia (complete gonadal dysgenesis) to a range of undervirilization of internal (i.e., Wolffian ducts) and/or external genitalia depending upon extent of androgen production (partial gonadal dysgenesis).

10. **g.** Testosterone production is present at birth and then rapidly declines in the first several days until rising again at 20–30 days of life ("mini-puberty of infancy"). Testosterone production in infancy peaks between 2–3 months of age, before falling to non-detectable levels by 6 months of age. Testosterone production again rises at the onset of puberty (range 9–14 years of age). Assessment of unstimulated testosterone outside of these times will not provide any useful clinical information; however, an hCG stimulation test can be performed to assess for the capability of testosterone production.

Chapter 30

1. **b.** Dopamine is a catecholamine synthesized in the adrenal medulla.
2. **c.** The fetal zone of the adrenal cortex produces pregnenolone, 17-hydroxypregnenolone, and DHEA which then must be converted into progesterone, 17-hydroxyprogesterone, and androstenedione by the placenta which expresses 3β-HSD in abundance.
3. **a.** Aromatase, because the conversion of androgens into estrogens is expressed primarily in gonads but is also found in other tissues such as adipose, liver, skin, and brain.
4. **d.** CYP11A1 mutation blocks the ability of cholesterol to be transported to the inner mitochondrial membrane; therefore synthesis of all steroid hormones will be diminished and will typically result in an undervirilized male.
5. **d.** In a well appearing infant without clinical signs of adrenal insufficiency or salt wasting, it is appropriate to assess a venous blood sample for 17-hydroxyporogesterone and electrolytes as the next step. Perinatal stress is one possible source of a false-positive newborn screen for CAH. Because clinical signs and electrolyte abnormalities of salt wasting may not manifest in the first few days of life, it is also prudent to repeat electrolytes at this time.
6. **c.** Based on the clinical picture and the finding of a 17-hydroxyprogesterone level greater than 10,000 ng/dL, this patient most likely has 21-hydroxylase deficiency CAH. Prematurity and timing of sample before 48 hours of age increase the possibility of a false-positive newborn screen result, however typically not to levels >10,000 ng/dL. A venous 17-hydroxyprogesterone sample should be obtained, but treatment should not be delayed as the clinical picture is concerning for adrenal crisis. During times of crisis, stress doses of hydrocortisone at 50–100 mg/m^2/day should be used.
7. **c.** 17-hydroxylase deficiency may cause ambiguous genitalia in XY males due to undervirilization as a result of decreased androgen synthesis. All other listed enzymatic defects can lead to ambiguous genitalia in XX females due to overvirilization as a result of excess androgen production.
8. **b.** Forms of CAH associated with early-onset hypertension include 11-beta-hydroxylase CAH and 17-hydroxylase CAH. Both conditions are marked by dramatically elevated serum levels of 11-deoxycorticosterone. 11-deoxycortisone has mineralocorticoid activity, when present at high levels leads to volume-expansion with resultant suppression of renin and aldosterone. Hypertension is a sign of overtreatment with Florinef in 21-hydroxylase CAH, the dose of which typically needs to be weaned after infancy. The clinical presentation of all forms of CAH is variable, therefore normal virilization does not rule out 17-hydroxylase CAH in an XY male. Some patients with severe 11-beta-hydroxylase deficiency may have 17-hydroxyprogesterone levels high enough to trigger an abnormal newborn screen result, although the majority will be diagnosed later. An elevated 11-deoxycorticosone level on ACTH stimulation is the gold-standard diagnostic technique.
9. **d.** ACTH is not a reliable marker for the adequacy of hydrocortisone dose. Linear growth should be monitored for signs of undertreatment (increased growth velocity) and overtreatment (suppressed growth velocity). Bone age is checked every 1–2 years for evidence of androgen-induced skeletal maturation. Androstenedione should be followed and maintained in the normal range for age. Plasma renin activity is used to assess adequacy of mineralocorticoid replacement.
10. **a.** 21-hydroxylase is an autosomal recessive disorder that affects males and females equally. Statistically, assuming that both mother and father are carriers, there is a one in four chance of giving birth to an affected child with each pregnancy, so the risk of having another affected female is one in eight. Prenatal treatment with dexamethasone to reduce virilization of affected females is controversial; existing protocols suggest starting treatment at 6–8 weeks gestational age, around the time that external sexual differentiation occurs. Hydrocortisone is not effective because it is metabolized by the placenta.

Chapter 31

1. **b.** Graves disease is associated with a mix of both TSH receptor stimulating and blocking antibodies, therefore the fetus/neonate is at risk of both hyper- and hypothyroidism. T3 is inactivated, however TSH antibodies do cross the placenta. Antibodies can persist even after definitive therapy, so the fetus/neonate is at risk even if mother has had surgery/ablation. Untreated maternal hyperthyroidism results in increased risk of miscarriage, premature labor, intrauterine growth restriction, hyper- and hypothyroidism. PTU is generally considered first-line treatment for Graves disease in USA, though methimazole is used in other countries and it is unclear whether the risk of birth defects is actually higher in PTU versus methimazole. Either way, the goal of therapy is to maintain maternal free T4 levels in the upper end of the normal range on the lowest possible antithyroid dose.
2. **a.** An activating mutation in the TSH receptor gene leads to hyperthyroidism and is a rare form of neonatal thyrotoxicosis. Consumptive hypothyroidism is due to overexpression of deiodinase 3, typically hepatic hem-

angiomas, that leads to excessive inactivation of thyroid hormones. Inactivating mutations in the sodium-iodine-symporter prevent iodine from entering the follicular cell and are a form of thyroid hormone dyshormonogenesis. Ectopically located thyroid glands are a common cause of congenital hypothyroidism, often they are located near the base of the tongue.

3. **c.** The infant likely has septo-optic dysplasia with clinical evidence of pituitary hormone deficiency (hypoglycemic seizure) and is therefore at risk for having central hypothyroidism. Central hypothyroidism is marked by low thyroid hormone levels; TSH can be low, normal, or even slightly elevated–as such, states that employ a TSH only newborn screen may miss infants with central hypothyroidism. An elevated TSH with low thyroid hormone levels is diagnostic of primary hypothyroidism. A low T_4 with normal TSH and free T_4 is consistent with TBG deficiency. A pattern of low TSH with elevated thyroid hormone levels is seen in hyperthyroidism.
4. **a.** A finding of fetal goiter can be a sign of either fetal hypo- or hyperthyroidism. Large goiters can cause airway obstruction and subsequent respiratory failure at birth. Fetal goiters due to hyperthyroidism that result from placental passage of TSH receptor stimulating antibodies can be treated with maternal antithyroid medication (methimazole or PTU) administration, therefore fetal blood sampling may be indicated if there is a significant goiter and the thyroid status of the fetus is not apparent. Fetal blood sampling is associated with 1%–2% risk of miscarriage, so risks and benefits must be weighed on a case-by-case basis.
5. **b.** In most situations, infants should be managed with levothyroxine tablets due to variability in the potency and stability of liquid preparations. Initial dosing is weight-based, and then titrated based upon biochemical findings and clinical response. Infants with congenital hypothyroidism therefore require frequent clinical and biochemical monitoring during the first year of life. The goal of therapy is to normalize TSH within two weeks and maintain T_4 levels in the upper one-half of the normal range. Overtreatment is possible; the infant may demonstrate signs/symptoms of hyperthyroidism including feeding intolerance, poor weight gain or weight loss, irritability, jitters. Labs will show a suppressed TSH value with an elevated T_4 (or free T_4).
6. **d.** Labs are most consistent with TBG deficiency, a benign condition characterized by low TBG. Treatment with levothyroxine is not indicated as free thyroid hormone levels are normal. The inherited form of this condition is due to mutations in *SERPIN7A.* This gene is located on the X-chromosome, therefore a father can only pass an abnormal copy to a daughter. TBG deficiency due to *SERPIN7A* can be partial (with one abnormal copy in a female) or complete (with no normal copies in either a male or female). Acquired forms of TBG deficiency are also possible in the setting of protein-losing conditions. THOP is characterized by low levels of all thyroid hormones; elevated TRAb levels can be seen in mothers with Graves disease.
7. **b.** Consumptive hypothyroidism will result in elevated reverse T_3 levels due to overexpression of deiodinase 3. Reverse T_3 levels are most likely to be low in congenital hypothyroidism and normal in TBG deficiency and THOP. The etiology of hypothyroxinemia in premature infants is not well understood; defective TSH surge and diminished iodide stores have been suggested as possible contributors, but definitive data is lacking.
8. **d.** Only 1%–10% of infants born to mothers with Graves disease are affected, therefore treatment is initiated only with clinical and biochemical evidence of hyperthyroidism. Therapy includes management of symptoms of hyperthyroidism with a beta-blocker and reduction in thyroid hormone production with an antithyroid medication (typically methimazole). High dose iodine (as provided in Lugol solution) transiently inhibits thyroid hormone production by blocking iodide organification (Wolff-Chaikoff effect). The thyroid gland escapes this effect in 7–10 days, possibly due to decreased transport of iodine across the sodium-iodine symporter. Neonatal Graves is transient and usually resolves by 6 months of age or sooner.
9. **c.** This patient most likely has defective thyroid hormone transport due to a mutation in *MCT8 (*also known as *SLC16A2).* This transporter is required for transport of T_3 into neurons, in its absence low intracellular T_3 levels result in abnormal neurologic findings including seizure, hypotonia, and developmental delay. Other body cells are able to transport T_4 across the cell membrane with intracellular conversion into T_3. Therefore treatment with either T_4 or T_3 can result in a hypermetabolic state in conjunction with hyperthyroidism. MCT8 deficiency is inherited in an X-linked recessive pattern.

Chapter 32

1. **c.** The patient most likely has glycogen storage disease 1 (GSD-1) due to glucose 6-phosphatase deficiency. This mutation blocks gluconeogenesis from glycogenolysis during fasting and presents with severe lactic acidosis. Often presents at a few months of age when infants begin to decrease feeding frequency and sleep through the night. Glycogen synthase deficiency (GSD-0) leads to inability to synthesize glycogen and therefore does not present with hepatomegaly. Neither congenital hyperinsulinism nor fatty acid oxidation disorder present with severe acidosis.
2. **d.** The labs are most c/w hyperinsulinism. Neither adrenal nor growth hormone deficiency can be diagnosed based upon a critical sample alone. An ACTH or CRH stimulation to test confirm normal hypothalamic-pituitary-adrenal axis would be appropriate in this case; GH was normal so growth hormone stimulation testing is not needed. If clinically appropriate, the next step in the management of hyperinsulinism would be try diazoxide. It can take up to 5 days to see full effect of treatment; infant will continue to need intravenous or continuous enteral dextrose support, target BG > 70 mg/dL.
3. **c.** Based upon the clinical history provided and the high GIR, this infant most likely has hyperinsulinism. While there is controversy regarding the definition of

a normal blood glucose range in healthy and preterm infants, it is essential that all infants with suspected or confirmed congenital hypoglycemia be maintained at plasma glucose levels > 70 mg/dL. Normally, as plasma glucose levels fall below 70, counterregulatory mechanisms kick in to provide the brain with alternate fuel sources (i.e., ketones) and the body with substrate for gluconeogenesis (fatty acids, amino acids). In HI, ketogenesis and lipolysis are blocked, leading to more rapid and more severe neurologic damage because of the lack of an alternate fuel source.

4. **b.** Diazoxide can cause fluid retention and may be associated with development of pulmonary hypertension, therefore it must be used with caution in patients with congenital heart disease with frequent monitoring of cardiac status. Most infants with stress-induced HI will respond to diazoxide, while only some forms of congenital HI (GCK-HI, SCHAD-HI, GDH-AD AD-HI) are responsive; patients with mutations in the K_{ATP} channel will need surgery. Diazoxide causes hypertrichosis (reversible when discontinued) and can cause cytopenia.
5. **d.** Patients with transient neonatal diabetes typically have a remission period during childhood where insulin is not needed, but permanent insulin requirement is likely to return in adulthood. Diffuse HI d/t K_{ATP} channel will require near-total pancreatectomy; there is an increased risk of diabetes and insulin requirement after this surgery. Hypopituitarism is not associated with increased risk of diabetes.
6. **c.** Glucose is the main source of energy for the brain. During times of prolonged fasting, ketone bodies and lactate can be used as alternate fuel sources. Free fatty acids do not cross the blood brain barrier so are unable to be utilized directly by the brain for energy.
7. **d.** Labs and clinical findings are strongly suggestive of neonatal hypopituitarism, however GH and ACTH or CRH stimulation tests should be done to confirm the diagnosis. The patient will most likely require lifelong hormone replacement. He is also at risk of central hypothyroidism, which could have been missed on newborn screen in states that use a primary TSH screening program. Uncooked cornstarch is used to manage patients with glycogen storage disease and has no role here.
8. **a.** The patient most likely has late-dumping syndrome. This condition is characterized by postprandial hypoglycemia, most commonly in patients with gastrostomy and history of Nissen fundoplication. The etiology is not entirely understood, but appears to be a condition of excessive insulin secretion as a result of rapid glucose absorption and altered incretin hormone signaling. These patients do not have fasting hypoglycemia and hypoglycemia will not persist once oral feeds have been established. In some cases, hypoglycemia can be prevented by lowering rate of bolus feeds and tapering rate over the last 30 minutes; acarbose given with each bolus feed is also effective.
9. **c.** The secretion and action of a number of hormones contribute to intermediary metabolism. As plasma glucose levels fall below 70 mg/dL, insulin secretion decreases while secretion of glucagon increases. Further declines in glucose levels induce secretion of epinephrine, growth hormone, and cortisol. Thyroid hormone is not known to play a role in intermediary metabolism.
10. **d.** Distinguishing between endogenous and exogenous hyperinsulinism can be difficult. Biochemically, laboratory results at time of critical sample and glucagon stimulation test will be identical, with the exception of C-peptide, which is expected to be elevated or inappropriately elevated with endogenous insulin oversecretion but suppressed in the setting of exogenous administration.

Chapter 33

1. **c.** Mutations in the alkaline phosphatase gene cause hypophosphatasia, a type of early onset osteoporosis characterized by absent/diminished skeletal mineralization. The femurs, like all long bones, are formed by endochondral ossification. Defects in chondrocyte function lead to a number of skeletal dysplasias because of impaired endochondral ossification. PTHrP is an important regulator of calcium status and osteoblast function prenatally, but has a limited role after birth.
2. **c.** Normal magnesium levels are required for PTH. Both high and low magnesium levels inhibit PTH secretion, the mechanism is not fully understood. Both calcium and magnesium form divalent cations, so magnesium would not be expected to bind to calcium and decrease availability for absorption (as is seen with phosphate anions).
3. **b.** DiGeorge syndrome results in hypocalcemia because of defective parathyroid gland development. In many cases the hypoparathyroidism is transient, though can be exacerbated by illness and acute stress. Mutations in CPY27B1 cause vitamin D-dependent rickets type 1A and can result in hypocalcemia due to decrease synthesis of active vitamin D. PTH resistance as seen in pseudohypoparathyroidism due to mutations in GNAS. Inactivating mutations in PHEX cause hypophosphatemia in X-linked hypophosphatemic rickets.
4. **a.** Severe hypocalcemia can result in prolonged QTc interval and resultant cardiac dysfunction.
5. **b.** Transient hypoparathyroidism due to hypomagnesemia. Large for gestational age is suggestive of infant of diabetic mother, which is a risk factor for early neonatal hypocalcemia related to low magnesium levels and impaired parathyroid hormone release. Inactivating mutations in the CaSR causing NSHPT and FHH cause hypercalcemia and typically do not present with seizure. Infants born with DiGeorge (22q11.2 deletion) syndrome are typically small in size.
6. **b.** Alkaline phosphatase. This child most likely has congenital rickets due to hypophosphatasia. This condition is caused by mutations in the ALP gene and results in markedly low serum alkaline phosphatase levels. Urine phosphorus is most helpful in differentiating malabsorptive from renal hypophosphatemic rickets, which is not present based upon the elevated

serum phosphorus. 25-OHD would be the test of choice if vitamin D deficiency rickets is suspected, which would not typically present with this severity and would be associated with low/normal serum calcium and phosphorus. An elevated intact PTH would, in the setting of hypercalcemia, confirm diagnosis of hyperparathyroidism, which would not present with rickets as described here.

7. **b.** Large for gestational age and/or infant of diabetic mother are not risk factors for osteopenia of prematurity, though they may be associated with other disorders of bone mineral homeostasis such as early postnatal hypocalcemia.
8. **c.** The amount of calcium/phosphorus that can be provided in TPN is limited; transition to full enteral feeds should be encouraged as soon as feasible. DXA scans are capable of assessing bone mineral density, but there is limited data in neonates so they are not currently a recommended procedure in the monitoring of osteopenia of prematurity. Premature infants should be supplemented with 200–400 IU of vitamin D, and increased as needed for confirmed vitamin D deficiency.
9. **b.** Based upon finding of elevated calcium and 1,25-OH vitamin D with appropriately suppressed PTH, the patient most likely has infantile hypercalcemia due to 24-hydroxylase mutation. This condition is associated with hypercalciuria and risk of nephrocalcinosis and kidney stones in late childhood/early adulthood. Vitamin D intoxication would be associated with elevated 25-OH vitamin D (typically above 70–100 ng/mL). Low calcium formulas can be helpful in managing this condition; he should also avoid vitamin D supplementation and sun exposure.
10. **b.** The patient most likely has nutritional hypophosphatemic rickets related to exposure to elemental formula. Labs will show low serum phosphorus, undetectable urine phosphorus, elevated alkaline phosphatase. Treatment includes oral phosphate supplementation and requires close laboratory monitoring for the development of hypocalcemia as a result of exuberant gastrointestinal phosphorus absorption. This condition is self-limited and will resolve with appropriate phosphorus supplements.

Chapter 34

1. **c.** Norepinephrine is the key counterregulatory hormone released in response to acute cold stress. Actions include peripheral vasoconstriction to reduce heat loss and stimulation of brown adipose tissue for thermogenesis. Thyroid hormone secretion ± cortisol secretion play a role in the long-term adaption to cold, but are not thought to play a crucial role in the acute response to cold stress. Growth hormone is not known to have a regulatory role in the response to short- or long-term cold exposure.
2. **a.** Free fatty acids, released via lipolysis, form the substrate for thermogenesis by brown adipose tissue. Thermogenesis occurs in the mitochondria of the brown adipocyte and is "nonshivering" as heat is generated in the absence of muscle contraction. Brown adipose tissue is more prominent in newborns than adults and was once thought to be an embryonic remnant, but is now recognized as being present throughout the life span.
3. **c.** Neonates can lose heat through conduct convective, conductive, radiant, and evaporative heat loss. Premature infants are at greater risk for convective, conductive, and radiant loss as a result of diminished subcutaneous fat that acts as an insulator and greater risk of evaporative heat loss because of thinner skin. Nonshivering thermogenesis is a primary physiologic response to generate heat in response to cold stress.
4. **a.** Skin-to-skin contact with the mother is the optimal heat source for stable infants immediately following delivery. Air and oxygen used for respiratory support can be a source of both convective and evaporative heat loss; therefore, warmed or humidified air is recommended, if available. Windows or other cool objects can be a source of radiant heat loss. Nonwarmed blankets can be a source of conductive heat loss.

Chapter 35

1. **b.** Extremely low-gestational-age infants are highly susceptible to infection for multiple reasons. Many natural defenses, including skin barriers, ciliary clearance, and gastric pH are naturally underdeveloped and also decreased due to medical interventions such as percutaneous catheters. Interferon-γ, a cytokine central to initiating and propagating many protective (and inflammatory) immune mechanisms, is suppressed in neonatal innate and adaptive immune cells. There are three pathways to complement activation, including the classic (antibody-activated), lectin (lectin and IgA activated), and alternative (spontaneous hydrolysis). Generally speaking, all three pathways have diminished activity in neonates compared to adults, and the classic and lectin pathways, due to lower maternal antibody transfer, are more affected in preterm infants born prior to 28 weeks' gestation. Primitive hematopoiesis, which takes place in the fetal yolk sac, transitions to definitive hematopoiesis by 5–8 weeks' gestation.

Chapter 36

1. **b.** Testing for SCID is currently included in the Recommended Uniform Screening Panel of Core Conditions, compiled by the Secretary of the Department of Health and Human Services. The SCID screen is considered positive when the TREC content falls below a threshold value that varies by laboratory. T cell receptor excision circles are circular episomal DNA fragments present in recent thymic emigrants that are formed during T cell receptor rearrangement. Cell TREC content is normally diluted through cell division, but overall content in the blood is kept relatively steady in the healthy term newborn by her or his high rate of new T cell release. Preterm infants have a lower TREC content developmentally, but due to the many comorbid conditions that

can blunt their thymic function, there are no published standards to account for gestational age when measuring TRECs. The false-positive rate for SCID, therefore, is much higher in preterm infants. Furthermore, there are no agreed standards for lymphocyte subsets measured by flow cytometry in the preterm infant, which makes confirmatory testing by flow problematic. In this case, the infant had measurable but low TRECs. In the absence of a family history or obvious stigmata for SCID, the recommended practice is to repeat the screen until the patient reaches term-corrected gestational age.

2. **a.** Conjugate vaccines contain a linked polysaccharide-protein antigen and are tailored to improve the B cell response to polysaccharide (encapsulated bacteria) antigens. A major source of protection against encapsulated bacteria is antibody generated by B cells in a T-independent fashion. T-independent responses bypass normal antigen processing and presentation by antigen-presenting cells (APC's) and interact directly with B cell receptors. Splenic marginal zone B cells (MZBs) are highly active against T-independent antigens, but neonates are deficient in MZBs. Linked protein-polysaccharide antigens in conjugate vaccines simultaneously activate B and T cells, providing necessary secondary cytokine signals from T cells that can then stimulate B cell and antibody maturation. Aluminum adjuvant, not monophosphoryl lipid A, is used in both Hib and pneumococcal vaccines. Hepatitis B is the only recombinant protein vaccine given to children. Recombinant protein vaccines generally stimulate a weaker immune response and require adjuvant. There are no current DNA vaccines administered to newborns in the United States.
3. **a.** IgG is actively transported from the mother to the fetus via IgG-specific receptors that are expressed on the placenta during the late second trimester. By term gestation, the neonate's IgG concentration is higher than the mother's. IgA is produced mainly at mucosal surfaces following expos1. ure to commensal microbes, which does not occur to a substantial degree until after delivery. IgM forms pentamers, which cannot cross the placenta, and there are no IgM-specific receptors to facilitate transport. IgE also does not cross the placenta but may be similar between mother and fetus due to a genetic predisposition to allergy.

Chapter 37

1. **c.** This patient presents with heterotaxy syndrome, including inappropriate cardiac and abdominal situs. The midline liver and stomach suggests that there is a right-sided isomerism, which is associated with asplenia or hyposplenia. Splenic anatomy can be evaluated by ultrasound, and diminished function can be assessed by detection of Howell-Jolly bodies or pitted erythrocytes or by nuclear imaging modalities. Patients with asplenia are at high risk for infection with encapsulated bacteria, such as *Klebsiella pneumonia, Haemophilus influenzae type b,* and *Streptococcus pneumoniae.* The spleen is enriched with marginal zone B cells, which rapidly produce neutralizing IgM antibodies against polysaccharides. The spleen also plays a central role in generating memory B cells against T-independent antigens, such as polysaccharides and haptens.
2. **a.** This infant's presentation (conotruncal cardiac anomaly, craniofacial findings, and hypocalcemia) is most consistent with 22q11 deletion syndrome (22q11DS), which affects pharyngeal pouch-derived structures. Patients with complete 22q11DS syndrome may suffer from athymia. The thymus is essential for common lymphoid progenitors to differentiate into naïve T cells, and athymic newborns will have low or absent naïve T cells in their circulation. Live vaccines, therefore, are contraindicated in athymic individuals who have not received immune replacement therapy. Enumeration of naïve T cell subsets is best accomplished by flow cytometry. A complete blood count with differential quantifies lymphocytes, which combines T cells, B cells, and NK cells. T cells may be diminished, even when the absolute lymphocyte count falls within the normal range. Furthermore, maternal memory T cell engraftment can occur in the absence of an endogenous T cell population in the newborn and will falsely elevate the neonate's absolute lymphocyte count on a CBC. Flow cytometry can be used to differentiate memory and naïve T cell subsets and can therefore distinguish maternal from fetal T cells. Older athymic patients often have diminished immunoglobulin levels, but immunoglobulin in a term neonate is largely derived by placental transfer and is likely to be normal at birth. Complement levels are typically normal in patients with 22q11DS.
3. **d.** IVIG is pooled donor, concentrated human immunoglobulin. IVIG contains mostly IgG, but some IgA and IgM is present. IVIG modulates immune system activity through multiple mechanisms, including inhibitory complement activation, inhibition of cytotoxic T cells, and inhibition of phagocytosis. The antibody structure includes a variable portion, which binds to its specific antigen. Once bound, the constant portion (Fc) is available to bind to Fc receptors on phagocytes, such as splenic macrophages, and signals internalization and destruction of bound erythrocytes. IVIG neutralizes macrophage activity by saturating their Fc receptors, which then leaves antibody-bound erythrocytes free to circulate.
4. **a.** The lymphocytes affected (T, B, NK) for a given SCID syndrome are dependent on the differential effects that molecular pathways have on the development of each lymphocyte subset. IL-7 signaling is critical during thymic T cell development and, in its absence, T cells fail to mature. IL-7 is not an essential cytokine for either NK or B cell development, and therefore B and NK cells are unaffected in IL-7rα deficiency. The RAG complex is necessary for V(D)J recombination, which occurs in both T and B cells, and a deficiency therefore leads to failed T and B cell development. T cell CD40L binds to CD40 on B cells and signals antibody class switching and affinity maturation. Absent expression causes X-linked hyper IgM, or failure to produce mature, high-affinity antibodies. T, B, and NK cell numbers are intact in CD40L deficiency. ADA is involved in purine salvage, and intracellular accumulation of purines in ADA SCID causes apoptosis of T, B, and NK cells.
5. **d.** G-CSF is a growth factor that selectively stimulates neutrophil production in the bone marrow and improves survival in preterm infants with sepsis-

induced neutropenia. Granulocyte-macrophage colony-stimulating factor (GM-CSF) is a growth factor for multiple hematopoietic cell lineages, including both neutrophils and macrophages. Dexamethasone inhibits the adhesion and margination of neutrophils, which increases the number of measured circulating neutrophils in a blood sample without increasing the total body number. IVIG can dampen complement-induced inflammatory pathways, but does not directly improve neutrophil number. IVIG has not been shown to improve survival in neonatal bacterial sepsis.

6. **c.** This patient presents with pancytopenia, a pronounced neutropenia, skeletal abnormalities, and signs of pancreatic insufficiency, consistent with a diagnosis of Shwachman-Diamond syndrome (SDS). The bone marrow failure of SDS places patients at risk for life-threatening infections and blood cell dyscrasias and may require bone marrow transplantation for treatment. Cystic fibrosis is the most common cause of pancreatic insufficiency in children, but does not typically present with skeletal abnormalities. Asphyxiating thoracic dystrophy presents with respiratory failure due to poor development of the thoracic ribs, but does not include pancreatic insufficiency or cytopenias. Hemophagocytic lymphohistiocytosis (HLH) can also present with cytopenias, but is usually associated with immune system activation, including hepatomegaly, lymphadenopathy, rash and fever. HLH is not associated with skeletal anomalies.

Chapter 38

1. **a.**
2. **d.**

Chapter 40

1. **c.**

Chapter 41

1. **c.** Swallowing is first seen as early as week 16, non-nutritive sucking can be seen as early as gestation week 20, nutritive sucking does not appear until weeks 32-34.
2. **b.** Premature infants have a prolonged period of alkaline pH.
3. **a.** Primitive gut tube forms by week 4, when a portion of the yolk sac incorporates into the embryo during craniofacial and lateral folding. The lumen is occluded as third epithelial lining rapidly proliferates and then later recanalizes. Failure to recanalize results in intestinal atresia or stenosis.
4. **d.** At gestation week 24, lactase activity is <25% of that found in term infants. Increase in lactase activity occurs at week 32-34.
5. **d.** Peyer patches are lymphoid follicles that are the sites of T and B cell Activity.
6. **b.** The duodenum rotates, resulting in movement of the ventral pancreatic bud poster and inferior to the dorsal pancreatic bud. The ductal systems of the two buds join at week 8.
7. **d.** The bile acid pool size in preterm infants is one-third of that seen in term infants. Sepsis is another contributing factor in preterm infants for the development of cholestasis.
8. **a.** By week 4 of gestation, the intrahepatic biliary tree is formed.
9. **b.** At week 11, the midgut loop rotates counterclockwise around the superior mesenteric artery as it returns to the abdominal cavity. Failure of this loop to return to the abdomen results in omphalocele.
10. **a.** Incomplete fusion of the lateral grooves results in failure of separation of the dorsal and ventral tubes, leading to a tracheoesophageal fistula (TEF).

Chapter 42

1. **c.** Epstein pearls are small cystic lesions on the hard palate. They typically disappear within one month of life.
2. **b.** Symptoms of GERD include poor weight gain, irritability, feeding aversion, apnea, cyanosis and bradycardia. Bilious emesis is indicative of intestinal obstruction and is not seen with GERD.
3. **d.** Cystic fibrosis, small left colon syndrome and Hirschsprung's disease are all associated with delayed passage of meconium. Milk protein intolerance can present with blood in the stool and irritability.
4. **c.** In infants with TEF, coexisting congenital anomalies can occur in up to 70%. Up to 7% of infants have a chromosomal abnormality.
5. **a.** Esophageal atresia with distal TEF accounts for 85 % of cases.
6. **d.** GER is a normal physiologic condition in neonates. Most cases are related to transient relaxation of the lower esophageal sphincter.
7. **a.** Pyloric stenosis presents between 3-6 months of age with progressive projectile emesis. Hypochloremic hypokalemic alkalosis is seen.
8. **a.** This abdominal radiograph illustrates the "double bubble" sign. It is associated with duodenal atresia which is more common in infants with Trisomy 21.
9. **d.** This presentation is concerning for Hirschsprung's disease. A barium enema would be the next step in management. Contrast enema would demonstrate a different caliber of the smaller aganglionic segment and proximal dilated segment of bowel.
10. **a.** Long term consequences of gastroschisis include poor motility, feeding intolerance and need for prolonged parenteral nutrition.

Chapter 43

1. **c.** Congenital sucrose-isomaltase deficiency is the most common congenital enzyme deficiency. This commonly presents around age 3-6 months when baby is introduced to foods containing sucrose.
2. **a.** It typically presents with the introduction of lactose into the diet in the form of either breast milk or a lactose-based formula.

3. **b.** This infant is suffering from glucose-galactose malabsorption. This is an autosomal recessive disorder which leads to a defect in sodium-glucose linked transporter protein.
4. **a.** Hypobetalipoprotenemia is due to low or absent plasma concentrations of apolipoprotein B lipoproteins and low-density lipoprotein cholesterol. Treatments is a low-fat diet and fat-soluble vitamin supplementation.
5. **d.** Congenital chloride diarrhea is the most common cause of congenital secretory diarrhea. Patients have severe watery diarrhea beginning immediately after birth. This persists when NPO.
6. **d.** Risk factors associated with NEC are: intrauterine growth restriction, small for gestational age, birth asphyxia, congenital heart disease, gastroschisis, polycythemia, hypoglycemia, sepsis, exchange transfusion
7. **d.** Complications of short bowel syndrome include: malabsorption of nutrients, gastric hypersecretion, small bowel bacterial overgrowth, intestinal adaptation difficulties, cholestatic liver disease typically from chronic use of parenteral nutrition, catheter-related complications, enterocolitis
8. **b.** Intermittent treatment with antibiotics for bacterial overgrowth is used in the management of short bowel syndrome. Chronic antibiotic use may predispose patients to antibiotic resistance.
9. **d.** In an otherwise thriving infant with stable blood work, the most common cause of blood in the stool is milk protein allergy. Diagnosis is based on clinical improvement with a milk-free diet or recurrence of symptoms with the reintroduction of milk.
10. **a.** Neonatal intussusception presents as abdominal distention, feeding intolerance, vomiting and bloody stools. Most cases involve small bowel.

Chapter 44

1. **d.** This infant is presenting with Alagille Syndrome. This is due to mutations in the JAG1 and NOTCH2 genes.
2. **b.** Infants with biliary atresia do not typically have characteristic or abnormal facies. Infants with Alagille Syndrome are seen to have triangular facies.
3. **c.** Chylous ascites is most commonly due to the congenital failure of lymphatic channels to communicate. Treatment can include paracentesis and formula containing medium-chain triglycerides.
4. **a.** The Kasai procedure is a Roux-en-Y jejunostomy that allows for biliary drainage. Infants have a better prognosis if this is done before 60 days of age.
5. **b.** PFIC presents as severe cholestasis, intractable pruritis, and possible coagulopathy. GGT is decreased or normal in types 1 and 2 and is increased in type 3.
6. **d.** Infants with Alagille Syndrome, present with very high GGT, this may be up to 20 times the normal value.
7. **b.** In biliary ascites, the bilirubin is typically found to be >4 g/dL
8. **d.** If a choledochal cyst goes untreated, it can result in obstructive symptoms such as cholangitis, pancreatitis, hepatitis, cirrhosis, and /or portal hypertension.
9. **b.** The pathogenesis of extrahepatic biliary atresia is not clearly elucidated at this time. Proposed mechanisms for the pathogenesis include a defect in morphogenesis of the biliary tract, defect in fetal or prenatal circulation, environmental toxin exposure and viral infections.
10. **c.** A1AT deficiency presents with neonatal jaundice. GGT is often high, and A1AT level is low/ A1AT abnormal phenotypes include ZZ, SZ, and MZ.

Chapter 45

1. **b.** The iron eliminated from heme oxidation is recycled. Bilirubin is formed from biliverdin catalyzed by biliverdin reductase. Carbon monoxide is produced as a byproduct during the production of biliverdin not bilirubin.
2. **b.** Unconjugated bilirubin is lipophilic and crosses the placenta easily. Conjugated bilirubin and its derivatives are lipophobic and do not cross the placenta. Lumirubin is a photoisomer of bilirubin created by phototherapy.
3. **d.** Serum bilirubin is measured by blood sampling using spectrophotometric measurement of a chemical reaction between bilirubin or its derivatives with a diazo agent, which yields a yellow pigment. Transcutaneous bilirubin a noninvasive method of measurement using optical technology. End-tidal carbon monoxide (ETCO) is an indirect measurement of carboxyhemoglobin generated as a byproduct of bilirubin metabolism and excreted via the lung. The reticulocyte count, on the other hand, is a measure of red blood cell production from the bone marrow and does not reflect bilirubin levels.
4. **a.** Ethnicity (Asian), gestational age (inversely proportional), and bruising (directly proportional) are all risk factors for hyperbilirubinemia. Formula-fed infants are at lower risk for hyperbilirubinemia compared to breast-fed infants.
5. **f.** Beta-glucuronidase is involved in the uptake of the bilirubin-albumin complex by hepatocytes. UDP glucuronyl transferase catalyzes the binding of bilirubin to glucuronic acid, converting it to a water-soluble form that can be excreted in bile. Heme oxygenase is an enzyme that breaks down hemoglobin to produce biliverdin. This step initiates bilirubin metabolism but is not part of bilirubin conjugation.
6. **d.** The RBC life span in a newborn is shorter than adults (90 vs. 120 days), conjugating enzymes are immature in a newborn, and bacterial flora is typically lower, which reduces enterohepatic circulation and increases the likelihood of hyperbilirubinemia.
7. **d.** A low serum albumin level and acidosis, as seen in sick infants, reduces the binding capacity of free bilirubin. Medications such as ceftriaxone competitively bind with bilirubin, reducing albumin to bilirubin binding.
8. **b.** UDP glucuronyl transferase, an enzyme involved in conjugation, is developmentally regulated and increases after 30 weeks' gestation. At term, this enzyme is present at 1% of adult values.
9. **a.** Ligandin is a carrier protein that helps transport the bilirubin-albumin complex into the hepatocyte for conjugation. Glucuronyl S-transferase is a conjugating enzyme.

10. **a.** Spectrophotometry is the most commonly used technique to measure serum bilirubin. The other choices can measure serum bilirubin but are less commonly used.

Chapter 46

1. **c.** Bilirubin toxicity affects the neurons in the subthalamic nuclei, hippocampus, and basal ganglia. These areas are typically seen as stained yellow on pathology. The cerebral cortex is usually spared.
2. **f.** Acute bilirubin encephalopathy is associated with a severely elevated serum bilirubin level, abnormal auditory brainstem response, and abnormal MRI. Because cochlear function is spared. the otoacoustic emission (OAE) test is usually normal.
3. **e.** Increased bilirubin production and in situ production and/or decreased serum albumin reduce albumin-bilirubin binding and increase free bilirubin, which is then able to cross the blood-brain barrier. Alteration of the blood-brain barrier in situations such as infection increase its permeability, thereby increasing the possibility of bilirubin crossing the barrier.
4. **e.** Extraneural injuries due to bilirubin toxicity include intestinal and pancreatic necrosis, renal tubular necrosis, and accumulation of bilirubin crystals.
5. **e.** Long-term sequelae of kernicterus may include choreoathetoid cerebral palsy, abnormal upward gaze, dental dysplasias and sensorineural hearing loss. The intellect is typically normal.
6. **e.** Photoisomerization which occurs with phototherapy is influenced by wavelength of light (420–490 μm blue range), irradiance, distance to the baby (closer more effective), and surface area of exposure (directly proportional to the surface area of exposure).
7. **a.** Hypocalcemia is a known risk from exchange transfusions. Other potential complications include necrotizing enterocolitis, graft-versus-host disease, thrombosis, and thrombocytopenia. Stroke, IVH, and renal failure are not known to be associated with exchange transfusions.
8. **d.** Hypocalcemia is a known complication of exchange transfusions, not phototherapy. Rash, dehydration, gonadal and retinal injury, bronze baby syndrome, and acute intermittent porphyria are known side effects of phototherapy.

Chapter 47

1. **a.** The clinical history of this infant is consistent with breastfeeding jaundice. Symptoms include a history of exclusive breastfeeding and decreased urine output; signs include dry mucous membranes and tachycardia. Although intensive phototherapy and laboratory tests will be needed, intravenous hydration is the first step in resuscitation of this infant because the primary causative factor is dehydration.
2. **c.** The infant described in this clinical vignette is experiencing breast milk jaundice. Because signs and symptoms suggest adequate hydration status, the first step in treatment would be intensive phototherapy. Suspension of breastfeeding and supplementation with formula would help aid the diagnosis and treatment but is not the mainstay of therapy. Exchange transfusion may be considered if intensive phototherapy fails to reduce bilirubin levels.
3. **d.** The presence of beta-glucuronidase in maternal milk, metal ions, and steroids, which affect the conjugation enzymes, and elevation of serum bile acids have all been known to increase the potential for breast milk jaundice.
4. **c.** Although breast milk jaundice typically occurs after 7 days of life, it may range anywhere from 5 to 15 days of life. Breastfeeding jaundice is known to occur at 2–6 days of life, and pathologic jaundice due to other causes such as blood group incompatibility presents at ~3 days of life.
5. **d.** Any process that interrupts an infant's ability to latch, suck, and swallow contributes to breastfeeding jaundice. Cleft lip, engorgement, or cracked nipples are examples of such scenarios. Maternal age does not increase the risk of breastfeeding jaundice.
6. **e.** Evaluation of hyperbilirubinemia should be directed at an evaluation of severity and identification of the cause. Fractionated serum bilirubin levels help determine the severity and whether direct of indirect, thereby directing therapy. A complete blood count and reticulocyte count help identify ongoing hemolysis. Serum electrolyte level determination can reveal dehydration, and urine culture aids in the diagnosis of urosepsis. All these tests help determine the diagnosis and direct treatment toward the underlying cause.
7. **e.** All the listed factors increase the severity of physiologic jaundice. Delayed cord clamping increases the hematocrit and thereby increases RBC turnover. Maternal diazepam crosses the placenta and binds competitively to albumin, increasing free bilirubin in the fetal blood. Conjugating enzymes are developmentally regulated, and this increases the likelihood of unconjugated hyperbilirubinemia in preterm infants. Delayed feeding reduces enterohepatic circulation, thereby increasing the risk of hyperbilirubinemia.

Chapter 49

1. **c.**
2. **a.**
3. **e.**
4. **b.**
5. **d.**
6. **d.**
7. **b.**
8. **e.**
9. **a.**
10. **c.**

Chapter 50

1. The liver **(b)**. Erythropoietin is produced primarily in the fetal liver and does not shift to the kidney until near the time of birth. Erythropoietin does not cross the placenta. Bone marrow erythropoiesis requires erythropoietin, but the bone marrow is not a primary site of erythropoietin production.

2. **c.** Inability of EPO to stimulate erythropoiesis in premature infants. Frequent blood sampling, the shorter lifespan of preterm erythrocytes compared to the erythrocytes of term infants, and suppression of erythropoiesis due to systemic illness are major contributors to AOP. Preterm infants are capable of increasing erythropoiesis in response to EPO treatment; however, they have lower EPO production in response to hypoxia than term infants. The use of EPO to treat AOP is currently controversial.
3. **d.** Only infants with an A or B blood group whose mother has the O blood type are at risk of hemolysis due to ABO incapability. ABO blood group incompatibilities between mother and fetus are common; however only ~10% of such pregnancies result in an infant affected by hemolysis and jaundice. In contrast to Rh disease, ABO incompatibility does not worsen with each pregnancy and is not a common cause of fetal anemia.
4. Hb F [α2 γ2] **(a)**. The other choices are embryonic globins present in the primitive erythroblasts produced by the yolk sac in the first trimester.
5. α-thalassemia **(b)**. Severe forms of α-thalassemia, including hemoglobin H and hemoglobin Barts (due to deletion or disruption of three or four of the 4 α-globin genes) can lead to severe fetal anemia and hydrops fetalis. Milder forms of α -thalassemia (silent carrier state and α-thalassemia trait) may not be diagnosed until later in childhood. α-thalassemia and sickle cell anemia are due to mutations in the β-chain and do not manifest until after fetal hemoglobin levels decline, generally around 6 months of age.
6. Sickle cell trait **(b)**. Following birth, it is appropriate for Hb F (fetal hemoglobin) to predominate. The presence of both Hb S and Hb A indicates the patient has one normal β-chain and one β-chain with the sickle cell mutation (Hb S). A newborn screen suggestive of sickle cell anemia would show Hb F with Hb S and no Hb A. A normal newborn screen would show only Hb F and Hb A.
7. X-linked recessive **(c)**. Due to this inheritance pattern the majority of affected individuals are male; however females can be affected if they are homozygous for the mutated G6PD allele or in the setting of unbalanced X-inactivation.
8. During the third trimester **(c)**.
9. Four months **(a)**. Iron supplementation is important, as iron deficiency has been associated with neurologic deficits and anemia. Term neonates have sufficient iron stores for 4–6 months, and iron supplementation is recommended starting at 4 months for term infants who receive more than half their feeds form breast milk. Breast milk has lower levels of iron than formula, but the iron in breast milk is highly bioavailable. Iron supplementation should be considered for preterm infants beginning at 1 month of age. Preterm infants have higher iron requirements due to more rapid rates of postnatal growth.
10. To prevent neurodevelopmental delays **(a)**. Polycythemia has been associated with neurodevelopmental delays, however PET has not been shown to improve neurologic outcomes.

Chapter 52

1. **c.** Neonatal thrombocytopenia is associated with preeclampsia and is typically a self-limited mild thrombocytopenia that nadirs by 2–4 days and resolves at around one week of life.
2. **b.** NAIT is due to maternal antibodies against fetal platelet antigens. Maternal thrombocytopenia is suggestive of autoimmune thrombocytopenia. NAIT can cause severe thrombocytopenia. Random donor platelets will increase the platelet count and are more readily available than type-matched platelets, although the response may be transient.
3. **a.** Neonatal autoimmune thrombocytopenia is frequently associated with maternal thrombocytopenia and maternal ITP or SLE.
4. **d.** Neonates have lower levels of antithrombin and protein C. Coagulation factors do not pass from the mother to the fetus. Neonates have higher von Willebrand factor levels than adults. Normative platelet values are similar for neonates and adults.
5. **c.** Early onset VKDB occurs in the first 24 hours of life and can result in severe bleeding. It is associated with maternal medications including warfarin, isoniazid, or antiepileptics. The other factors are associated with late onset VKDB.
6. **a.** Intracranial hemorrhage. Late onset VKDB occurs after two weeks of age and is frequently associated with intracranial hemorrhage. Infants at risk for late VKDB include exclusively breastfed babies who did not receive the vitamin K shot, infants with cholestatic liver dysfunction, and infants with chronic intestinal malabsorption.
7. **a.** The classic triad of renal vein thrombosis is thrombocytopenia, hematuria, and a palpable flank mass.
8. **b.** DVTs are frequently associated with central lines and often result in thrombocytopenia.
9. **b.** Infants with TAR have severe thrombocytopenia at birth that improves over the first year of life. The presence of thumbs helps to distinguish infants with TAR from infants with Fanconi anemia.
10. **d.** PF can be due to an inherited deficiency in protein C or protein S or PF can be secondary to infection. Central lines are associated with DVTs, which cause thrombocytopenia, but generally not PF.

Chapter 53

1. **d.** Of the choices listed, the first three are thought to be critically important for a safe PRBC transfusion in a neonate. All patients of all ages will require a type and cross to ensure ABO matching and no reaction. All patients, but especially neonates, should have PRBC products leukocyte reduced to decrease viral infectious transmission. Irradiation (or CMV negative units) would be strongly preferred for neonates. In addition, giving fresh PRBC (ideally < 14 days old) would also be preferred by most centers. Washing, which is done to decrease risk of allergic reaction, is typically only done if a patient has had a previous allergic reaction; it would not be necessary for all neonates.

2. **a.** Random donor PRBC are almost always preferred to related family member donors. There are multiple reasons for this. First, in neonates, and also in patients with any immune system dysfunction, related donor blood products pose additional risks, include the risk of alloimmunization, and the risk of transfusion-associated graft versus host disease. Second, many family members are first-time donors, which make them statistically higher risk to have an infection. Random donor units need to be ABO compatible, and type O patients require type O blood, as they have naturally occurring anti-A and anti-B antibodies.
3. **c.** Transfusion related acute lung injury (TRALI) is now the most common cause of morbidity and mortality during blood product transfusions. However, it remains relatively rare in neonates and children. Management consists of stopping the infusion (if still running), considering diuresis, and good supportive care and respiratory support. TRALI is thought to occur through immunologic mechanisms including recipient neutrophil activation by donor antigens. Hemolytic transfusion reaction is unlikely unless clerical error. CMV transmission would not present as acute symptoms and signs. Transfusion associated circulatory overload (TACO) is relatively excluded by the normal cardiac size. Sepsis is also much less likely than TRALI.

Chapter 54

1. **a.** Respiratory distress, hepatosplenomegaly, significant bruising, and palpable nodules may all be symptoms of congenital leukemia. The most common subtype of congenital leukemia is acute myeloid leukemia (AML), and prognosis is very poor. Leukemia cutis is the term for leukemia nodules which may be seen. This should be differentiated from bluish nodules which may be seen in neuroblastoma as well as the dry, scaly rashes consistent with Langerhans cell histiocytosis (LCH). For the patient in the vignette, next steps would include complete blood work, bone marrow aspiration/biopsy, lumbar puncture, and pediatric hematology/oncology consultation. Unfortunately, prognosis for congenital leukemia is poor.
2. **d.** Children with Down syndrome have a markedly increased risk of multiple hematologic abnormalities, including AML, ALL, TAM, and thrombocytopenia. However, the most common and most likely diagnosis in the first week of life is transient abnormal myelopoiesis (TAM [formerly called transient myeloproliferative disorder, TMD]). TAM is truly a transient leukemia and is specific to neonates (age < 7 days) with Down syndrome, occurring in about 10% of neonates with Down syndrome. Neonates with TAM develop proliferation of a leukemia clone, the cells are indistinguishable from AML cells, and the presentation is otherwise identical to AML. However, for reasons that are unclear, TAM typically resolves spontaneously and does not require therapy.
3. **b.** As the majority of neonates with Down syndrome will have the TAM resolve, observation is typically recommended. A small number of neonates may require some chemotherapy if significantly symptomatic, but this is not the norm. However, neonates with TAM do have a very high absolute risk of 25% for the development of true AML within the first 4 years of life. For this reason, very close follow up, including screening CBCs, is recommended.
4. **c.** Langerhans cell histiocytosis may affect any organ, though most commonly affects bone and skin. Skeletal survey would be the only test above required for all patients with LCH. Additional diagnostic workup would be considered if the patient had localizing symptoms or signs. Ultrasound rather than CT is typically used to evaluate for hepatic and splenic involvement, if indicated. Complete laboratory screening including CBC, chemistries, kidney and liver function testing, and coagulation studies are also required in all patients. The treatment and prognosis of LCH is dependent upon disease extent and organ involvement. Infants with disease limited to skin or bone do extremely well, while those with multi-organ involvement will typically need chemotherapy for cure. Vinblastine and prednisone are the most commonly recommended agents for LCH.
5. **b.** Neonatal teratoma is the most common tumor in newborns, when benign and malignant tumors are taken together. The vast majority of teratomas are "mature" or benign, and thus do not have any malignant potential, and do not produce AFP or beta-hCG. About 10% of teratomas will have malignant elements, and may be labeled "immature" or have germ cell tumor components. Immature or germ cell tumors do often produce AFP or beta-hCG, and these tumor markers can be used to follow patients. Surgical resection is the mainstay of therapy and is recommended up front.
6. **c.** Large facial hemangiomas raise concern for PHACES syndrome (posterior fossa malformations, hemangioma, arterial/aortic abnormalities, cardiac defects, eye abnormalities, sternal cleft/supraumbilical raphe syndrome). MRI brain is required to evaluate for brain abnormalities, typically in the posterior fossa. In general, large hemangiomas (> 5 cm) or multiple hemangiomas (> five cutaneous lesions) will require additional workup and often imaging for internal abnormalities. Kasabach-Merritt syndrome is the association of thrombocytopenia and DIC which may be associated with giant hemangiomas or vascular anomalies.
7. **b.** Historically, corticosteroids (prednisone) were the mainstay of treatment. However, steroid side effects are significant and have led to decreased use. Currently, propranolol is a very well tolerated, safe, and effective medical treatment for hemangiomas, and it should be considered first-line. Additional or second-line therapies may include laser therapy, embolization procedures, and sirolimus.
8. **a.** This patient very likely does have congenital neuroblastoma. However, biopsy and pathology confirmation are absolutely required to make the diagnosis. Especially in a neonate with multiple system affected, biopsy or adrenal resection is critical to gain additional histologic information about the neuroblastoma, including evaluating for favorable histology and N-MYC amplification. This patient likely has stage IV-S (M-S) neuroblastoma, which often may be

safely observed, as neonates with this presentation of neuroblastoma are very likely to have spontaneous resolution of their disease. However, one would not observe without first confirming the diagnosis. MIBG scan as well as urine HVA/VMA would also be supportive of the diagnosis, though would not supersede tissue biopsy. Most neonates will not require intensive chemotherapy or stem cell transplants for cure. The prognosis for neonates with neuroblastoma is excellent.

9. **e.** There is a very strong association between rhabdomyomas and tuberous sclerosis (TS). In fact, about 80% of patients with rhabdomyomas will be diagnosed with TS; half of TS patients will have rhabdomyomas. Workup for TS would include brain MRI as well as consideration of genetic testing. Sturge-Weber syndrome is a neurological disorder associated with port-wine stain on the face as well as intracranial abnormalities. Beckwith-Wiedemann is a syndrome including large tongue, hemi-hypertrophy, and risk of pediatric tumors including Wilms tumor and hepatoblastoma. Down syndrome has no association with solid tumors. Rhabdomyomas are benign and have no association with malignant rhabdomyosarcomas.
10. **a.** Renal masses are relatively uncommon in neonates, though may occur. The most common renal mass is congenital mesoblastic nephroma, while the most common malignant renal mass is Wilms tumor. However, without biopsy and pathology it can be impossible to determine the tumor type. For that reason, immediate pediatric surgical consultation and nephrectomy are advised. Genetic testing for familial syndromes could be considered if there was a family history of pediatric cancer, though this would not be urgent. MIBG and urine HVA/VMA would be helpful in the diagnosis of neuroblastoma, which is an adrenal tumor. Hematuria may present with Wilms tumor, though simple urinalysis is adequate for evaluation.

Chapter 56

1. **d.** The greatest risk for recurrent myelomeningocele for a mother is having a prior affected child with the same father. This pattern indicates a yet unidentified genetic factor for neural tube defects.

Folic acid supplementation starting now, at 8 weeks gestation, will not affect the risk of myelomeningocele. Open neural tube defects are a result of neurulation errors occurring at 3–4 weeks gestation. Folic acid supplementation initiation is recommended pregestation with 400 μg daily for most women and 4000 μg daily for women with a prior affected child.

B_{12} deficiency is also a risk factor for neural tube defects and should be considered in women on vegan diets and in women with pernicious anemia.

Cocaine use and smoking are not documented risk factors for the development of neural tube defects. Alcohol is weakly associated with increased rates.

Her acne medication may be isotretinoin, which is a known teratogen and does increase the development of neural tube defects. Other classic medication risks include valproate and carbamazepine.

The maternal metabolic environment also elevates the risk of neural tube defects including maternal obesity, maternal pregestational diabetes, and first trimester maternal hyperthermia.

Chapter 57

1. **b.** Moderate HIE. Lethargy, hypotonia, exaggerated grasp reflex and weak suck are present in Sarnat stage 2 (moderate encephalopathy).

Chapter 58

1. **b.** Periventricular Leukomalacia represents injury and maldevelopment of the periventricular white matter that may be cystic or non-cystic and is best identified on ultrasound at about 4 weeks after birth. While injurious processes may be occurring in the time period just after birth, the development of white matter abnormalities that are visible on ultrasound takes time and thus will not be apparent at 24 hours after birth and is unusual to see at just 7 days after birth.
2. **c.** Significant intracranial hemorrhages are not usually associated with the routine uncomplicated use of vacuum to assist in the delivery of a term infant. A 32 week infant who does not require significant resuscitation at the time of birth is also unlikely to develop a significant intracranial hemorrhage. Neonates born at 26 weeks in the setting of a placental abruption that require significant resuscitation after birth are at high risk of developing significant intracranial hemorrhages in the form of Intraventricular Hemorrhage.

Chapter 59

1. **c** and **d.** Increased risk of these from traction and torsion of head. These movements would not increase the risk of cephalohematoma and skull fracture.

2a. **c.** Subgaleal hemorrhage: pale baby, boggy head, fluctuant scalp.

2b. **d.** 80 cc. Calculation: for every increase in head circumference by 1 cm estimated blood loss = 30–40 cc.

2c. **d.** Large subgaleal hematoma is a life-threatening complication that carries a high mortality if not treated with replacement of blood products and monitoring for disseminated intravascular coagulopathy.

Chapter 60

1. **c.** Pyridoxine-dependent seizures. Neonatal seizures that present early (in the first hours after birth) and are

resistant to multiple antiepileptic medications, in the context of an uncomplicated pregnancy and delivery—are unlikely to be hypoxic-ischemic encephalopathy. These will rapidly improve with administration of pyridoxine. Other causes listed are unlikely to present this early and should have additional history (jaundice in the case of kernicterus, perinatal risk factors/events in case of hypoxic-ischemic encephalopathy).

Chapter 61

1. **b.** Although Group B *Streptococcus* (GBS) is the most common cause of neonatal meningitis overall, *Escherichia coli* has become the most commonly isolated organism in very low birthweight infants. Other major pathogens causing early onset meningitis in neonates include *Listeria* and *Streptococcus pneumoniae.* Other pathogens causing late onset meningitis include coagulase negative *Staphylococcus, Staphylococcus aureus*, *Klebsiella, Enterococcus, Enterobacter*, and *Pseudomonas.*

Chapter 62

1. **d.** This neonate has classic symptoms of neonatal abstinence syndrome from opiate withdrawal. The timing of symptom onset depends on the both the medication and timing of last dose prior to delivery. In utero clearance occurs much more rapidly than neonatal opiate clearance. Withdrawal symptoms from chronic maternal short-acting opiate use may peak in the first 1–2 days, while the long-acting opiate withdrawal (methadone/buprenorphine) peaks day 3–4 and may extend for weeks to months.
   Maternal buprenorphine does not cross the placenta as readily as methadone. This is likely the physiology behind the association between buprenorphine therapy and less frequent/severe withdrawal in neonates when compared with methadone. Early studies did not demonstrate a dose-effect on withdrawal. Later evidence has shown some trend with lower maternal opiate doses resulting in less neonatal withdrawal.
   The Modified Finnegan scoring is the recommended scoring system by the AAP. It is used for serial evaluation of neonatal withdrawal from opiates and is not diagnostic of opiate withdrawal. Many neonatal states can result in increased scores.
   Routine urine toxicology screens do not include buprenorphine and methadone. These synthetic opiates do not result in a positive opiate result on routine screen. This mother's negative urine screen does not indicate buprenorphine noncompliance.
   Breastfeeding is recommended in this setting and is associated with reduced withdrawal. The effects are not attributed to medication exposure in breast milk, as buprenorphine and methadone only cross into the breast milk in small amounts. Breastfed babies benefit from increased frequency feeds. Formula fed neonates often require increased volume and caloric density feeds.

Chapter 63

1. **c.** Congenital myotonic dystrophy is an autosomal dominant disorder, typically inherited from the mother. In the congenital form, neonates are hypotonic at birth, often demonstrating poor respiratory effort. Classic examination findings include facial hypotonia, with decreased nasolabial folds bilaterally, with a carp-like appearance to the mouth, and severe hypotonia on examination. Deep tendon reflexes are absent, and talipes equinovarus is frequent. Many require respiratory support initially with ventilator or positive pressure ventilation, such as bilevel positive airway pressure (BiPAP) or continuous positive airway pressure (CPAP).
   The disorder demonstrates anticipation, with each generation affected more significantly than the prior, which is caused by a CTG repeat in the 3′ UTR of the *DMPK* gene on chromosome 19. Unaffected individuals have between 5 and 27 repeats, but affected neonates present with greater than 1000 repeats. The number of repeats correlates with disease severity, and affected mothers have between 50 and 1000 repeats. Frequently, the mother may not be diagnosed with a neuromuscular condition but, on discussion, has a history of hand weakness or cramping. Examination of the mother reveals facial hypotonia, myotonic response of the hand muscles, and frontal balding.
   Although decreased fetal movements or prior fetal losses may be present in congenital myotonic dystrophy, and may support the diagnosis, these are features present in numerous neuromuscular and genetic conditions.
   Fetal alcohol syndrome does not present with neuromuscular weakness.
2. **c.** This examination is most consistent with a moderate encephalopathy. The description of the mental status is equivalent to lethargy, given the necessity for persistent stimulation to arouse the neonate. This is supported by the absence of some primitive reflexes and the hypotonic examination.
   Severely encephalopathic neonates do not arouse to stimulation, but may show posturing on stimulation. Primitive reflexes such as plantar grasp, Moro, and suck are absent, and deep tendon reflexes may be hyperreflexic or completely absent.

Chapter 67

1. **b.** The presence of unilateral corneal edema, enlarged corneal diameter, tearing and photophobia is most consistent with unilateral congenital glaucoma. The intra-ocular pressure would be expected to be high, and treatment is usually surgical. Microbial keratitis usually presents as a localized infiltrate in the cornea, and would not cause an increased corneal diameter. Storage diseases can cause diffuse corneal clouding, but would be bilateral with normal corneal diameter in most cases. There is no role for corneal biopsy in congenital glaucoma, and corneal transplant is not indicated for the primary treatment of glaucoma.

2. **c.** Common causes of ophthalmia neonatorum include Neisseria, Chlamydia, Herpes virus, and chemical. While awaiting results of gram stain and culture, it is appropriate to cover both Neisseria and Chlamydia with systemic ceftriaxone and erythromycin.
3. **a.** The most concerning diagnosis in this scenario is unilateral retinoblastoma, which requires prompt diagnosis and treatment. Retinopathy of prematurity is not likely to develop in a full-term infant. Strabismus may cause a bright red reflex when viewing both eyes simultaneously, but would not cause leukocoria. Congenital rubella syndrome can cause an abnormal red reflex due to cataract, but would be expected to be a bilateral disease.

Chapter 68

1. **c.** Genetic congenital hearing loss is 70% nonsyndromic (isolated hearing loss) and approximately 80% autosomal recessive.
2. **d.** *DFNB-1/GJB2* (connexin 26 mutation) accounts for 50% of cases of congenital, nonsyndromic, autosomal recessive hearing loss.
3. **d.** The goal of newborn hearing screening is to identify hearing loss by 1 month of age, and institute early intervention by 6 months of age.
4. **f.** All the factors listed are considered risk factors for hearing loss.
5. **d.** CMV accounts for up to 20% of hearing loss in newborns in the United States. Approximately 90% of patients with congenital CMV infection are asymptomatic at birth; 10%–15% of these asymptomatic infants have hearing loss.
6. **c.** Bilateral preauricular pits should raise concern for branchio-oto-renal (BOR) syndrome, so a renal ultrasound should be performed. Genetic testing may be appropriate if the renal ultrasound raises further concern for BOR. Surgical excision would be premature at this point because the lesions are asymptomatic. CT of the face and ophthalmology evaluation are not indicated at this time.
7. **b.** At-risk newborns who pass the newborn hearing screening (NBHS) should be evaluated by an audiologist every 6 months for the first 3 years of life to identify any changes in hearing.

Chapter 69

1. **b.** The triad of findings in Pierre Robin sequence is cleft palate, micrognathia and glossoptosis. A cleft lip is not commonly seen.
2. **d.** Patients with DiGeorge syndrome are at risk for hypocalcemia.
3. **c.** This scenario describes a type 2 branchial cleft anomaly, which will commonly have a tract that opens internally in the tonsillar fossa.
4. **a.** This scenario describes an infant with torticollis, which is confirmed with an ultrasound and managed with physical therapy.
5. **c.** The cricoid cartilage is the narrowest portion of the pediatric airway. The vocal folds are the narrowest portion of the adult airway.
6. **e.** All answer options are associated with increased risk of subglottic stenosis.
7. **d.** The child in this scenario has laryngomalacia but, given the lack of significant respiratory symptoms or failure to thrive, no surgical intervention is indicated.
8. **b.** In the absence of significant airway symptoms, propranolol should be initiated. A tracheostomy is not necessary given that the airway obstruction is mild, and the infant does not have significant respiratory symptoms.
9. **b.** The risk of having another child with cleft lip/palate without family history is 4%.
10. **e.** If a flexible suction catheter cannot be passed, choanal atresia is the most likely diagnosis of the options listed.

Chapter 77

1. **a.** making reduction in communication errors a key focus for quality improvement
2. **False,** most likely due to ability to aggressively treat infectious illnesses
3. **c.** regionalization has been demonstrated to improve both maternal and neonatal outcomes
4. **c** or **d** by designation
5. **c** by designation

Chapter 78

1. **b.** For a number of reasons, physicians are not approaching families as often as in past years.
2. **False.** Culture and sensitivity (C&S) requires maternal consent, even in a situation of fetal distress.
3. **e.** All these factors affect outcome when an infant is delivered extremely prematurely.
4. **c.** C&S requires maternal consent, even if considered an emergency.
5. **True.** Carrier screening for minors is indicated if therapy is available to protect a child's open future. It can be considered if therapy is not yet available in the case of severe parental anxiety after parents have been appropriately counselled.

Chapter 79

1. **b.** Traditional statistics test the null hypothesis of no difference between groups. A p value describes the likelihood of being able to accept the null hypothesis, given the observed value, specifically that a distribution based on no difference would produce a result as or more extreme as the observed difference. In this

particular example, it is very possible that both methods are effective in preventing IVH (but we do not have an untreated group to compare), but that one is more effective than the other.

2. **c.** Parametric tests are most appropriate for comparing groups of continuous data, with normal distribution, of reasonably large size. Although the t test is reasonably *robust* (resistant to error) even if these parameters are violated, nonparametric tests may be more appropriate.
3. **a.** ANOVA tests the null hypothesis that, among mean values derived from multiple groups, no group differs from any other group. A statistically significant result suggests that there is a difference among the groups but does not suggest which or how many groups differ. Further testing of individual comparisons with appropriate correction for multiple comparisons is needed.
4. **b.** Type II error is the error of concluding, based on a sample, that no difference between groups exists when a difference actually does exist in the population. The likelihood of making a type II error decreases as sample size increases. A more stringent p value would reduce the chance of type I error (concluding a difference exists when it doesn't). The Fisher exact test would also be an appropriate statistical test, but wouldn't address a type II error. One could argue that neither of the dressings is any good and the investigators should move on.
5. **b.** Correlation can range from 0 (no correlation) to 1 (complete correlation). Correlation coefficients above about 0.70–0.75 describe strong correlations. The coefficient of determination (r^2) describes the variance in one measure that can be attributed to another (and is, in this case, 0.81, or 81%). In the absence of a gold standard measure, it is not possible to determine whether one measure in superior to another in this example.
6. **a.** Sensitivity is the ability of a test to detect those with disease = true positive tests (in this case test positive in the presence of NEC) divided by all cases of disease (in this case all NEC) = 15/(15 + 5) = 15/20 = 75%.
7. **c.** Specificity is the ability of a test to detect those without disease = true negative tests/all without disease = 40/(10 + 40) = 40/50 = 80%
8. **b.** Positive predictive value is the ability of a test, when positive, to predict disease = true positive tests/all positive tests = 15/(15 + 10) = 15/25 = 60%.
9. **d.** Negative predictive value is the ability of a test, when negative, to predict absence of disease = true negative tests/all negative tests = 40/(5 + 40) = 40/45 = 89%
10. **c.** An ideal test (sensitivity and specificity of 100% each) has an AUC of 1.0. A test that performs no better than chance (sensitivity marches straight to 0 as specificity marches straight to 100% and vice versa) has an AUC of 0.50. This test is unlikely to have a good combination of sensitivity and specificity. By comparison, the AUC of Fig. 79.12 is about 0.80. Although ROC curves describe the relationship between sensitivity and specificity, the AUC does not directly describe a particular relationship (e.g., what sensitivity will be at a particular specificity or vice versa). The AUC also does not directly describe positive predictive value (a).

Chapter 80

1. **c.** Case control studies, by virtue of selecting currently existing cases (outcomes), can accrue a large number of cases without needing to follow large numbers of patients waiting for an outcome to occur. Neither case-control nor cohort studies are the gold standard for assessing causation. Since exposure data must be collected retrospectively in case-control studies, it is sometimes incomplete or biased. Relative risk cannot be assessed from case-control studies. (Odds ratios can be calculated–see Chapter 79.)
2. **a.** Since they are experimental studies in which only the intervention differs between groups, randomized controlled trials are more likely than observation trials to allow investigators to conclude that an exposure causes an outcome. Randomized controlled trials are resource intensive and time consuming, and unlike observational studies, involve the investigators exposing participants to interventions that could carry risk. (There may be the same risks in an observational study, but they are accrued in the course of treatment, not imposed by the study.)
3. **b.** Double blinding of studies is a method of decreasing bias in reporting of events, particularly if the events are subjective. Avoiding the use of a placebo would likely increase, rather than decrease bias. *A priori* definition of event severity is likely to avoid misclassification of events that are reported (and could avoid investigator bias), but would not be likely to change reports from participants. More frequent ascertainment of side effects is likely to improve the reliability of reports but may not decrease bias in reporting.
4. **b.** Multivariate analysis is one method of detecting and controlling for confounding factors. Other methods include matching and experimental (rather than observational) study designs. Since confounding factors are, by definition, related both to the exposure of interest and the outcome, targeting data collection toward suspected confounding factors would increase the likelihood confounding would be detected.
5. **c.** Dose response, biological plausibility, and consistency with other studies all support a causal effect of (A) on (B). If (A) always preceded (B), the temporal sequence would also support causation. However, experimental studies remain the best method for testing causal hypotheses.
6. **d.** Incidence is a rate, implying that the time over which risk accrues must be included in reporting it. An alternative way of expressing this incidence would be five cases per 10,000 child-years. A prevalence, for instance of survivors of childhood sepsis, could be expressed as a percentage or a number per 10,000. A rate without a denominator does not fully express incidence.
7. **b.** Presence of a presymptomatic period during which an effective treatment could minimize later harm, combined with a high-sensitivity, high-specificity test and a relatively high prevalence of disease all improve the suitability of a screening test. Other factors that make

a screening test more suitable include high severity of the disease, low invasiveness of the test, and reasonable cost.

8. **c.** To review, decision analysis attempts to quantify both the frequencies of outcomes of a given decision and the value (expected utility, EU) of those outcomes for patients and to combine these to predict the best decision for the average patient in that situation. A decision that clear data suggest leads to a high likelihood of an outcome for which there is high agreement on the value of that outcome (e.g., return to former state of good health vs. death) would be supported. Since decision analysis depends on applying only a few factors derived from population data to an individual case, it can serve only as a general guide for patient care.
9. **c.** In expanding from one rater to two, it would be most reasonable to assess the interrater reliability of reads. Another measure of reliability (and a close second for a correct answer) would be internal consistency; do the various components of the scoring system correlate with one another? Validity (does the test work?) is separate from reliability (reproducibility, can the test be applied?). Face validity (the subjective impression that brain injury might be associated with neurodevelopmental impairment) and predictive validity (previously shown to have high sensitivity and specificity for predicting outcome) have already been assessed for this test.
10. **d.** Answer a is both accurate (estimates the true pressure correctly) and precise (little scatter). Answer b is precise, but inaccurate. Answer d, although imprecise, estimates the pulmonary pressure accurately on average. Answer c is both inaccurate and imprecise.

Chapter 81

1. **b.** Brainstem auditory evoked response at 6 months of age is both correlated with and predicts behavioral audiometry results. A measure before therapy begins would not test the effect of the therapy (and is temporally more distant from the definitive outcome). Death is a competing outcome, rather than a surrogate. Although cholestatic jaundice might be correlated with therapy, it is less clear that it would predict hearing outcomes.
2. **a.** A larger expected difference between groups, larger α error, smaller variability (e.g., standard deviation), or a larger β (= lower power [1-β]) allows a smaller sample size for a study. See Table 81.2 for an illustration.
3. **b.** The likelihood ratio (negative) is the ratio of odds following a negative test to the prior odds (i.e., the odds before the test, in this case the population odds). Using the nomogram in Fig. 81.6, and knowing the pretest probability of 33%, we can calculate the posttest probability to be about 20%. The actual calculation is:
   Pretest risk 0.33 → odds 0.33:(1–0.33) = odds 0.33:0.67 = pretest odds 1:2
   × LR(–) 0.5 = odds 0.5:2 = posttest odds 1:4
   → risk 1/(4 + 1) = risk 1/5 = posttest risk 0.20.
   Remember, because it deals with odds, this is not as simple as pretest probability × likelihood ratio, which would have yielded about 17% (close, but not the same). Likelihood ratios (negative) are not directly connected with absolute percent changes, and cannot be directly translated into a comparison to likelihood ratios (positive).
4. **b.** The relative risk reduction is the change in risk compared to the original risk, in this case 0.20/0.70 = 0.29 or 29%. The absolute risk reduction is the absolute change in risk, in this case 20%. Relative risk or risk ratio (RR) is the ratio of risks, shown in these examples as both (risk untreated):(risk treated) = 0.70/0.50 = 1.4 and (risk treated):(risk untreated) = 0.50/0.70 = 0.71. The odds ratio (OR) of treated to untreated is (0.5/0.5)/(0.7/0.3) = 0.43, compared to RR 0.71, showing how ORs can exaggerate effects.
5. **a.** The number needed to treat (i.e., number who would need to receive an intervention in order for one patient to have an improvement) is 1/(absolute risk difference), in this case 1/0.07 ≈ 15. Note that the number needed to treat (NNT) does not depend on the initial risk, so changes from 97% to 90%, 40% to 33%, and 8% to 1% all have the same NNT.
6. **d.** Although an absolute definition of statistical significance is open to debate, a *p value* < 0.05 is usually accepted as statistically significant. A difference of 2 hours of cough, with wide overlap of groups, is not likely to be clinically important. The statistical significance is due to the large sample size (this result is for 500 subjects per group), which can show statistical significance for even small differences.
7. **c.** The sensitivity and specificity of a diagnostic test is best measured by comparison to a gold standard in a group of subjects all receiving both the new test and the gold standard evaluation.
8. **a.** Case control studies provide the opportunity to oversample for rare conditions and are particularly useful for the study of the antecedents of rare diseases.
9. **d.** Longitudinal evaluations allow assessment of disease prognosis. Full ascertainment of outcomes is important for full understanding of prognosis. A comparison group allows more certainty about whether a particular outcome is related to the disease itself, but is not always necessary. For instance, assessment of death from a primary cancer might not require a comparison group, but assessment of death from second cancers following cancer therapy might benefit from a comparison to incidence of the same cancers in the general population. Other, possible, but less appropriate answers would be (a) and (b). Cohort studies can also assess the association of disease with earlier exposure, but the sample often needs to be quite large and the earlier exposure needs to be predefined (in order to be able to establish the cohort). Cohort studies, particularly if they are large, can also assess the harm of a therapy that might not be detected in a clinical trial. Phase IV registry studies are, in fact, cohort studies.

10. **b.** Experimental studies, such as randomized controlled trials, allow the investigator to isolate the effect of a therapy by assigning groups of otherwise similar subjects (with variation minimized by randomization) to receive the therapy (intervention group) or not (control group).

Chapter 82

1. **d.** The characteristics of effective feedback include the following:
   1. timely
   2. nonjudgmental
   3. focused on changeable behaviors or attainable goals
   4. specific and based on observed behaviors
   5. focused on positive consequences of change

The main purpose of formative feedback is to help individuals learn new knowledge or skills, improve upon existing knowledge or skills, and reinforce behaviors that are desirable. In this vignette, telling the medical student that he did a "great job talking to the mother about jaundice" does not help him understand what was great about his communication skills. Specific information is needed to reinforce desirable behaviors (e.g., "You did a great job talking to the mother about jaundice by helping her understand why jaundice is important to follow"). Formative feedback should provide examples of observed behaviors (e.g., "When the mother asked how long her daughter needed to stay in the hospital, you estimated 1–2 days."), followed by a suggestion to improve upon the behavior (e.g., "I also suggest letting her know what her baby should accomplish before going home …") and why that suggestion is important (e.g., "… so that she understands the discharge criteria, just in case her baby does not respond to phototherapy as anticipated."). Within the same feedback session, supervisors or mentors may also provide strategies for change (e.g., "… please practice these communication skills with another person.")

2. **b.** Well-formulated learning objectives are specific (a), measurable (c), and outcome-based (d), stating what the learner should be able to do after a learning activity. These learning objectives set clear expectations and can serve as an educational guide for both learners and educators. Choice (b) is the incorrect response, because goals are different from learning objectives; goals provide aspiration towards a long-term outcome, whereas learning objectives provide more focused short-term steps towards achieving the long-term goal. In addition, the verb used in (b), "understand", is nonspecific and not measurable. Both learners and educators would not be able to define how understanding would be measured. The statements in choices (a), (c), and (d) would serve as learning objectives that define how understanding is measured.
3. **d.** Key concepts in creating an effective learning environment include making the learning relevant and based on clear learning objectives, respecting the experiences that adult learners bring to the environment, ensuring a safe space where all learners' opinions are valued, and creating an interactive environment (b and c). Interactive teaching styles engage the learner and allow them to bring their experiences, insights, and opinions to the group, reinforcing the relevance to the learner and their individual needs (c). The physical environment should have appropriate lighting, temperature control, and comfortable seating to ensure that the learner is not distracted by physical discomfort. A very bright room may cause discomfort, thereby causing distraction and detracting from learning.
4. **e.** All of the answer choices except *e* are true statements. Lectures enable the delivery of large amounts of material to a larger group of learners but lack in the interactive nature and ability to explore learners' understanding of the content (a). Small group discussions create a more interactive environment as the smaller numbers often help learners feel more comfortable in sharing ideas and opinions (b). In addition, given the lower learner-to-facilitator ratio, it is easier for the facilitator to engage learners, assess their understanding, and encourage discussion relevant to learner needs. Bedside teaching enables the facilitator to explore the application of learner knowledge as the facilitator can explore the learners' critical thinking skills and rationales for decision-making (c). Simulation-based training enables standardization of learning exposure because learners can be exposed to the same clinical conditions, presentation, and change in patient status (d). Option (e) is incorrect, because small group teaching requires a higher facilitator-to-learner ratio.

Chapter 83

1. **c.** Respect for persons is applied as informed consent. Beneficence is applied as assessment of risks and benefits. Justice is applied as subject selection. Data analysis is extremely important, but not mentioned as a primary application in the Belmont Report.
2. **a.** The investigator has only two realistic choices: completely removing his/her financial interest, or, completely removing him/herself from any aspect of performing the trial. Given the investigator's nonfinancial conflicts (this is his/her invention), having an independent investigator perform the trial might be an even better option (but wasn't given). Unfortunately, this is based on a real case, where option *d* was chosen, resulting in poor choices and the death of the first subject.
3. **b.** Some things are just too good to be true. The figures are identical. The *right-hand bars* are exactly half the *left-hand bars*, each time! The drug effect is consistently astounding. The standard errors (if that's what the whiskers depict) are nice, small, and equal. These figures are fabricated. If Figs. 1 and 4 differed from one another, but they were still too pretty, you might believe that the investigator was falsifying the data by cleaning it up to make his/her point. If the introduction of the author's paper looked like the discussion of your last paper, the author would be plagiarizing. This is extremely unlikely to be an honest difference of opinion.
4. **a.** You have made substantial contributions to the conception, design, analysis, and interpretation of the work. You both helped draft and revised the manuscript critically. You would, presumably, before this,

have agreed to be accountable for the work. You were not, however, allowed to give the manuscript final approval. If you and your coauthors can work out your differences, if you approve the version to be published, you will be eligible for authorship. Authors do not need to have performed or reviewed primary data from all the assays or have drafted the entire manuscript.

5. **a.** The American College of Obstetricians and Gynecologists recommends low-dose aspirin for the reduction of preeclampsia. Screening without revealing risk to the mothers and using placebo rather than an active control (aspirin) withholds potential benefits without clear scientific rationale. Studying a drug with an incomplete side effect profile in a large number of women poses an avoidable risk. There is no clear justification for including the low-risk group. (An observational study of known low-risk women without using a placebo could establish baseline rates, should the investigators truly need to do so.) A more appropriate strategy would be a smaller study, better to define risks and potential efficacy, followed by an active-control study only in women at high risk.
6. **b.** Clinical equipoise describes overall uncertainty in the medical community about the risk/benefit balance of a proposed therapy. The data suggest that equipoise exists: there are promising signs of efficacy, but no definitive studies. While individuals may have strong opinions that drive their treatment decisions, these do not in themselves signal a lack of equipoise in the community. If there were strong evidence of efficacy, equipoise would be lost, and the trial might be inappropriate.
7. **d.** The mistaking of an experimental intervention in a research setting for treatment in a clinical setting is termed the therapeutic misconception (or fallacy). Although it can happen with any study, it is a particular risk in early-phase studies of drugs for life-threatening conditions, where patients or parents feel as if they have no other therapeutic option. Note that while it is unclear whether the drug will be effective, there is a possibility for direct benefit for the infant, making the study both ethical and approvable. The problem is rather that the parents, presumably despite explanation, have not been able to articulate their understanding of the experimental nature of the biologic. Appropriate informed consent would entail further explanation of the nature of the study–the opposite of deception. (Emotional expressions of hope can coexist with an intellectual understanding of the risks and benefits. The goal is not to stamp out hope, but rather to assure understanding.) The infant is too young to assent.
8. **d.** Children cannot provide informed consent, so parental permission is appropriate. In general, a child with some capacity to understand a research study (e.g., school-age children) should provide assent for the study after having it explained at level appropriate to his/her development. While assent may be waived in the setting of a study that might have direct benefit, this study is not testing a therapy. It is correct to be concerned about risks, but this study likely represents a minor increase over minimal risk, and would thus potentially be approvable, with two parents providing permission (see Table 83.2).
9. **c.** Despite legal precedents that give women control over their bodies, even while pregnant, federal research regulations specifically consider risks and potential benefits to the fetus. While research with the prospect of direct benefit for mother, fetus, or both is approvable, research without benefit to either is not approvable if it entails greater than minimal risk to the fetus. Interestingly, if the prospect of direct benefit is only to the fetus, both the mother's and the father's consent is needed. (In the example of an experimental fetal surgery, a woman could agree to take anesthesia and hysterotomy risks on herself, but both parents would need to consent to experimentation on the fetus.)
10. **d.** This research represents more than a minor increase over minimal risk (risks experienced in daily living) and, although it offers the prospect of societal benefit, it does not offer the prospect of direct benefit to the participants. It falls into the "not otherwise approvable" category and would need special permission. If it were approved, the parents would also need to give permission and the children, assent (see Table 83.2).

Index

A

A1AT deficiency, 259t–260t
ABCA3 deficiency, 71
ABCA3 protein, 70
Abdominal imaging, 382–386
  in biliary atresia, 382, 383f
  in duodenal atresia, 382, 386f
  in esophageal atresia with fistula, 382, 385f
  in esophageal atresia without fistula, 382, 385f
  in Hirschsprung disease, 382, 384f
  in hypertrophic pyloric stenosis, 382, 386f
  in malrotation, 382, 386f
  in microcolon, 382, 384f
  in necrotizing enterocolitis, 382, 383f
Abdominal masses, neonatal, 259, 260b
Abdominal wall defects, 252–253
Abetalipoproteinemia, 256
ABO blood group, 290t, 289
ABO incompatibility, 289–290
Abscesses, cutaneous and soft tissue, 221
Absolute risk reduction, 420
Absorption, drug, 394, 395t
Abstinence syndromes, neonatal, 333–334.e1, 334t
Accessory mediated tachycardia, 61–62
Accountability, in quality improvement, 410
Accuracy, 430, 430f
Acetaminophen, for hyperthermia, 200
Achondroplasia, 388–389, 389f
Acid-base balance, 155–167.e2, 161–164
  regulation of, 163
Acidemias, organic, 130
Acidosis
  asphyxia and, 26
  metabolic
    acute kidney injury and, 173
    neonatal, 163, 163b
  renal tubular, 164
    distal, 165
    hyperkalemia, 165–166
    mixed, 166
    proximal, 165
  respiratory, neonatal, 163–164
Acne, neonatal, 272t, 273f
Acquired ptosis, 352
Acrodermatitis enteropathica, 143, 274, 274f
Acute bilirubin encephalopathy, 264
Acute kidney injury (AKI), 172–174
  causes of, 173b
  intrinsic, 173
  neonatal KDIGO, definitions, 172t
  obstructive, 173
  prerenal, 173
Acute lymphoblastic leukemia (ALL), 307
Acute myeloid leukemia (AML), 307
Acute pyelonephritis, in pregnancy, 12
Acyclovir, 404
Adaptive immune system, 214–215
Adenosine, 318
Adenosine triphosphate (ATP), 189
Adrenal androgens, 182
Adrenal cortex, 181
Adrenal disorders, 181–184.e2
Adrenal gland, 181, 181f
Adrenal hormone, physiology of, 181–182
Adrenal medulla, 181
Adrenergic agonists, 65, 65t
Adult learning theory, 437t
Adverse fetal effects, of drugs, in pregnancy, 400
Air leak, ventilation strategies for, 99
Airway
  management of, in asphyxia, 28
  neonatal, 363
  obstruction, causing respiratory distress, 90–92
Alagille syndrome, 258, 259t–260t
  congenital heart disease with, 42t–44t
Albumin, bilirubin binding to, 262, 264t
Alcohol
  abstinence syndromes after, 333
  in breastfeeding, 402t
  in pregnancy, 16
Aldosterone, 159, 182
  deficiency, 183
Aldosterone receptor antagonist, 174
Alimentary tract, normal rotation of, 245f
ALL. *see* Acute lymphoblastic leukemia
Alleles, 107
Allergic colitis, 255
Allergic enteritis, 255
Alloimmunization, in pregnancy, 13
Alobar holoprosencephaly, 369
Alpha-dystroglycanopathies, 335
Alprostadil (prostaglandin E1), 404
Alternative hypothesis (H_a), 419
Aluminum contamination, parenteral nutrition and, 153
Alveolar dead space, 74
Alveolar gas equation, 77
Alveolar oxygen pressure (PAO_2), 77
Alveolar stage, of lung development, 68–69, 69f, 69t
Alveolar surfactant, 80
Alveoli, 147
Ambiguous genitalia, 176–178
Amikacin, 403
Amino acids
  essential and nonessential, in newborn infants, 137–138
  in fetus, 136
Aminoglycosides, 403
Aminophylline, 99
Amiodarone, in breastfeeding, 402t
AML. *see* Acute myeloid leukemia
Amniocentesis, 13, 17
Amnionicity, 7
Amnioreduction, 20
Amniotic band sequence, 119
Amphetamines, in pregnancy, 16

Note: Page numbers followed by "f" indicate figures, "t" indicate tables, and "b" indicate boxes.

Amphotericin B (conventional, lipid complex, or liposomal), 404
Ampicillin, 403
Analgesia, in labor, 21
Analysis, assessment of, 431–433, 431f–432f, 432t–433t
Analysis of variance (ANOVA), 420
Anatomic dead space, 74
Anderson disease, 256
Androgen deficiency, 183
Androgen excess, 183
Anemia
  Diamond-Blackfan, 294
  Fanconi, 213, 294, 300
  of infancy, physiologic, 288
  iron deficiency, 294–295
  in pregnancy, 10
  of prematurity, 288–289
  sickle cell, 107, 291
    carrier screening in, 17
    newborn screening for, 110
  surveillance, 18
Anemic infant, approach to, 291, 292f
Aneuploidy, 107, 111
  in pregnancy, 12
  screening, 8
    ultrasound, 18
Angelman syndrome, 106, 117
Angiotensin II receptor antagonists (ARBs), teratogenic effects in pregnancy, 401t
Angiotensin-converting enzyme inhibitors (ACEIs), teratogenic effects in pregnancy, 401t
Annular pancreas, 249
Anomalies
  detection, in ultrasound screening, 18
  fetal, in pregnancy, 12
Anorectal malformations, 251
Antepartum hemorrhage, 15
Antibacterials, 403–404
Antibody-mediated thrombocytopenia, 305
Anticipation, 108
Anticonvulsants, in breastfeeding, 402t
Antiepileptic drugs (AEDs), 330
  teratogenic effects in pregnancy, 401t
Antifungals, 404
Antihypertensives, 58t
  in pregnancy, 9
Anti-Kell antibodies, hemolytic disease of newborn due to, 294
Antimicrobial drugs, 403–404
Antimicrobial peptides and proteins, 209, 210t
Anti-Mullerian hormone (AMH), secretion of, 176
Antipsychotic agents, fetal or neonatal adverse effects of, 401t
Antiretroviral drugs, teratogenic effects in pregnancy, 401t
Antivirals, 404
Anus, developmental anomalies of, 251
Aorta, coarctation of, 47–48
Aortic click, in congenital heart disease, 41
Aortic stenosis, 47
Apert syndrome, 359
Apgar scores, asphyxia and, 27t
Aphallia, 179
Aplasia cutis congenita, 278, 278f
Apnea, 95
  asphyxia and, 26
  of prematurity, 94–97.e1
Apparent life-threatening events (ALTE), 96–97
ARC syndrome, 259t–260t
Arginine vasopressin, 156
Array comparative genomic hybridization (aCGH), 109
Arterial blood gas, in congenital heart disease, 44
Arterial compensatory mechanisms, 39
Arterial hypoxemia, 76
Arterial oxygen tension (PaO_2), 76
Arterial switch operation, 52, 52f
Arterial thrombosis, neonatal, 303
Arterial vascular lesions, 54, 54f
Arteriohepatic dysplasia, congenital heart disease with, 42t–44t
Arthrogryposis, 336–337
Arthrogryposis multiplex congenita (AMC), 336
Ascertainment bias, 433
Ascites, neonatal, 259, 260t
Ash leaf spots, 125
Asphyxia, 25–30.e1
  cardiovascular considerations in, 29
  causes of, 26b
  chest compressions for, 29
  clinical presentation of, 26–27, 27f, 27t
  complications of, 29
  endotracheal intubation for, 28
  in fetal circulation, 39
  indications for, 29
  laryngeal mask airway for, 28
  management of, 28
  meconium in, 28
  oxygen for, 28–29
  pathophysiology of, 26
  resuscitation in, 28
    pharmacology and drugs used in, 30
    volume, 29–30
  techniques for, 29
  treatment of, 27
Aspiration, 85–88.e1
Aspiration pneumonia, 86
Asplenia, 212–213
Assent, in research ethics, 442, 442f, 443b
Assisted reproductive technology (ART), 7
  congenital defects and, 121
Assisted ventilation, 98–99
  mechanical ventilation, monitoring babies on, 99, 100f–102f, 102t
  respiratory support and, 98–99
  strategies based on pathophysiology, 99
  types of, 98
Association, 428, 428b
Asthma, in pregnancy, 10
Athymia, 213
Atrial balloon septostomy, 45
Atrial flutter, 62, 62f
Atrial natriuretic peptide (ANP), renal function and, 166
Atrial septal defects, 46, 46f
Atrioventricular (AV) block, 59
Atrioventricular valve, development of, 32, 35f
Auditory brainstem response (ABR), 359
Aural atresia, 357
Aural stenosis, 357
Autoimmune primitive neutropenia, 213t
Autonomy, in intrinsic motivation, 436
Autosomal dominant disorders, 107, 116
Autosomal dominant polycystic kidney disease (ADPKD), 171
Autosomal monosomies, 111
Autosomal recessive disorders, 107, 117
Autosomal recessive polycystic kidney disease (ARPKD), 171
Axial computed tomography, in choanal atresia, 371, 374f

B

B cell deficiencies, 214–215, 214t
B cell receptor (BCR), 208
B lymphocytes, 208, 208t

Baby Doe Rules, 413
Bacterial infections, 225–237
  anaerobic, 230
  Chlamydia trachomatis, 228–230
  coagulase-negative staphylococci, 226
  Escherichia coli, 227
  Gram-negative bacilli, 227
  group B *Streptococcus* (GBS), 225
  Listeria monocytogenes, 226–227
  prevention of, 238, 239f
  Staphylococcus aureus, 225–226
  syphilis *(Treponema pallidum)*, 227–228, 229f
  tuberculosis, 228
Bacterial meningitis, 331–332, 332t
Balanced translocations, 107–108
Barbiturate, exposure, abstinence syndromes after, 333, 334t
Barth syndrome, 213t
Bartter syndrome, 164, 165t
Basal ganglia, linear echogenicity in, 367
Basophils, 207
Bayesian statistics, 434
Bayley Scales of Infant and Toddler Development, 347
Bazett formula, 59
Beckwith-Wiedemann syndrome (BWS), 118, 190, 253
Bedside teaching, as teaching method, 438t
Belmont Report, 440, 440t
Benign familial neonatal seizures, 329
Benign idiopathic neonatal seizures, 329
Benzodiazepines, 404
  exposure, abstinence syndromes after, 333, 334t
Beriberi, 141
Bernard-Soulier syndrome, 301
Beta blockers
  fetal or neonatal adverse effects of, 401t
  for neonatal hyperthyroidism, 187
Beta-2 agonist bronchodilators, for bronchopulmonary dysplasia, 83
Bias, 427
Bidirectional Glenn operation, 45, 45f
Bile ducts, congenital malformations of, 258
Biliary ascites, 259
Biliary atresia, 259t–260t
  abdominal imaging in, 382, 383f
  extrahepatic, 258
Biliary tree, development of, 246
Bilirubin
  biochemistry of, 262
  excretion of, 262–263
  factors decreasing albumin binding, 264t
  physiology of, 262–263
  production of, 262
  toxicity of, 264–266.e1, 264t
Biliverdin, 262
Bioavailability, 394
Bioethical dilemmas, ethical and legal issues, 412–414
  limits of viability, 413–414
    case law in, 414
    federal regulations, 413–414
  maternal-fetal conflict, 412–413
    case law and legislation in, 412–413
Bioethical mediation, 412
Bioethics, 411
Biophysical profile (BPP), fetal, 19
Biostatistics, in research, 417–424.e2
  comparing risks in, 420, 420f–421f
  concepts in, 418
  correlation, measuring, 420–421, 421f
  data, distribution of, 418–419, 419f
Biostatistics, in research *(Continued)*
  diagnostic tests in, 422, 422f–423f
    assessing, 423–424, 423f
  hypothesis testing of, 419, 419f
  regression analysis in, 421
  statistical tests of, 419–420
  survival analysis in, 421–422
  systematic reviews and meta-analysis in, 424, 424f
  variables of, 418, 418f
Biotin, 142
Bladder, prenatal ultrasound of, 168, 169b
Bladder outlet obstruction, with oligohydramnios, 168
Blalock-Taussig shunt, 45, 45f
Blepharophimosis syndrome, 352
Blood
  destruction, immune mediated, 292
  loss, 291–292
  transfusions, 304
Blood gas
  analysis, 78
  interpretation, 79
Blood-brain barrier, newborn, 212
Body composition
  in drug distribution, 395t
  of fetus, changes in, 136–137
    developmental, 136
  of newborn infants, changes in, 137
Bohr effect, 78
Boils, 221
Bone marrow failure, 213
  congenital syndromes, 294
Bone mineral metabolism, 193–195
  composition of, 193
  development of, 193
  mineralization in utero, 193
  pathophysiology of, 193–195
  physiologic changes at birth, 193, 194f
Bone modeling, 193
Bone remodeling, 193
Bonferroni method, 419
Born Alive Infants Protection Act (BAIPA), 414
Bosentan, for persistent pulmonary hypertension, 88
Brachial plexus injury, 327–328
Brain abscess, 221
Brain parenchyma, extracranial meninges and, 316
Branchial apparatus, syndromes associated with, 360
Branchial (pharyngeal) arches, 360–361, 361t
Branchial cleft anomalies, 360–361
Branchio-oto-renal (BOR) syndrome, 359
Breast milk jaundice, 268
Breastfeeding, 22
  drugs
    with concerns in, 402t
    contraindicated in, 400, 401b
  jaundice, 267
  postnatal nutrition, 344
Breathing
  disorders of control of, 95–97
  fetal, 94
  neonatal, 94–95
  work of, 74, 74f
Breech vaginal delivery, 22
Brief resolved unexplained events (BRUE), 96–97
Bronchopulmonary dysplasia (BPD), 82–83, 342
  chest imaging in, 375, 375f
  ventilation strategies for, 99
Bumetanide, 174

C

Café-au-lait spots, 125, 279t
Caffeine, 99
  for bronchopulmonary dysplasia, 83
Calcipenic rickets, 196
Calcitonin, bone mineral metabolism and, 195
Calcitonin producing cells (C-cells), 185
Calcium (Ca)
  bone mineral metabolism and, 193–195
  metabolism of, 193–198.e1
  in parenteral nutrition, osteopenia and, 152
  requirements at various gestational ages, 141
Caloric content, of parenteral nutrition, calculation for, 152
Canalicular stage, of lung development, 68, 69f, 69t
Cancer, in neonates, 307
Candida albicans, 230–231
  prevention of, 238–239
Candida infection
  central nervous system infections, 332
  cutaneous and soft tissue infections, 221
  osteoarticular infections, 223
  sepsis, 220
  skin lesions, 280, 281f
  spontaneous intestinal perforation, 222
  urinary tract infection, 222
Candiduria, 230
Capnography, 78
Caput succedaneum, 326, 328f
Carbohydrate
  absorption, disorders of, 255
  intake of, in newborn infants, 139
  metabolism of, 189
    in newborn infants, 139
Carbon dioxide (CO_2)
  elimination, 76
  implications of increasing, 76
Cardiac auscultation, in congenital heart disease, 41
Cardiac development, 31–37.e1
  embryology, regulators of, 32
  maternal diseases with fetal cardiac manifestation, 34–37
  morphogenesis
    abnormal, 33–34
    normal, 32, 32f–36f
  myocyte and contraction, developmental changes of, 34
  transcription factors in, 33b
Cardiac output (CO), 39
Cardiac progenitor cells, 32, 32f
Cardiac tumors, 56
Cardio-limb syndrome, congenital heart disease with, 42t–44t
Cardiomyopathies, neonatal, 55–56, 55f, 56b
Cardiopulmonary bypass, maternal, in pregnancy, 9–10
Cardiopulmonary dysfunction, 55–58.e1
  cardiac tumors, 56
  neonatal cardiomyopathies, 55–56, 55f, 56b
  systemic blood pressure regulation, 57–58, 57b–58b, 58t
Cardiopulmonary exercise tests, 78
Cardiovascular drugs, 404
Cardiovascular function, intrapleural pressures and, 75–79
Cardiovascular physiology, 38–40.e1
  cardiovascular function, monitoring, 39, 39f–40f
  perinatal events, hemodynamic consequences of, 39
  transition of circulation with birth, 38–39
Caroli disease, 258, 259t–260t
Carpenter syndrome, congenital heart disease with, 42t–44t
Carrier screening, 17
Cartilage hair hypoplasia, 213t
Case reports, 425
Case series, 425
Case-control studies, 425, 426f
Cataract, congenital, 353
CATCH-22, 360
Catch-up hours, 1
Categorical variables, in biostatistics, 418
Causation, 428, 428b
Cavernous hemangiomas, 277t
Cavernous lymphangiomas, 277t
Cavum velum interpositum, neurologic imaging in, 367, 372f
CDH. *see* Congenital diaphragmatic hernia
Cefazolin, 403t
Cefepime, 403t
Cefotaxime, 403t
Cefoxitin, 403t
Ceftazidime, 403t
Ceftriaxone, 403t
Central chemoreceptors, 94
Central compartment, 397
Central hypothyroidism, 185
Central nervous system (CNS)
  drugs, 404–405
  infections, 331–332.e1, 220–221
Central shunts, fetal, 38–39
Central tendency, 418
Cephalexin, 403t
Cephalohematomas, 326, 328f
Cephalosporins, 403–404
  classification of, 403t
Cerebellar hemorrhage, 323–324
Cerebral arteries, end-diastolic velocities, 39, 40f
Cerebral blood flow, 318t
Cerebral infarction, perinatal, 324–325
Cerebral palsy, 341, 348–350
  classification of, 349–350, 349f
    functional, 350
  diagnosis of, 348–349
  preterm infants at risk, 348
  prognosis of, 350
  quality of life, 350
  term infants at risk, 348
Cerebral sinovenous thrombosis, 324
Cerebral (cortical) visual impairment, 346
Cerebrohepatorenal syndrome, congenital heart disease with, 42t–44t
Cerebrospinal fluid (CSF), reference ranges, 331t
Cervical vascular anomalies, 90
Cesarean delivery, neonatal complications from, 22
CHARGE syndrome, 359
  congenital heart disease with, 42t–44t
Chédiak-Higashi syndrome, 213t, 282t
Chemical burns, in neonates, 271
Chemical conjunctivitis, 222
Chest compressions, for asphyxia, 29
Chest imaging, 375–381
  in bronchopulmonary dysplasia, 375, 375f
  in congenital diaphragmatic hernia, 377, 377f
  in congenital lobar emphysema, 377, 378f
  in congenital pulmonary airway malformation, 377–378, 379f
  in meconium aspiration, 377, 377f
  in pleural effusion, 378, 379f
  in pneumomediastinum and pneumopericardium, 378–381, 380f
  in pneumonia, 375, 376f
  in pneumothorax, 378, 380f
  in pulmonary interstitial emphysema, 375, 376f
  in surfactant deficiency, 375, 375f
  in tension pneumothorax, 378, 380f

Chest imaging *(Continued)*
in tetralogy of Fallot, 381, 381f
in total anomalous pulmonary venous return, 381, 381f
in transient tachypnea of the newborn, 375, 376f
in transposition of the great arteries, 381, 381f
Chest radiograph, in congenital heart disease, 44
Chi square, 420
Chiari II malformation, neurologic imaging in, 367–369, 372f
Child Abuse Protection and Treatment Act (CAPTA), 413
Children, research ethics in, 443, 443t
Chlamydia trachomatis, 228–230
pneumonia, 86
Chlamydial ophthalmia, 222
Chloride (Cl)
congenital diarrhea, 256
requirements at various gestational ages, 141
Chlorothiazide, 66, 174
Choanal atresia, 90, 362
neurologic imaging in, 371, 374f
Choledochal cysts, 258, 259t–260t
Cholestasis, 259, 259t–260t
parenteral nutrition and, 152
Cholesterol synthesis, disorders of, 133
Choline, prenatal nutrition, 344
Chondroectodermal dysplasia, congenital heart disease with, 42t–44t
Chordee, 179
Chorioamnionitis, 22
Chorionic villus sampling, 17
Chorionicity, 7
Chromium
deficiency in, 143
toxicity of, 144
Chromosomal disorders, 111
types of chromosomal abnormalities, 111
Chromosomal segregation, incomplete failure of, 107
Chromosomal sexual determination, 176
Chromosome 1p36 deletion syndrome, 115
Chronic granulomatous disease, 215t
Chronic in utero hypoxemia, 85
Chylomicron retention disease, 256
Chylothorax, congenital, 93
Chylous ascites, 259
Clavicle fracture, 387, 387f
Clearance (Cl_s), 398
Cleft lip (CL), 362–363
Cleft palate (CP), 362–363
Clinical equipoise, 441
Clinical ethics, 411
Clinical prediction rules, 423–424
Clinical research design, epidemiology and, 425–430.e1
causation *versus* association in, 428, 428b
clinical studies, sources of error in, 427–428, 428f
cost analyses in, 429
decision analysis in, 429, 429f
incidence *versus* prevalence in, 428
measurement, qualities of, 429–430, 430f
screening in, 428–429, 428b
sensitivity analysis in, 429, 429f
study types in, 425–427, 426f–427f, 427t
Clinical seizures, 329
Clinical studies, sources of error in, 427–428, 428f
Clinical toxicology, 400–402
general considerations for, 400
lactation, drugs in, 400–402, 401b, 402f, 402t
pregnancy, drugs in, 400, 401t
Clonic seizures, 329
Clostridium difficile, 230
Coagulase-negative staphylococci, 226
Coagulation, 299–303.e1
disorders
acquired, 302–303
inherited, 301–302
system, 301, 302t
Coarctation of the aorta, 47–48
Cocaine
exposure, abstinence syndromes after, 333, 334t
in pregnancy, 16
teratogenic effects, 401t
Cockayne syndrome, congenital heart disease with, 42t–44t
Coefficient of determination, 421
Coercion, 442
Cognitive assessment tools, 347
Cohort studies, 425, 426f
Colitis, 222
Colleague, studying with, 3
Collecting duct, 162–163, 163f
Collodion membrane, 285f
Commitment, in research, 440–441, 441f
Common Rule, 440
Comparison groups, 431
Compartmental models, in quantitative pharmacokinetics, 397, 397f
Competence, in intrinsic motivation, 436
Competing outcomes, 433
Complement, 209, 209t
Complex molecules, disorders of, 132–133
Concurrent validity, 430
Confidence interval, 419
Confidentiality
in personalized decision making models, 412
in research ethics, to human subjects, 442
Conflicts of interest, in research, 440–441, 441f
Confounding, 427, 428f
Congenital adrenal hyperplasia (CAH)
clinical presentation of, 183, 183t
diagnosis and evaluation of, 183–184
excessive androgen production and, 178
incidence of, 182
pathophysiology of, 182–183
treatment for, 184
Congenital amegakaryocytic thrombocytopenia, 300–301
Congenital anomalies
basis for, 122
birth history in, 123
etiology of, 123–126
evaluation of infants with, 122–126.e1
family history in, 123
history of, 123
multiple, 122–123
physical examination in, 123–126, 124t–125t
Congenital brain malformations, 336
Congenital cerebral neoplasms, 337–338
Congenital cystic adenomatoid malformation (CCAM), 377
Congenital defects, nongenetic etiologies for, 119–121.e1
Congenital dermal melanocytosis, 279t
Congenital diaphragmatic hernia (CDH), 89, 342–343
chest imaging in, 377, 377f
ventilation strategies for, 99
Congenital disorders, patterns of, 111–118.e1
Congenital hearing loss, 358
Congenital heart disease, 342
arterial vascular lesions, 54, 54f
cyanotic and single-ventricle infants, surgical interventions in, 45, 45f
cyanotic heart disease, medical interventions in infant with, 45

Congenital heart disease *(Continued)*
double-outlet right ventricle, 54
infant with suspected, evaluation of, 41–44, 44t
left-sided obstructive lesions, 47–50, 48f–49f
left-to-right shunting lesions, 45–47, 46f–47f, 46t
l-transposition of the great arteries, 54
mixing lesions, 52–54, 52f–53f
presentation of, 41–54.e1
right-sided obstructive lesions, 50–52, 50t, 51f–52f
syndromes and medications associated with, 42t–44t
Congenital ichthyosis erythroderma (CIE), 284, 284f
Congenital infections, in eye, 354
Congenital lactase deficiency, 255
Congenital leukemia, 307, 308t
Congenital lobar emphysema (CLE), 92, 377, 378f
chest imaging in, 377, 378f
Congenital muscular dystrophies, 335
Congenital myasthenic syndromes, 336
Congenital myopathies, 335
Congenital myotonic dystrophy, 335
Congenital nephrogenic diabetes insipidus, 157
Congenital neuroblastoma, 310
Congenital nevi, 279f, 279t
Congenital peripheral neuropathies, 336
Congenital ptosis, 352
Congenital pulmonary airway malformation (CPAM), 92–93
chest imaging in, 377–378, 379f
Congenital smooth muscle hamartoma, 279t
Congenital sucrase-isomaltase deficiency, 255
Congenital toxoplasmosis, 236
Conjoined twins, 14
Conjugated bilirubin, levels, 267
Conjunctivitis, neonatal, 222, 228
Connexin mutations, 358
Conotruncus
development of, 32
incomplete rotation of, 34
Consent, in research ethics, 442, 442f, 443b
Construct validity, 430
Consumptive hypothyroidism, 185
Content validity, 429
Continuous murmurs, in congenital heart disease, 41
Continuous positive end expiratory pressure, 98
Continuous renal replacement therapy (CRRT), for acute kidney injury, 174
Continuous variables, in biostatistics, 418
Contraction stress test (CST), fetal, 19
Copper
deficiency in, 143
toxicity of, 143
Coppock cataract, 353
Cordocentesis, 17
Corneal opacification, 352
Cornelia de Lange (de Lange) syndrome, congenital heart disease with, 42t–44t
Correlation, measuring, 420–421, 421f
Correlation coefficient, 420, 421f
Cortical laminar necrosis, 366, 370f
Cortisol, 182
deficiency, 183
in surfactant production, 71
Cost analyses, 429
Cost-benefit analysis, 429
Cost-effectiveness analysis, 429
Co-twin death, 14
Counterregulatory hormones, 189
Cranial and neurologic trauma, 326–328.e1
brachial plexus injury, 327–328
caput succedaneum, 326, 328f
cephalohematomas, 326, 328f
epidural hemorrhage, 328f
facial nerve injury, 328
laryngeal nerve injury, 328
phrenic nerve injury, 328
skull fractures, 327
spinal cord injuries, 327
subgaleal hemorrhages, 326–327, 328f
Cranial nerves, neurologic evaluation, 314
Craniofacial dysostosis, 359
congenital heart disease with, 42t–44t
Creatinine clearance, 166
Cri-du-chat syndrome, 116
congenital heart disease with, 42t–44t
Criterion validity, 430
Cronbach's alpha, 430
Crossover studies, 419, 427f
Cross-sectional studies, 425
Crouzon syndrome, 359
congenital heart disease with, 42t–44t
Cryoprecipitate, 305
Cryptorchidism, 179
treatment for, 180
Crystalline amino acids, 151
Curriculum, hidden, 436
Cutaneous and soft tissue infections, 221–222
Cutaneous hemangiomas, 310
Cyanocobalamin, 142
Cyanosis, congenital heart disease with, 41
Cyanotic and single-ventricle infants, surgical interventions in, 45, 45f
Cyanotic heart disease, medical interventions in infant with, 45
Cyclophosphamide, teratogenic effects in pregnancy, 401t
Cyclosporine, in breastfeeding, 402t
Cyst volume ratio (CVR), 92
Cystatin C, 166
Cystic fibrosis (CF), 107, 252, 259t–260t
carrier screening in, 17
newborn screening for, 110
in pregnancy, 10
Cystic hygroma, 277t, 387, 388f
Cystic lymphangioma, 387, 388f
Cytokines, 208–209
Cytomegalovirus (CMV), 231–232, 232f
in newborn, 276t
transmission through blood products, 306
Cytosine, 106
Cytotrophoblast, 6

D

Damage-associated molecular patterns (DAMPs), 211
Dandy-Walker malformation (DWM) spectrum, neurologic imaging in, 371, 373f
Data, distribution of, in biostatistics, 418–419, 418f–419f
Data analysis, in quality improvement, 410
Data and safety monitoring boards, in research ethics, to human subjects, 442
Data collection
in quality improvement, 410
timing of, 425
Dead space, 74
Death and dying, ethical and legal issues and, 411–412
Debriefing, as teaching method, 438t
Deception, 441

Decision analysis, 429, 429f
Decision-making
  capacity, 411
  models of, 411
Deep tendon reflexes, 315
Deep vein thrombosis (DVT), neonatal, 303
Defective thyroid hormone transport, 185
Definitive hematopoiesis, 204
Definitive monocytes, 206
Deformations, 119, 122
Deletion, 111
  syndromes, 115
Deletion 5p syndrome, congenital heart disease with, 42t–44t
Delivery, 21–24.e1
  complications, 21–22
  normal, 21
Delta wave, 61, 62f
Denys-Drash syndrome, 176
Deoxyribonucleic acid (DNA)
  decoding blueprint of, 106
  methylation, 106
Dependent variables, in biostatistics, 418
Dermatoglyphics, congenital anomalies and, 125
Dermatoses, newborn, 272, 272t
Dermoid cysts, 361
Developmental anomalies, 247–253.e1
Developmental coordination disorder (DCD), 347–348
Dexamethasone, 100
  for bronchopulmonary dysplasia, 83
Dextrose solutions, 151
Diabetes insipidus
  congenital nephrogenic, 157
  secondary nephrogenic, 157
Diabetes mellitus (DM)
  maternal, with fetal cardiac manifestations, 34–35
  in pregnancy, 8
  type 1, 191
Diagnostic tests, 422, 422f–423f
  assessing, 423–424, 423f
Diamond-Blackfan anemia (DBA), 294
Diaper dermatitis (thrush), 230
Diaphragm, eventration of, 89
Diarrheal illness, 222
Diastolic murmurs, in congenital heart disease, 41
DIC. *see* Disseminated intravascular coagulation
Dichorionic twins, 14
Diet, reviewing and, 3–4
Dietary supplementation, in pregnancy, 7
Diffusing capacity test, 78–79
Diffusion, 75
DiGeorge syndrome, 116, 360
  athymia and, 213
  congenital heart disease with, 42t–44t
Digoxin, 65
Dilated cardiomyopathies, 55–56
  causes of, 56b
Disability paradox, 411
Disruptions, 119, 122
Disseminated candidiasis, 280–281
Disseminated intravascular coagulation (DIC), 302
Distribution, drug, 394, 395t
Diuretics, 100, 174
  for bronchopulmonary dysplasia, 83
DNA microarray, 126
DNA polymerase, 106
"Do not resuscitate" (DNR) orders, 416
Dobutamine, 65, 405t
Donor human milk, 147–148
Dopamine, 65, 405t
  renal function and, 166
Double effect, doctrine of, in personalized decision making models, 411
Double-outlet right ventricle, 54
Down syndrome, 111
  congenital heart disease with, 42t–44t
Doxapram, 96
Drugs
  absorption of, 394, 395t
  of abuse
    congenital defects and, 119–121
    in pregnancy, 16
  disposition of, 393–399
  distribution of, 394, 395t
  elimination of, 396
  indications, mechanisms, and adverse reactions for, 403–406
  maternal, associated with fetal cardiac abnormalities, 66t
  metabolism of, 394–396, 396f
Ductus arteriosus, in transition of circulation with birth, 39
Ductus venosus flow, in transition of circulation with birth, 38
Duodenal atresia
  abdominal imaging in, 382, 386f
  and stenosis, 249, 249f–250f
Duplications, 111
  of small intestine, 249
Dysmorphism, 122
Dysplasia, 122
Dysrhythmias, 59–64.e1
Dystocia, 21
Dystrophic epidermolysis bullosa, 286f

E

Eagle-Barrett syndrome, 169, 170f
Ear development and anomalies, 357–359.e1
  hearing loss
    congenital, 358
    general management concepts for, 358–359
    risk factors for, 359
  middle and inner ear, 357–358
  outer ear, 357
Early intervention, of neurodevelopmental impairment, 345–346
Early onset meningitis, 331
Early-onset sepsis (EOS), 218
Ebstein anomaly, 51–52, 52f
Echocardiogram
  in congenital heart disease, 44
  fetal, 39
Echodensities, 323
Eclampsia, in pregnancy, 9
Ectopic atrial tachycardia, 62–63
Ectopic thyroid, 185
Educational theory, 436–437, 437t
  assessments in, 436–437, 437t
  motivational strategies in, 436
  teaching methods in, 437, 438t
Edward syndrome, 112–113
  congenital heart disease with, 42t–44t
EEC syndrome, 253
Effect modification, 427–428
Egg-on-a-string sign, 381
Ehlers-Danlos syndrome, congenital heart disease with, 42t–44t
Ejection click, in congenital heart disease, 41
Elastase mutation, 213t
Electrocardiography (ECG), 59–64.e1
  in congenital heart disease, 44
Electroclinical disassociation, 329
Electroencephalogram (EEG), 329

Electrographic seizures, 329
Electrolyte absorption, disorders of, 256
Electronic health records, in quality improvement, 410
Electrophysiology, 59–64.e1
Elemental and extensively hydrolyzed formulas, 149
Elimination, drug, 396
Elimination half-life ($t_{½}$), 398
Elimination rate constant (k_e), 398
Ellis-van Creveld syndrome, congenital heart disease with, 42t–44t
Embryo, sites of erythropoiesis, 288
Embryonic stage, of lung development, 68, 69f, 69t
EMPTALA, 414
Encephalocele, 316
Encephalopathy, 314
  acute bilirubin, 264
  hypotonia with, 336
  hypoxic-ischemic, 319–320, 319t, 343
    asphyxia and, 27
    clinical staging of, 320t
  metabolic, 133, 320–321, 320t
  neonatal, 319–321.e1
    causes of, 319b
    risk factors for, 319t
Endochondral ossification, 193
Endocrine system, in pregnancy
  adaptation of, 6
  function, 7
Endothelin receptor antagonists, for persistent pulmonary hypertension, 88
Endotracheal intubation, for asphyxia, 28
Energy content, of parenteral nutrition, 151–152
Energy deficiency, disorders of, 130–132
Energy metabolism
  fetal, 189
  physiology of, 189
  during transition to postnatal life, 189
Energy requirements, of newborn infants, 137, 137t
Enlarged vestibular aqueduct, 358
Enrollment bias, 433–434
Enteral nutrition, 145–150.e1
  formula and, 148–150
  human milk and, 145–148
Enterohepatic circulation, 262–263
Enteroviral sepsis, of newborn, 220
Enterovirus, 234
Environment
  causes and effects on neurodevelopmental impairment, 344–346
  exposures, congenital defects and, 119–121
Enzyme
  defects, 293
  deficiencies, 255
Eosinophils, 207
Epidermolysis bullosa simplex, 285, 285f
Epidermolytic hyperkeratosis, 285
Epidural hematoma, 322
Epidural hemorrhage, 328f
Epigenetic gene regulation, 106
Epigenetics, 106
Epignathus, 247, 361
Epilepsy, in pregnancy, 11
Epinephrine, 65–66, 405t
  for asphyxia, 30
Epispadias, 179
  treatment for, 180
Epstein pearls, 247
Epulis, congenital, 247
Erb-Duchenne palsy, 328
Ergotamine, in breastfeeding, 402t
Error, types of, 419
Erythema toxicum neonatorum, 272t, 273f
Erythrocytes, 287–295.e1
  antioxidant defenses of, 293f
  membrane, 294f
Erythropoiesis
  regulation of, 288
  sites of, 288
Erythropoietin, 288
Escherichia coli infection, 227
  sepsis, 218
Esophageal atresia
  with fistula, abdominal imaging in, 382, 385f
  without fistula, abdominal imaging in, 382, 385f
Esophageal duplication cysts, 247
Esophagus, development of, 244
  anomalies, 247–248
Essential amino acids, in newborn infants, 137
Essential fatty acids, in newborn infants, 138
  deficiency, features of, 138
Estimated due date (EDD), 18
Ethanol, teratogenic effects in pregnancy, 401t
Ethical debates, 411
Ethics in research, 440–443.e2
  in children, 443, 443t
  conflicts of interest and commitment in, 440–441, 441f
  consent, assent, and permission in, 442, 442f, 443b
  definition of, 411
  with human subjects
    application of, 441–442
    definitions of, 441
  Institutional Review Board in, 441
  misconduct and professionalism in, 441
  in vulnerable populations, 442–443
Ethosuximide, in breastfeeding, 402t
Evaluations, 436
Evaporation, 199
Eventration of diaphragm, 89
Exercise, reviewing and, 3–4
Experimental studies, 425–426, 427f, 427t
External validity, 430, 433
Extracellular water (ECW), 156
Extracorporeal membrane oxygenation (ECMO), 102–103
  for meconium aspiration, 86
  for persistent pulmonary hypertension, 88
Extracranial hemorrhages, sites of, 328f
Extracranial meninges, brain parenchyma and, 316
Extradural hemorrhages, sites of, 328f
Extrahepatic biliary atresia, 258
Extrapyramidal (athetoid) cerebral palsy, 349
Extravascular absorption, 394
Extremely-low-birth-weight (ELBW) infants, milk for, 147
Extremities-associated syndromes, minor anomalies of, 126t
Extrinsic motivators, 436
Eye, 351–356.e1
  acquired abnormalities, 354
  congenital abnormalities, 352
  congenital infections, 354
  development and anatomy of, 352
Eyelids, congenital abnormalities of, 352

F

Fabrication, 441
Face validity, 429
Facial nerve injury, 328
Facial strength, evaluation, 314

Falsification, 441
Family risk factors, influencing development, 345
Fanconi anemia (FA), 213, 294, 300
Fat
  absorption, disorders of, 256
  intake of, in newborns, 138–139
  metabolism of, 189
    in newborn infants, 138–139
  requirements of, in preterm and full-term infants, 138
Fat-soluble vitamins
  deficiencies of, manifestations of, 142
  pharmacologic use of, potential adverse effects of, 143
Fatty acids
  essential and nonessential, in newborn infants, 138
  in fetus, 136
  oxidation, disorders of, 131–132, 191
Feedback, 436
  characteristics of, 437
  types of, 437
Fetal akinesia, 336
Fetal alcohol spectrum disorders, 119
Fetal alcohol syndrome (FAS), 333
  congenital heart disease with, 42t–44t
Fetal assessment and treatment, 17–20.e1
  genetic testing, 17–18
  invasive fetal testing, 17
  status, evaluation of, 19–20
  therapy, 20
  ultrasound screening, 18–19
Fetal blood sampling (cordocentesis), 17
Fetal breathing, 94
  movement, 69
Fetal circulation, 38, 38f
Fetal growth restriction (FGR), 13, 341–342
Fetal heart rate monitoring, intrapartum, 21
Fetal hydrops, 13
Fetal infections, 13
Fetal lung fluid
  changes during labor, 70
  clearance, mediators of, 70, 70t
  dynamics and composition of, 69–70, 70t
Fetal lung maturity testing, fetal, 19–20
Fetal movement surveillance, 19
Fetal surgery, 20
Fetal surveillance, 8–9
Fetal transfusion, 20
Fetus
  bilirubin physiology in, 263
  changes in body composition of, 136–137
    developmental, 136
  intrauterine growth of, 136–137
    hormonal factors of, 136
    maternal, placental, and fetal factors of, 137
  nutrient requirements of, 136
  sites of erythropoiesis, 288
  size of, growth of, 136
FGR. *see* Fetal growth restriction
Fibroadhesive peritonitis, 252
Fibroblast growth factor 23 (FGF-23), bone mineral metabolism and, 195
Fibroblast pneumocyte factor, in surfactant production, 71
Fick's equation of diffusion, 76
First heart field, 32, 33f
First-degree atrioventricular block, 59–60
First-order multiple-compartment elimination, 397
First-order single-compartment elimination, 397
Fisher exact test, 420
Flow-inflating bag, for asphyxia, 28
Fluconazole, 404
  for *Candida albicans*, 238–239
Fluorescence in situ hybridization (FISH), 109, 109f
  for congenital anomalies, 126
  for Down syndrome, 112
  for Edward syndrome, 113
  for Patau syndrome, 114
Folate, 142
  postnatal nutrition, 344
  prenatal nutrition, 344
Fontan operation, 45, 45f
Food and Drug Administration (FDA), approval, 405
Foramen ovale, flap of, in transition of circulation with birth, 38
Formative feedback, 437
Formulas, infant, 148–150
  distribution of nutrients in, 148–149
  nonstandard
    medical indications for, 149
    soy proteins in, benefits and risks of, 149, 149t
  nutritional composition, human milk *versus*, 145–146, 146t
  standard, modification for use in preterm infants, 150
Fortification, of human milk, 147
Fragile X syndrome, 117
Fragile X-associated tremor/ataxia syndrome (FXTAS), 117
Fresh frozen plasma (FFP), 305
Friedreich ataxia, congenital heart disease with, 42t–44t
Fructose 1,6 bisphosphatase deficiency, 131
Fully autonomous, 411
Functional residual capacity (FRC), 71
Fungal infection
  Candida albicans, 230–231
  Malassezia furfur, 231
  prevention of, 238–239
Funisitis, 223
Furosemide, 66, 174
  for bronchopulmonary dysplasia, 83
Futility, in personalized decision making models, 411

G

Gag reflex, 314
Galactosemia, 130, 259t–260t
Gallbladder, development of, 246
Gamma-aminobutyric acid (GABA), 318
Gas exchange, 76
  processes for, 75
  respiratory, in placenta, 6
Gastric pH, newborn, 212
Gastric volvulus, 248
Gastroenteritis, 222
Gastroesophageal reflux (GER), 247
Gastrointestinal anomalies, 247
Gastrointestinal bleeding, 254–255, 254t
Gastrointestinal development, 243–246.e1, 245f, 246t
  biliary tree, 246
  esophagus, 244
  gallbladder, 246
  hepatobiliary liver, 245–246
  intestine, 244–245, 245f
  pancreas, 245
  stomach, 244
Gastrointestinal infections, 222
Gastrointestinal tract
  acquired disorders of, 254–257.e1
  maternal, to pregnancy, 6
Gastroschisis, 252–253
GATA4, in cardiac embryology, 32
Gaucher disease, 259t–260t
G-banding, 108–109

Gene regulation, epigenetic, 106
Gene therapy, 414–415
  controversies associated with, 415–416
Generalizability, assessment of, 433–434, 433f
Genetic counseling
  for Down syndrome, 112
  for Edward syndrome, 113
  for Patau syndrome, 114
  for Turner syndrome, 114
Genetic disease, structural chromosomal abnormalities that contribute to, 107–108
Genetic exceptionalism, 415
Genetic heterogeneity, 117
Genetic neonatal syndromes, 282–285
Genetic testing, 108–109, 414–415
  for chromosome 1p36 deletion syndrome, 115
  for Down syndrome, 112
  for Edward syndrome, 113
  fetal, 17–18
  for Patau syndrome, 114
  in pregnancy, 7
  for Wolf-Hirschhorn syndrome, 116
Genetics, molecular, 105–110.e1
Genital differentiation, 176
Genitourinary infections, 222
Genomic imprinting, non-Mendelian inheritance and, 117
Gentamicin, 403
Germinal matrix and intraventricular hemorrhage (GMH/IVH), neurologic imaging in, 366, 366f–368f
Gestational age determination, 18
Gestational diabetes mellitus, 8
Gestational hypertension, 9
Glaucoma, congenital, 353
Glomerular filtration rate (GFR), 396
Glossoptosis, 90
Glucocorticoids
  inhaled, 100
    for bronchopulmonary dysplasia, 83
  for neonatal hyperthyroidism, 188
  in surfactant production, 71
Gluconeogenic amino acids, 189
Glucose
  in fetus, 136
  metabolism, 189–192.e1
Glucose-galactose malabsorption, 256
Glucose-6-phosphate dehydrogenase deficiency, 292–293
Glutamate, 318
Glycogen storage diseases, 190–191
Glycosylation, congenital disorders of, 259t–260t
Goldenhar syndrome, congenital heart disease with, 42t–44t
Gonadal differentiation, 176
Gonadal dysgenesis, 178
Gonococcal ophthalmia, 222
Gram-negative bacilli, 227
Granulocyte-macrophage colony-stimulating factor (GM-CSF), 206
Granulocytes, 207, 296
Graves disease, neonatal, 187
Great arteries
  development of, 32
  transposition of, 381, 381f
Gross Motor Function Classification System (GMFCS), 350
Group B *Streptococcus* (GBS)
  osteoarticular infections, 223
  prevention of, 238, 239f
  screening for, 17–18
  sepsis, 218
Growth
  assessment, ultrasound screening in, 18–19
  of fetus, 135–140.e1
Gut-associated lymphoid tissue (GALT), 202, 245

H

Hairy epidermal nevus, 279t
Haldane effect, 78
Harlequin color change, 275f
Harlequin ichthyosis, 284
Hazard ratio, 422
Health-related QOL, 411
Hearing loss
  congenital, 358
  general management concepts for, 358–359
  newborn screening for, 110
  risk factors for, 359
Hearing screen, for Down syndrome, 112
Heart disease
  congenital, 342
  pharmacologic therapy of, 65–66.e1
  in pregnancy, 9
Heat loss, after delivery, 199
Heel stick nodules, in neonates, 271
HELLP syndrome, in pregnancy, 9
Hemangiomas, 308t, 310
  infantile, 310
Hematologic system, maternal, in pregnancy
  adaptation, 6
  disease, 10
Hematopoiesis, 202–204, 203f, 297f
  impaired, 213
Hematopoietic stem cells (HSCs), 203, 296
Hemochorial architecture, in pregnancy, 6
Hemodialysis, for acute kidney injury, 174
Hemodynamics, in maternal adaptation to pregnancy, 6
Hemoglobin
  developmental biology of, 288, 289f
  oxygen dissociation curve, 289f
Hemoglobinopathies, 290–291
  newborn screening for, 291, 292t
  in pregnancy, 10
  sickle cell anemia and other sickle cell, 291
Hemoglobin-oxygen affinity, effect of altitude on, 77–78, 78f
Hemolysis, 292
  in pregnancy, 9
Hemolytic disease of newborn, alloimmune, 290
Hemolytic transfusion reaction, 305–306
Hemophilia, 301
Hemorrhage, 291–292
Hepatitis B virus (HBV), 235
  fetal screening for, 18
  prevention of, 239, 240f
  transmission through blood products, 306
Hepatitis C virus (HCV), 235
  in pregnancy, 12
  transmission through blood products, 306
Hepatobiliary liver, development of, 245–246
Hereditary fructose intolerance, 130
Hereditary hemorrhagic telangiectasia, congenital heart disease with, 42t–44t
Hereditary spherocytosis, 293
Hering-Breuer (HB) inflation reflex, 94
Heroin
  fetal or neonatal adverse effects of, 401t
  in pregnancy, 16

Herpes simplex virus (HSV), 232–233
central nervous system infections, 332
conjunctivitis, 222
cutaneous and soft tissue infections, 221
pneumonia, 86
prevention of, 241
skin lesions, 276f, 276t, 281
Herpes simplex virus-1 (HSV-1), 232
Heterotaxy syndrome, 212
HIE. *see* Hypoxic-ischemic encephalopathy
High flow nasal cannula (HFNC), 96
High frequency jet ventilator (HFJV), 98
High frequency oscillator ventilator (HFOV), 98
High saturations, infant with, 49
Hirschsprung disease, 251
abdominal imaging in, 382, 384f
Hirschsprung-associated enterocolitis (HAEC), 251
Holoprosencephaly, neurologic imaging of, 369, 373f
Holt-Oram syndrome, congenital heart disease with, 42t–44t
Homocystinuria, congenital heart disease with, 42t–44t
Hormones, involved in surfactant production, 71
Human genetics, basics of, 106
Human immunodeficiency virus (HIV), 234–235
fetal screening for, 18
prevention of, 239–241
transmission through blood products, 306
Human milk, 145–148
composition of, 145
donor, 148
effects of different processing methods on, 146–147
fortification of, 147
heat treatment of, 147
immunological and anti-infective constituents in, 146
nutritional composition, infant formulas *versus*, 145–146, 146t
oligosaccharides, 146
physiology and pathophysiology of, 147–148
production in NICU, 148
Human subjects, research ethics to, 441–442
Hunter syndrome (type II), congenital heart disease with, 42t–44t
Hurler syndrome (type I), congenital heart disease with, 42t–44t
Hutchinson-Gilford syndrome, congenital heart disease with, 42t–44t
Hydrocephalus, 317
Hydrochlorothiazide, 66, 174
Hydrocortisone, 100
Hydrocortisone ± mineralocorticoid replacement, 178
Hydromyelia, 371
Hydronephrosis, 389, 389f
postnatal evaluation of, 168
prenatal diagnosis of, 168
Hydrophobic surfactant, 80
Hydrops fetalis, 93
Hydroxyapatite, 193
Hyper IgE, 214t
Hyperbilirubinemia
physiologic, 267
risk of, 263
Hypercalcemia, 63, 64f
neonatal, 195
Hypercapnia, 76
asphyxia and, 26
Hypercyanotic spell, treatment of, 50t
Hyperglycemia, 191–192
clinical presentation of, 191
diagnosis and evaluation of, 191
parenteral nutrition and, 153
Hyperglycemia *(Continued)*
permanent forms of, 191
transient forms of, 191
treatment of, 191–192
Hyperinsulinism
congenital, 190
perinatal stress induced, 190
treatment for, 190–191
Hyperkalemia, 63, 64f, 161, 162t
acute kidney injury and, 173
Hypermagnesemia, 198
Hypernatremia, 158, 160f
Hyperoxia test, in congenital heart disease, 44
Hyperparathyroidism, neonatal, 195
Hypersplenism, 300
Hypertension, neonatal, 57–58
causes of, 58b
Hypertensive disease, in pregnancy, 9
Hyperthermia, 200
Hyperthyroidism, neonatal, 187–188
Hypertriglyceridemia, parenteral nutrition and, 153
Hypertrophic cardiomyopathy, 56
causes of, 56b
Hypertrophic pyloric stenosis, abdominal imaging in, 382, 386f
Hypobetalipoproteinemia, 256
Hypocalcemia, 63, 64f
neonatal, 195–196
Hypoglycemia, 189–191
clinical presentation of, 190, 190t–191t
congenital disorders of, 190
definition of, 189–190
diagnosis and evaluation of, 190
transient forms of, 190
treatment for, 190–191
Hypoglycemic agents, fetal or neonatal adverse effects of, 401t
Hypokalemia, 63, 64f, 161
Hypomagnesemia, 198
Hypomelanosis of Ito, 125, 338
Hyponatremia, 158, 160f
Hypophosphatasia, 195
Hypophosphatemic rickets, treatment/monitoring for, 197
Hypopituitarism, 190
Hypoplastic left heart syndrome, 49, 49f
Hypoplastic lung, 89
Hypoproduction, platelet, 300–301
genetic causes of, 300–301
Hypospadias, 179
treatment for, 180
Hyposplenia, 212–213
Hypotension
maternal, in labor, 22
neonatal, 57
causes of, 57b
Hypothermia, 199
therapeutic, 320
Hypothesis testing, 419, 419f
Hypothyroidism, 259t–260t
congenital, 185–187, 187t
clinical presentation of, 186
diagnosis and evaluation of, 186
epidemiology of, 185
etiology of, 185
treatment of, 186–187
screen for, in Down syndrome, 112
Hypotonia, aspects of, 335–338.e1
arthrogryposis, 336–337
congenital cerebral neoplasms, 337–338
hypotonia and weakness, 335–336

Hypotonia, aspects of *(Continued)*
neurocutaneous disorders, 338
vascular malformations, 337
Hypoxemia, asphyxia and, 26
Hypoxia
acute, biphasic response to, 94
neurologic imaging in, 366–367, 370f
Hypoxic-ischemic brain injury, asphyxia and, 26–27, 27f
Hypoxic-ischemic encephalopathy (HIE), 319–320, 319t, 343
asphyxia and, 27
clinical staging of, 320t
Hysteresis, 74

I

Ibuprofen, 404
Ichthyosis vulgaris, 284
Idiopathic infantile hypercalcemia, 195
Idiopathic neonatal giant cell hepatitis, 259t–260t
Idiopathic thrombocytopenia purpura, in pregnancy, 11
IgA
deficiency, 214t
in human milk, 146
IgG, in human milk, 146
IgM, in human milk, 146
Immune hydrops, 13
Immune system
components of, 206–210.e1
cellular, 206–208, 206t
humoral and soluble, 208–209
development of, 201–205.e1
abnormal, 211–216.e1
cellular, 202–204, 203f–204f
solid organs, 202
Immunization, 238–242.e1
in pregnancy, 7–8
Immunologic disease, in pregnancy, 10–11
Immunomodulating medications, 212t
Impetigo, 221
Imprinting, disorders of, 106–107
In vitro fertilization (IVF), 7
Inborn errors of metabolism, 127–134.e1, 320
classification of, 127–133, 128t, 128b
intoxication, disorders of, 127–130, 129f
metabolic tests for, 127, 127t
Incidence, 428
Incontinentia pigmenti, 282t, 283f, 338
Incubator, for hypothermia, 199
Indels, 107
Independent variables, in biostatistics, 418
Indomethacin, 404
Infant of mother with diabetes, congenital heart disease with, 42t–44t
Infantile hemangiomas, 277t, 310
Infants
evaluation of, with congenital anomalies, 122–126.e1
mortality, 410t
physiologic anemia of, 288
Infections
congenital defects and, 121
maternal, with fetal cardiac manifestations, 37
of organ systems, 217–224.e1
in pregnancy, 11
prevention of, 238–242.e1
bacterial, 238, 239f
fungal, 238–239
immunization for, 238
parasitic, 241–242
viral, 239–241
transmission, from blood product, 306
Inference, in statistics, 418
Infertile, assistance, 7
Inflammation, 211
maternal (prenatal), influencing development, 344–345
Influenza, neonatal pneumonia and, 86
Information bias, 433
Informed consent doctrine, 411
Inhaled glucocorticoids, 100
for bronchopulmonary dysplasia, 83
Inhaled nitric oxide (iNO), 100–101, 103f
for persistent pulmonary hypertension, 88
Inheritance, mode of, 107, 108f
Inherited ichthyoses, 284–285
Innate immune system, 203
Innate lymphoid cells, 208
Innate system, 213
Inner curve, of heart, 32, 34f
Inner ear, 357–358
Input step, 2
Insensible water losses, 156, 157t
Institutional Review Board (IRB), 441
Insulin resistance, congenital syndromes of, 191
Internal comparison group, 431
Internal consistency, 430
Internal validity, 430–431
Interobserver reliability, 430
Interrater reliability, 430
Interrupted aortic arch, 48–49, 48f
Interstitial pneumonitis, 87
Intestinal atresia, 250
Intestine, development of, 244–245, 245f
Intoxication, disorders of, 127–130, 129f
Intracellular buffering system, 161
Intracranial hemorrhage, 322–325.e1
cerebellar, 323–324
epidural hematoma, 322
intraventricular, 322–323
subarachnoid, 322
subdural, 322
Intracranial pressure, abnormalities suggesting increased, 315
Intrahepatic biliary hypoplasia, 258
Intramembranous ossification, 193
Intraparenchymal cysts, 323
Intrapartum hemorrhage, 15
Intrapleural pressures, 75–79
Intrauterine growth restriction (IUGR), 140, 341–342
Intrauterine insemination, 7
Intravenous antihypertensives, 58, 58t
Intravenous fat emulsion, 151
Intravenous immunoglobulin, for kernicterus, 266
Intravenous infiltration, in neonates, 270–271
Intraventricular hemorrhage (IVH), 322–323
Intrinsic motivation, 436
Intubation, considerations for, 363
Intussusception, neonatal, 255
Invasive fetal testing, 17
Inversion, 108, 111
Iodide, 185
Iodine
deficiency, 143
for neonatal hyperthyroidism, 188
postnatal nutrition, 344
prenatal nutrition, 344
Iron, 143
postnatal nutrition, 344
prenatal nutrition, 344
Iron deficiency, 294–295
anemia, 294–295

Iron homeostasis, 294
Ischemia, neurologic imaging in, 366–367, 370f
Islet1 (Isl1), in cardiac embryology, 32
Isochromosomes, 111
Isoproterenol, 66, 405t
Isotretinoin, teratogenic effects in pregnancy, 401t
Ivemark syndrome, 212

J

Jaundice
  breast milk, 268
  breast feeding, 267
Jejunoileal atresia, 249, 250f–251f
Jervell and Lange-Nielsen syndrome, 358
  congenital heart disease with, 42t–44t
Junctional epidermolysis bullosa, 286f

K

Kangaroo care, 345
Kaplan-Meier analysis, 422, 422f
Kappa (κ) statistic, 430
Kartagener syndrome, congenital heart disease with, 42t–44t
Karyotype, 18, 108–109
  for congenital anomalies, 126
  for Down syndrome, 112
  for Edward syndrome, 113
  for Patau syndrome, 114
Kasabach-Merritt syndrome, 277t, 300, 310
Keratitis-ichthyosis-deafness (KID) syndrome, 285
Kernicterus, 264–266
Ketoacidosis, 130
Ketogenic amino acids, 189
Kidneys, prenatal ultrasound of, 168, 169b
Kirkpatrick's model, for effectiveness of training, 438t
Klinefelter syndrome, 178
Klippel-Feil syndrome, 359
Klumpke paralysis, 328
Knowles' theory of "andragogy," 436, 437t
Kostmann syndrome, 213t

L

Labor, 21–24.e1
  analgesia, 21
  complications, 21–22
  normal, 21
Laboratory values, maternal, in pregnancy, 6
Lactation
  drugs in, toxicology of, 400–402, 401b, 402f, 402t
  hormonal control of, 147–148
Lactoferrin (LF), in human milk, 146
Lactogenesis, 148
Lactoperoxidase, in human milk, 146
Lamellar ichthyosis, 284
Langerhans cell histiocytosis (LCH), 308–309, 308t
Laplace law, 71, 71f, 80
Large for gestational age (LGA) infants, 140
Large intestine, developmental anomalies of, 250–251
Laryngeal cleft, 91
Laryngeal mask airway (LMA), for asphyxia, 28
Laryngeal nerve injury, 328
Laryngeal webs, 364
Laryngocele, 364
Laryngomalacia, 91, 363–364
Larynx, development of, 360
Laser therapy, for twin-twin transfusion syndrome (TTTS), 20
Late dumping, 190
Late onset meningitis, 331
Late-onset sepsis (LOS), 218
Lead, exposure to, in pregnancy, 16
Leadership, in quality improvement, 410
Learning environments, effective, 436
Lecture, as teaching method, 438t
Left colon syndrome, 250
Left-sided obstructive lesions, congenital heart disease, 47–50, 48f–49f
Left-to-right shunting lesions, 45–47, 46f–47f, 46t
Legal issues, 409
LEOPARD syndrome, congenital heart disease with, 42t–44t
Letdown reflex, 148
Leukemias, 307–312.e2
  congenital, 307, 308t
  Down syndrome and, 112
Leukocoria, 352–353
Leukocyte adhesion deficiency, 215t
Leukocyte function defects, 215, 215t
Levothyroxine (T_4), for congenital hypothyroidism, 186
Leydig cells, induces differentiation of, 176
LF-iron-binding capacity, 146
Likelihood ratios, 423, 434
  nomogram, 423f
Linear pharmacokinetics, 397, 398f
Linear regression, 421
Lines, 387, 387f
Lipolysis, 189
Listeria infection
  cutaneous and soft tissue infections, 221
  neonatal pneumonia, 86
Listeria monocytogenes, 226–227
  sepsis, 218
Lithium
  in breastfeeding, 402t
  teratogenic effects of, 401t
Liver
  congenital malformations of, 258
  disease, 258–260.e1
  hepatobiliary, development of, 245–246
Lobar holoprosencephaly, 369
Logistic regression, 421
Long-chain fatty acid oxidation, disorders of, 132
Long QT syndrome, congenital heart disease with, 42t–44t
Longitudinal studies, 425
Loop diuretics, 174
Loop-backs, 1
Lumbar puncture, 332
Lung, human, development of, 68
  functional, 70–72
  physical influences on growth, 69–70
  structural, 68–69, 69f
    abnormal morphologic development, 69t
Lung compliance, 73–74, 73f, 73t
Lung volumes, 71–72, 72f
Lymph nodes, 202
Lymphadenopathy, 202
Lymphatic malformation, 277t
Lymphoid lineages, 207–208
Lysosomal storage disorder (LSD), 132–133
Lysozyme enzyme activity, in human milk, 146

M

Macrocephaly, 318
Macroglossia, 90–91
  relative, 90
Macrosomia, 13
Magnesium
  bone mineral metabolism and, 193
  metabolism of, 193–198.e1

Magnetic resonance imaging (MRI)
in hypoxia and ischemia, 366
in periventricular leukomalacia, 366
Major anomaly, 122
Malabsorption syndromes, 255, 255t
Malaria, 236
Malassezia furfur, 231
Malformations, 119, 122
Malrotation
abdominal imaging in, 382, 386f
of small intestine, 249–250
Maltase-glucoamylase deficiency, 255
Mammary tissue, 147
Mammogenesis, 148
Manganese
deficiency in, 143
toxicity of, 143–144, 153
Mann-Whitney U test, 420
Maple syrup urine disease (MSUD), 128
Marcus Gunn jaw-winking syndrome, 352
Marfan syndrome, congenital heart disease with, 42t–44t
Marijuana, in pregnancy, 16
Mast cells, 207
Maternal health optimization, before pregnancy, 7
Maternal serum AFP (MSAFP), 17
Maternal-fetal conflict, 412–413
Maternal-infant bonding
breastfeeding and, 344
influencing development, 345
May-Hegglin anomaly, 301
McCune-Albright syndrome, 282t
McNemar test, 420
Mean, 418
Measurement, qualities of, 429–430, 430f
Mechanical ventilation
in bronchopulmonary dysplasia, 82–83
monitoring babies on, 99, 100f–102f, 102t
Meconium, in asphyxia, 28
Meconium aspiration, 85–86
chest imaging in, 377, 377f
Meconium aspiration syndrome (MAS), 85
ventilation strategies for, 99
Meconium ileus, 252
Meconium peritonitis, 252
Meconium plug syndrome (MPS), 250, 252
Meconium syndromes, 252
Meconium-stained amniotic fluid (MSAF), 21, 85
Median, 418
Medical literature, 434–435
Medications
congenital defects and, 119–121
exposures, in pregnancy, 15–16
Medium-chain acyl-CoA dehydrogenase (MCAD) deficiency, 132
Meiosis, 107
Membrane protein deficits, 293
Mendelian disorders, 116–117
Meninges, neural tube defect, 316
Meningitis, 219–220
bacterial, 331–332
treatment regimens for, 332t
Mental status, neurologic evaluation, 314
Mercury, exposure to, in pregnancy, 16
Messenger RNA (mRNA), 106
Meta-analysis, 424, 424f
Metabolic acidosis
acute kidney injury and, 173
neonatal, 163, 163b
Metabolic alkalosis, neonatal, 164, 164b
Metabolic bone disease of prematurity, 197–198
Metabolic encephalopathies, 133, 320–321, 320t
Metabolism
of carbohydrate, 139
drug, 394–396, 396f
of fat, 138–139
of potassium, 158–161, 161f
in pregnancy, maternal, 7
of proteins, 138
of sodium, 158, 159f
disorders of, 158
water, 156, 157t
disorders of, 157–166
Methimazole, for neonatal hyperthyroidism, 188
Methotrexate, teratogenic effects in pregnancy, 401t
Methylxanthines, 95–96
Metolazone, 174
MHC I deficiency, 215t
MHC II deficiency, 215t
Michel aplasia, 358
Microarray, 18
Microcephaly, 317
Microcephaly vera, 317
Microcolon, abdominal imaging in, 382, 384f
Microdeletion syndrome, 116
Microgastria, 248
Micropenis, 179
treatment for, 180
Microtia, 357
Microvillus inclusion disease, 256
Middle cerebral artery (MCA) Doppler, fetal, 19
Middle ear, 357–358
Midline nasal masses, 361, 362t
Mild encephalopathy, 314
Mild functional motor impairment, 347
Miliaria rubra, 272t, 273f
Milk
human, 145–148
protein allergy, 255
Milrinone, 405t
Mineralizing vasculopathy, neurologic imaging of, 367, 371f
Minerals, 141, 142t
neonatal requirements at various gestational ages, 141
Mini-breaks, 2
Minor anomaly, 122
of extremities-associated syndromes, 126t
Minor neuromotor dysfunction, 347
Misconduct, in research, 441
Misoprostol, teratogenic effects in pregnancy, 401t
Mitochondria, 107
disorders, 107, 117, 131, 259t–260t
Mitosis, 107
Mixed gonadal dysgenesis (45 X/46 XY), 178
Mixing lesions, in congenital heart disease, 52–54, 52f–53f
Mobitz type I block, 60
Mobitz type II block, 60
Mode, 418
Moderate encephalopathy, 314
Molecular genetics, 105–110.e1
basics of human genetics and, 106
decoding the DNA blueprint and, 106
diagnostic approach to the infant with suspected genetic disease, 109
epigenetic gene regulation and, 106
genetic tests, 108–109
newborn screening and, 109–110
protein synthesis and, three different types of RNA in, 106
single gene disorders and mode of inheritance and, 107, 108f

Molecular genetics *(Continued)*
structural chromosomal abnormalities that contribute to human genetic disease, 107–108
transmission of genetic information in, enzymes in, 106
trinucleotide repeat expansion, 108
uniparental disomy and disorders of imprinting and, 106–107
Mondini aplasia, 358
Mongolian spot, 279t
Monoamniotic twins, 14
Monochorionic diamniotic (MCDA) twins, 341
Monochorionic twins, 14
Monocytes, 206–207
Monosomies, autosomal, 111
Montgomery glands, 147
Moro response, 314–315
Morquio syndrome (type IV), congenital heart disease with, 42t–44t
Mosaicism, 111
Mother's own milk, 146–147
problems and strategies to acquire and feed, in the NICU, 148
Motivational strategies, in educational theory, 436
Motor tone and strength, 315
Mouth
development and anomalies of, 362–363
tumors of, 247
MR SOPA mnemonic, 29
Mucolipidosis type II, 133
Mucopolysaccharidosis, congenital heart disease with, 42t–44t
Mucosal epithelium, newborn, 212
Multicystic dysplastic kidney (MCDK), 170–171, 171f, 391, 391f
Multifactorial disorders, 118, 118t
Multifetal gestations, 7
Multiple congenital anomalies, 122–123
Multiple lentigenes syndrome, congenital heart disease with, 42t–44t
Multiple regression, 421
Multiple sclerosis, in pregnancy, 11
Multiple-compartment elimination, first-order, 397
Multiple-compartment model, in quantitative pharmacokinetics, 397
Murmurs, in congenital heart disease, 41
Muscular dystrophy (Duchenne type), congenital heart disease with, 42t–44t
Myasthenia gravis, in pregnancy, 11
Mycoplasma genitalium, 230
Mycoplasmas, genital, 230
Myeloid lineage immune cells, 206–207
Myelomeningocele, 316
Myeloperoxidase deficiency, 215t
Myocarditis, neonatal, 56
Myoclonic seizures, 329
Myocyte
developmental changes of, 34
immature, 34
mature, 34
Myopathic ptosis, 352

N

Nafcillin, 403
Nasal continuous positive airway pressure (nCPAP), 96
for respiratory distress syndrome, 81
Nasolacrimal duct, obstruction, 354
NDI. *see* Neurodevelopmental impairments
Neck masses, 360–361
Necrotizing enterocolitis (NEC), 222, 254
abdominal imaging in, 382, 383f
Necrotizing tracheobronchitis, 363–364
Negative breaks, 2
Negative predictive value (NPV), 422
Neonatal abstinence syndromes (NAS), 333–334.e1, 334t
Neonatal alloimmune thrombocytopenia (NAIT), 13, 299–300, 305
Neonatal arterial thrombosis, 303
Neonatal autoimmune thrombocytopenia, 300
Neonatal breathing, 94–95
Neonatal encephalopathy, 319–321.e1
causes of, 319b
risk factors for, 319t
Neonatal epilepsy syndromes, 329
Neonatal ethics, 411
Neonatal Graves disease, 187
Neonatal intensive care unit (NICU)
breast milk production in, problems associated with, 148
designation of, in perinatal services, 408
Neonatal lupus, 275f
Neonatal meningitis, 331
Neonatal mortality, 410t
Neonatal myocarditis, 56
Neonatal neurology, cranial and neurologic trauma, 326–328.e1
Neonatal pustular melanosis, 272t, 273f
Neonatal respiratory depression, 94–97.e1
Neonatal skin lesions, 272–286.e1
Neonatal tumors, common, 308t
Neonates
sites of erythropoiesis, 288
skin embryology of, 270t
transfusion therapy in, 304
Neonatology, ethical and legal issues in, 411–416.e1
death and dying, 411–412
gene-based therapies, controversies associated with development of, 415–416
genetic testing and gene therapy, 414–415
specific bioethical dilemmas, 412–414
technology, limits of, 414
Nervous system, development of, 316–318e1
encephalocele, 316
hydrocephalus, 317
macrocephaly, 318
microcephaly, 317
myelomeningocele, 316
neonatal neurotransmitter effects, 318
stages and associated anomalies, 317t
Netherton syndrome, 285
Neural tube defect, myelomeningocele, 316
Neuroblastoma, 308t, 310–311
congenital, 310
neonatal, 310–311
Neurocutaneous disorders, 338
Neurodevelopment, nutrition and, 344
Neurodevelopmental impairments, 339–343
bronchopulmonary dysplasia, 342
causes of, 341
and effects of environment on, 344–346
clinical features of, 347–350
definition of, 340
developmental assessments, 347
developmental coordination disorder, 347–348
incidence of, 340
potential protective factors in preterm deliveries, 341
risk factors for, 340–341
transient neurologic abnormalities, 347
Neurofibromatosis, congenital heart disease with, 42t–44t
Neurologic disease, in pregnancy, 11

Neurologic evaluation, 313–315
abnormalities suggesting increased intracranial pressure, 315
cranial nerves, 314
deep tendon reflexes, 315
encephalopathy, 314
mental status, 314
motor tone and strength, 315
physical examination of, 314
primitive reflexes of, 314–315
Neurologic imaging, 365–374
in cavum velum interpositum, 367, 372f
in Chiari II malformation, 367–369, 372f
in choanal atresia, 371, 374f
in Dandy-Walker malformation (DWM) spectrum, 371, 373f
in germinal matrix and intraventricular hemorrhage, 366, 366f–368f
in holoprosencephaly, 369, 373f
in hypoxia and ischemia, 366–367, 370f
in mineralizing vasculopathy, 367, 371f
in periventricular leukomalacia, 366, 369f
in syrinx, 371, 373f
Neurotransmitter, neonatal, effects, 318
Neutral thermal environment, 199
Neutropenia, 213, 213t
Neutrophils, 207, 213, 296
maturation, 298f
New York Heart Association (NYHA), 9
Newborn, 137–139
alloimmune hemolytic disease of, 290
bilirubin physiology of, 262–263
carbohydrate intake in, 139
changes in body composition of, 137
congenital infections of, 276t
dermatoses, 272, 272t
energy requirements of, 137, 137t
fat intake in, 138–139
protein intake in, 137–138
requirements for vitamins in, 141
susceptibility to infection, 212, 212t
Newborn screening, 109–110
genetic, 415
hearing, 359
Niacin deficiency, 142
Nicotine, fetal or neonatal adverse effects of, 401t
Nipple, 147
Nitric oxide (NO)
inhaled, 100–101, 103f
for persistent pulmonary hypertension, 88
renal function and, 166
Nkx2.5, in cardiac embryology, 32
Nominal variables, in biostatistics, 418
Non–cerebral palsy motor impairment, 348
Nonessential amino acids, in newborn infants, 138
Nonessential fatty acids, in newborn infants, 138
Nongenetic etiologies for congenital defects, 119–121.e1
Nonimmune hydrops, 13
Nonlinear pharmacokinetics, 397–398
Non-Mendelian inheritance, 117–118
Nonobstetric surgery, in pregnancy, 12
Nonparametric test, 420
Nonprotein intoxication disorders, 130
Nonprotein nutrients, importance of, optimal energy and, 151–152
Nonsteroidal antiinflammatory drugs (NSAIDs)
fetal or neonatal adverse effects of, 401t
for hyperthermia, 200
Nonstress test (NST), fetal, 19
Nonsustained ventricular tachycardia, 63
Noonan syndrome (Turner-like syndrome), congenital heart disease with, 42t–44t
Norepinephrine, thermoregulation and, 199
Normal distribution, 418
Normal intervals, 59, 59f
Norwood operation, 49, 49f
Nose, development and anomalies of, 361–362, 362t
Nuchal lymphangioma, 387, 388f
Nucleic acid amplification tests (NAATs), for *Chlamydia trachomatis* and, 228–230
Null hypothesis, 419
Nuremberg Code, 440, 440b
Nutrient requirements, of fetus, 136
Nutrition
of fetus, 135–140.e1
neurodevelopment and, 344
postnatal, 344
prenatal, 344
in pregnancy, 7

O

Obesity, in pregnancy, 8
Observational studies, 425, 426f
Octreotide, for hypoglycemia, 191
Ocular infections, 222–223
Ocular trauma, 354
Oculoauriculovertebral spectrum, congenital heart disease with, 42t–44t
Oculocephalic reflex, 314
Oculocutaneous albinism, 282t
Odds ratio (OR), 420, 421f
OEIS complex, 253
Oligohydramnios, 15
bladder outlet obstruction with, 168
sequence, 168–169, 169f
Omega-3 fatty acids, prenatal nutrition, 344
Omphalitis, 223, 278f
Omphalocele, 253
One-compartment model, in quantitative pharmacokinetics, 397
One-tailed test, 420
Open-label studies, 426
Ophthalmia neonatorum, 222, 354
Opiate, exposure, abstinence syndromes after, 333, 334t
Opioids, 405
fetal or neonatal adverse effects of, 401t
in pregnancy, 16
Optic nerve, congenital abnormalities of, 353
Optical blink reflex (dazzle reflex), 314
Optokinetic reflex, 314
Orbit, congenital abnormalities of, 352
Ordinal variables, in biostatistics, 418
Organ development, abnormal, 212–213
Organic acidemias, 130
Oropharynx, developmental anomalies, 247
Orthodromic reciprocating tachycardia, 62
Osler-Rendu-Weber syndrome, congenital heart disease with, 42t–44t
Ossicles, 358
Osteoarticular infections, 223
Osteoblasts, 193
Osteoclasts, 193
Osteocytes, 193
Osteogenesis imperfecta, congenital heart disease with, 42t–44t
Osteomyelitis, 223
Osteopenia
calcium and phosphorus content of parenteral solutions and, 152
of prematurity, 197–198
Otitis media, 223

Otoacoustic emissions (OAEs), 359
Outer curve, of heart, 32, 34f
Outer ear, 357
Ovarian cyst, ruptured, 259
Ovulation induction, 7
Oxacillin (penicillinase-resistant), 403
Oxygen
  affinity, factors that affect, 77
  for asphyxia, 28–29
  delivery
    and consumption, 77, 77f
    to tissues, 76
  dissociation curve, 77f
Oxygen challenge test, in congenital heart disease, 44
Oxygen tension-based indices, 76–77
Oxygenation, 76
  index, 76
Oxytocin, 147–148
  breastfeeding and, 344
  reflex, 148

P

P value, 419, 419f
P wave, 59
Packed red blood cells, 304–305
  clinical indications for, 304–305
Palate, development and anomalies of, 362–363
Palmar response, 315
Pancreas, development of, 245
  anomalies, 251–252
Pancreatic agenesis/hypoplasia, 251
Pancreatic ascites, 259
Panhypopituitarism, 259t–260t
Pantothenic acid, 142
Papulosquamous disorders, in neonates, 274
Parasitic infection, prevention of, 241–242
Parathyroid hormone-related protein (PTHrP), 193
Parens patriae, 411, 413
Parental platelet antigen typing, in pregnancy, 13
Parenteral nutrition, 151–154
  caloric content of, calculation for, 152
  complications of, 152–153
    catheter, 152
    metabolic, 153
  composition of, 151–152
    nutritional, 151
  energy content of, 151–152
  indications of, 151
  potential toxicities associated with, 153
Parvovirus, 293–294
  maternal, with fetal cardiac manifestations, 37
Parvovirus B19, human, 234
Pasteurization, of human milk, 147
Patau syndrome, 113–114
  congenital heart disease with, 42t–44t
Patent ductus arteriosus, 47, 47f
Paternalism, 411
Pathogen-associated molecular patterns (PAMPs), 211
Patient case, information for, 434, 434f
Pearson product moment correlation, 420
Pearson syndrome, 294
Pediatric ethics, 411
Peer review, in quality improvement, 410
Pellagra, 142
Pendred syndrome, 358
Penicillin, 403
  for syphilis, 228
Penicillin G, 403
Penis, developmental anomalies of, 179–180
Pentalogy of Cantrell, 253
Performance, assessment of, 431–433, 431f–432f, 432t–433t
Perfusion, 75
  poor, congenital heart disease with, 41
Perinatal aspiration, 86
Perinatal care, organization of, 407–410.e1
  issues in, 408
  practice guidelines in, 409
  public health issues, services, and delivery, awareness of, 410, 410t
  quality control for, 409
  quality improvement in, 409–410
  regionalization for, 408
  transport in, 408–409
Perinatal hypovolemia, in circulation, 39
Perinatal mortality, 410t
Periodic breathing, 95
Peripheral chemoreceptors, 94
Peripheral compartment, 397
Peritoneal dialysis, for acute kidney injury, 174
Peritonitis, *Candida* infection, 230
Periventricular leukomalacia (PVL), 323
  neurologic imaging in, 366, 369f
Permanent junctional reciprocating tachycardia, 62
Permanent neonatal diabetes, 191
Permission, in research ethics, 442, 442f, 443b
Peroxisomal assembly defects, 132
Peroxisomal defects, 132
Peroxisomes, 132
Persistent pulmonary hypertension of newborn (PPHN), 87–88, 342
Personalized decision making models, 411–412
Peutz-Jeghers syndrome, 282t
Peyer patches, 202
PHACE syndrome, 337
Phakomatoses, 125, 338
Pharmaceutical therapy, 394
Pharmacokinetics, 393–399
  quantitative, 397–399, 397f–399f, 399t
Pharmacologic agents, respiratory, 99–101
Phase I (nonsynthetic) reactions, in drug metabolism, 395
Phase II (synthetic) reactions, in drug metabolism, 396, 396f
Phenobarbital, 405
  in breastfeeding, 402t
Phenylketonuria (PKU), 127–128, 282t
  maternal, with fetal cardiac manifestations, 37
  in pregnancy, 11
Phosphatidylcholine (lecithin), 70
Phosphatidylglycerol, 70
Phosphodiesterase inhibitors, for persistent pulmonary hypertension, 88
Phosphopenic rickets, 196
Phosphorus
  bone mineral metabolism and, 193–195
  metabolism of, 193–198.e1
  in parenteral nutrition, osteopenia and, 152
  requirements at various gestational ages, 141
Phototherapy, for kernicterus, 265
Phrenic nerve injury, 89, 328
Physiologic dead space, 74
Physiologic hyperbilirubinemia, 267
Piebaldism, 282t
Pierre Robin sequence (PRS), 90, 360
Pierre Robin syndrome, congenital heart disease with, 42t–44t
Pigmentation, irregular, congenital anomalies and, 125
Pigmented lesions, 279, 279t
Pineal region, cystic space in, 367

Piperacillin-tazobactam (antipseudomonal), 403
Placenta, maternal, 6–7
Placenta accreta, 14
Placenta increta, 14
Placenta percreta, 14
Placenta previa, 14
Placental abruption, 15
Placental transport, 7
Placentation, abnormal, 7
Plagiarism, 441
Plasma acylcarnitine profile analysis, 127
Plasma amino acid analysis, 127
Platelet hypoproduction, genetic causes of, 300–301
Platelets, 299–303.e1
  consumption and sequestration, 300
  production and regulation of, 299
  transfusion therapy, 305
Pleural disorders, causing respiratory distress, 93
Pleural effusion, 93
  chest imaging in, 378, 379f
Pneumomediastinum, chest imaging in, 378–381, 380f
Pneumonia, 224
  chest imaging in, 375, 376f
  neonatal, 86–87, 228
  postnatal, bronchopulmonary dysplasia and, 83
  ventilation strategies for, 99
Pneumonia alba, 87
Pneumopericardium, chest imaging in, 378–381, 380f
Pneumothorax, chest imaging in, 378, 380f
Polycythemia, 295
  Down syndrome and, 112
Polyhydramnios, 15
Polyploidy, 111
Pompe disease, congenital heart disease with, 42t–44t
Positive mini-breaks, 2–3
Positive predictive value (PPV), 422
Positive thinking, reviewing and, 4
Positive-pressure ventilation, indications for, in asphyxia, 28
Posterior fossa, 367
Posterior urethral valve, 169, 170f
  urinary tract dilation, 389, 390f
Post-hoc analyses, 426
Postnatal aspiration, 86
Postnatal nutrition, 344
Postneonatal mortality, 410t
Postterm pregnancy, 15
Potassium (K)
  metabolism of, 158–161, 161f
  requirements at various gestational ages, 141
Potter syndrome, 168–169, 169f
PPHN. *see* Persistent pulmonary hypertension of newborn
PR interval, 59
Prader-Willi syndrome, 106, 118
Preauricular pits, 357
Preauricular tags, 357
Precision, 430, 430f
Preconception care, 7
  in perinatal services, 408
Predictive validity, 430
Preeclampsia, in pregnancy, 9
Pregestational diabetes mellitus, 8
Pregnancy, 5–16.e1
  complications, 8–16
    drug and environmental exposures, 15–16
    fetal conditions, 12–14
    maternal health conditions, 8–12
    obstetric, 14–15
    serial maternal-fetal assessment, 15
Pregnancy *(Continued)*
  drugs, toxicology of, 400, 401t
  hormones, 147
  maternal adaptation to, 6–7
  prenatal care, 7–8
Premature atrial contractions, 61, 61f
Premature ventricular contraction, 63, 63f
Prematurity, anemia of, 288–289
Prenatal maternal factors, neurodevelopment, 344
Prenatal vascular injury, 324
Prenatal visit
  initial, 8
  subsequent, 8
Pressure targeted ventilation, 98
Pressure-volume (P-V) relationships, 73–74, 74f
Preterm deliveries, potential protective factors in, 341
Preterm labor, 15
Preterm premature rupture of membranes (PPROM), 15
Prevalence, 428
Primary apnea, asphyxia and, 26
Primary bile acid malabsorption, 256
Primary immunodeficiencies (PIDs), 212–215, 212t
Primary intestinal enteropeptidase deficiency, 256
Primary ovarian failure, 114
Primidone, in breastfeeding, 402t
Primitive heart tube, 32, 33f
Primitive hematopoiesis, 204
Primitive monocytes, 206
Primitive reflexes, 314–315
Privacy
  in personalized decision making models, 412
  in research ethics, to human subjects, 442
Professionalism, in research, 441
Progeria, congenital heart disease with, 42t–44t
Progressive familial intrahepatic cholestasis, 259t–260t
Prolactin, 147
Prominauris, 357
Prospective studies, 425
Prostacyclin, 38
Prostaglandin E1 (PGE1), 66
Prostaglandins, renal function and, 166
Protein
  absorption, disorders of, 256
  deprivation, postnatal nutrition, 344
  importance of, optimal energy and, 151–152
  intake of, 137–138
  metabolism of, 138, 189
  requirements of, 138
  synthesis, RNA in, 106
Protein binding
  bilirubin and, 262
  in drug distribution, 394, 395t
Protein coding genes, 106
Protozoa, 235–236
Proximal esophagus, development of, 360
Proximal tubule, 162, 163f
Pseudoglandular stage, of lung development, 68, 69f, 69t
Pseudohypoaldosteronism (PHA), 164
Pseudomonas aeruginosa, conjunctivitis and, 222
Pseudoparalysis of Parrot, 223
Pseudotumor of infancy, 361
Psoriasis, 275f
Psychiatric illness, in pregnancy, 12
Public health, issues, services, and delivery of, awareness of, 410, 410t
Pulmonary click, in congenital heart disease, 41
Pulmonary disease, in pregnancy, 10

Pulmonary edema, 74–75
  inhaled nitric oxide and, 101
Pulmonary function, 74–79
  testing, 78
Pulmonary hypertension, in bronchopulmonary dysplasia, 83
Pulmonary hypoplasia, ventilation strategies for, 99
Pulmonary interstitial emphysema, 375, 376f
  chest imaging in, 375, 376f
Pulmonary stenosis, 50
Pulmonary vascular bed, remodeling of, 38
Pulmonary vascular resistance (PVR), 38
  four phases to transition of, 87
Pulse oximetry, in congenital heart disease, 44, 44t
Pupillary response, 314
Purpura fulminans, neonatal, 303
Pyelonephritis, 222
Pyloric atresia, 249
Pyloric stenosis, 248–249
Pyridoxine, 142
Pyriform aperture stenosis, 90
Pyruvate carboxylase deficiency, 131
Pyruvate dehydrogenase (PDH) deficiency, 131

Q

Q waves, 59
QRS axis, 59, 60f
QRS duration, 59
QT interval, 59
Quality control, in perinatal care, 409
Quality improvement, in perinatal care, 409–410
Quality metrics, in quality improvement, 410
Quality of life (QOL), 411
Quality-adjusted life years (QALYs), 429
Quantitative pharmacokinetics, 397–399, 397f–399f, 399t
Quizzing step, 2

R

R value, 420–421
Radiant heat loss, thermoregulation and, 199
Radiant warmer, for hypothermia, 199
Radiation exposures, in pregnancy, 16
Randomized controlled trials (RCTs), 425–426
Rapamycin, for hemangiomas, 310
Rare blood products, 305–306
Receiver operating characteristic (ROC) curves, 423, 423f
Recombination, 107
Rectum, developmental anomalies of, 251
Recurrent respiratory papillomatosis, 364
Red blood cells (RBCs)
  antigens, 289
  enzyme defects, 292–293
  hemolysis due to intrinsic (nonimmune mediated hemolysis), 292–293
  hypoproduction, 293–294
  indices during development, 288, 290t
  membrane protein defects, 293
  packed, 304–305
Reducing variation, in quality improvement, 410
Reflective practice, 436
Reflective practitioner, 436
Regionalization, in perinatal care, 408
Regression analysis, 421
Regurgitant systolic murmurs, in congenital heart disease, 41
Relatedness, in intrinsic motivation, 436
Relative infant dose (RID), 401, 402f
Relative risk, 420, 420f
  reduction, 420
Reliability, 430
Renal agenesis, 169–170
Renal artery thrombosis, 171, 171b
Renal compensatory mechanism, 162
Renal development, abnormal, 168–174.e2
Renal dysplasia, 170
Renal elimination, 396
Renal function
  evaluation of, 166
  hormonal control of, 166
Renal system, maternal, in pregnancy
  adaptation, 6
  disease, 10
Renal tubular acidosis, 164
  distal, 165
  hyperkalemia, 165–166
  mixed, 166
  proximal, 165
Renal vein thrombosis, 172, 172b
  neonatal, 303
Renin-angiotensin system (RAS), renal function and, 166
Reproductive planning, in pregnancy, 7
Research, applied to clinical practice, 431–435e.1
  generalizability, assessment of, 433–434, 433f
  medical literature in, 434–435
  patient case, information for, 434, 434f
  study design, performance, and analysis, assessment of, 431–433, 431f–432f, 432t–433t
Residual volume (RV), 72
Respiration, mechanics of, 72–74, 72t
Respiratory acidosis, neonatal, 163–164
Respiratory compensatory mechanism, 162
Respiratory distress
  additional causes of, 89–93.e1
  airway obstruction causing, 90–92
  extrapulmonary lesions causing, 89–90
  miscellaneous lesions causing, 92–93
  pleural disorders causing, 93
Respiratory distress syndrome (RDS), 80–84.e1, 80f–81f
  ventilation strategies for, 99
Respiratory support
  assisted ventilation and, 98–99
  modes of, 99t
Respiratory syncytial virus (RSV), neonatal pneumonia and, 86
Respiratory system
  embryology and physiology, 67–79
  maternal adaptation, to pregnancy, 6
Retina
  congenital abnormalities of, 353
  vascular development of, 355
  zones of, 356f
Retinitis, candidiasis, 230
Retinoblastoma, 354–355
  influence on development, 346
Retinoic acid, prenatal nutrition, 344
Retinoids, teratogenic effects in pregnancy, 401t
Retinopathy of prematurity (ROP), 346, 355–356, 356f
Retrospective studies, 425
Reverse transcriptase, 106
Rh incompatibility, alloimmune hemolytic disease of newborn and, 290
Rh locus, 289
Rhabdomyomas, 311–312
  cardiac, 56, 308t
RhoGAM (anti-D antibody), 290
Riboflavin deficiency, 141

Ribonucleic acid (RNA)
messenger, 106
protein synthesis of, 106
ribosomal, 106–107
transfer, 106
Ribosomal RNA (rRNA), 106–107
Rickets, 196–197, 197t
Right-sided obstructive lesions, congenital heart disease, 50–52, 50t, 51f–52f
Rings, 111
Risk ratio, 420
Risk-benefit analysis, 429
RNA polymerase, 106
Romano-Ward syndrome, congenital heart disease with, 42t–44t
Rooting reflex, 315
Round pneumonia, 375
RR interval, 59
Rubella, 234
congenital defects and, 121
congenital heart disease with, 42t–44t
fetal screening for, 18
maternal, with fetal cardiac manifestations, 37
in newborn, 276t
Rubinstein-Taybi syndrome, congenital heart disease with, 42t–44t

S

S1, in congenital heart disease, 41
S2, in congenital heart disease, 41
S3, in congenital heart disease, 41
S4, in congenital heart disease, 41
Saccular cyst, 364
Saccular stage, of lung development, 68, 69f, 69t
Salivary gland, developmental anomalies, 247
Salmon patches, 277t
Salt wasting, treatment of, 184
Sarcomere, 34
Saturation kinetics, 398, 399f
Scheibe aplasia, 358
Schwachman syndrome, 252
Sclerosing cholangitis, neonatal, 259t–260t
Screening, 428–429, 428b
Seborrheic dermatitis, 274
Second heart field, 32, 33f
Second stage, prolonged, in labor, 22
Secondary nephrogenic diabetes insipidus, 157
Second-degree atrioventricular block, 60, 60f
Seizures, neonatal, 329–330.e1
benign familial, 329
benign idiopathic, 329
classification and clinical characteristics of, 330t
differential diagnosis of, 330t
Selection bias, 433–434
Selective serotonin reuptake inhibitors (SSRIs)
abstinence syndromes after, 333
fetal or neonatal adverse effects of, 401t
Selenium
deficiency in, 143
toxicity of, 144
Self-assessment, 1
Self-inflating bag, for asphyxia, 28
Semilobar holoprosencephaly, 369, 373f
Sensitivity, 422
analysis, 429, 429f
Sepsis, 218–220
postnatal, bronchopulmonary dysplasia and, 83
Septic arthritis, 223
Sertoli cells, induces differentiation of, 176
Serum bilirubin, levels, 267
Severe combined immunodeficiency (SCID), 214, 214t
Severe congenital cyclic neutropenia, 213t
Severe encephalopathy, 314
Sexual development, disorder of, 176, 179f
Sexual differentiation, 175–180.e2
normal, 176, 177f
Shared decision making, 411
Short bowel syndrome, 254–255
Shoulder dystocia, 22
SHOX gene, 114
Shwachman-Bodian-Diamond syndrome (SBDS), 294
Shwachman-Diamond syndrome, 213, 213t
Sickle cell anemia, 107, 291
carrier screening in, 17
newborn screening for, 110
Sildenafil, 404
Simulation, as teaching method, 438t
Single gene peroxisomal disorders, 132
Single-compartment elimination, first-order, 397
Single-gene disorders, 107, 116–117
Single nucleotide polymorphisms (SNPs), 107
Sinus arrhythmia, 59
Sinus bradycardia, 59
Sinus rhythm, normal, 59
Sinus tachycardia, 61
Sirolimus, for hemangiomas, 310
Skewed distribution, 418
Skin
development and function of, 269–271, 270t
injuries, in neonates, 270–271
newborn, 212
Skin-to-skin contact, for hypothermia, 199
Skull fractures, 327
Sleep, reviewing and, 3–4
Sleep disordered breathing (SDB), 97
Small for gestational age (SGA) infants, 139–140
classification of fetal growth in, 140
fetal origins of adult onset disorders and, 139–140
intrauterine growth restriction and, 140
postnatal growth patterns of, 139
Small group discussion, as teaching methods, 438t
Small intestine, developmental anomalies of, 249–250
Small left colon syndrome, 250
Smith-Fineman-Myers syndrome, 212
Smith-Lemli-Opitz syndrome, 133
congenital heart disease with, 42t–44t
Sodium (Na)
congenital diarrhea, 256
metabolism of, 158, 159f
disorders of, 158
requirements at various gestational ages, 141
Soft tissue infections, 221–222
Solid tumors, 307–312.e2
Sonic hedgehog (Shh), in cardiac embryology, 32
Soy protein formula, 149
Spastic cerebral palsy, 349
Spastic diplegia, 349
Spastic hemiplegia, 349
Spastic quadriplegia, 349
SP-B deficiency, 71
SP-C deficiency, 71
Spearman rank order correlation, 420
Specificity, 422
Spinal cord
injuries, 327
cord transection and, 89–90
in pregnancy, 11
neural tube defect, 316

Spinal muscular atrophy (SMA), 335–336
Spirometry, 78
Spironolactone, 66, 174
Spleen, 202
Splintzen syndrome, congenital heart disease with, 42t–44t
Spontaneous intestinal perforation, 222
Staff, responsibilities of, 409
Standard deviation, 419
Standard error, 419
Staphylococcus aureus infection, 225–226
  osteoarticular infections, 223
  scalded skin syndrome, 221, 280f
  sepsis, 218
Statistical tests, 419–420
Steady-state concentration, 398, 399f
Steroid acute regulatory protein (StAR), 181
Steroid hormone, synthesis of, 181, 182f
Steroid sulfatase deficiency, 284
Stickler syndrome, 359
Stomach, development of, 244
  anomalies, 248–249
Streptococcus agalactiae, 225
Stridor, 363
  causes of, 364
  evaluation of, 363
Stroke work, 39
Structural chromosomal abnormalities, 107–108
Study calendar, 1
Study design, assessment of, 431–433, 431f–432f, 432t–433t
Study kit, 1
Study map, 1
Sturge-Weber syndrome, 337
Subarachnoid hemorrhage, 322
Subcutaneous fat necrosis, 195
Subdural hemorrhage, 322
Subgaleal hemorrhages, 326–327, 328f
Subglottic hemangioma, 91
Subglottic stenosis, 91, 364
  intubation and, 363
Subgroup analyses, 426–427
Substance use, in pregnancy, 7
Subtle seizures, 329
Suckling, 147
Sudden infant death syndrome (SIDS), 96
Summative feedback, 437
Suppurative pneumonia, 86
Supraventricular tachycardia (SVT), 61
Surfactant, 70–71, 80, 99
  abnormal development, 71
  administration, for respiratory distress syndrome, 81
  deficiency, 375, 375f
  effects on lung pressure volume curves, 80f
  Laplace law, 71, 71f
  lipids, 70
  production, hormones involved in, 71
  proteins, 70
  surface tension, 71, 71f
Surrogate decision making, models of, 411
Surrogate endpoints, 431, 432f, 432t
Survival analysis, 421–422
Survival bias, 433
Sustained ventricular tachycardia, 63
Sympathetic nervous system, renal function and, 166
Syncytiotrophoblast, 6
Syndrome of inappropriate antidiuretic hormone (SIADH), 157
Syphilis, 227–228, 229f
  cutaneous and soft tissue infections, 221
  in newborn, 276t
  osteitis, 223
Syringomyelia, 371, 373f
Syrinx, neurologic imaging of, 371, 373f
Systematic reviews, 424, 424f
  in perinatal care, 409
Systemic blood pressure, regulation of, 57–58, 57b–58b, 58t
Systemic candidiasis, 280–281
Systemic inflammatory response syndrome (SIRS), 218
Systemic lupus erythematosus, maternal, with fetal cardiac manifestations, 35–37
Systemic perfusion, decreasing, infant with, 49
Systemic vascular resistance, in transition of circulation with birth, 39
Systolic blood pressure, in congenital heart disease, 44
Systolic ejection murmurs, in congenital heart disease, 41
Systolic murmurs, in congenital heart disease, 41

T

T cell deficiencies, 214, 214t
T lymphocytes, 207–208
T test, 419
T waves, 59
Tachypnea, congenital heart disease with, 41
Tandem mass spectrometry, 109–110
Targeted mutation screening, 109
Tay-Sachs disease, carrier screening in, 17
TBx5, in cardiac embryology, 32
Teaching and learning, principles of, 436–439.e1
  educational theory in, 436–437, 437t
    assessments in, 436–437, 437t
    motivational strategies in, 436
    teaching methods in, 437, 438t
  preparation and planning in, 438–439, 438t
Teaching methods, 437, 438t
Tears, newborn, 212
Technology, limits of, 414
Tension pneumothorax, chest imaging in, 378, 380f
Teratogenic effects, of drugs, 400, 401t
Teratogens, 119, 120t
  substance use and, 7
Teratomas, 361
  neonatal, 308t, 309–310
Test performance, 1–4
Testicles, developmental anomalies of, 179–180
Testing center, visiting, 3
Testing step, 2
Test-retest reliability, 430
Tetanus, neonatal, 223
Tetracyclines, teratogenic effects in pregnancy, 401t
Tetralogy of Fallot (TOF), 50, 50t, 51f
  with absent pulmonary valve, 50–51
  chest imaging in, 381, 381f
Thalassemia, carrier screening in, 17
α-Thalassemia, hemoglobinopathies and, 290
β-Thalassemia, hemoglobinopathies and, 290
Thalidomide, teratogenic effects in pregnancy, 401t
Thanatophoric deformity, 387–388, 388f
Therapeutic cooling, for asphyxia, 27
Therapeutic fallacy, 441
Therapeutic misconception, 441
Thermal burns, in neonates, 271
Thermoregulation, 199–200.e1
Thiamine
  deficiency, 141
  prenatal nutrition, 344

Thiazide diuretics, 174
for bronchopulmonary dysplasia, 83
Thick ascending limb (TAL), 162
Third-degree atrioventricular block, 61
Throat, development and anomalies of, 360–364.e1
Thrombocytopenia, 299
antibody-mediated, 305
maternal factors associated with, 299
neonatal disorders causing, 300–301, 301f
placental factors associated with, 300
in pregnancy, 9
Thrombocytopenia-absent radius (TAR) syndrome, 300
congenital heart disease with, 42t–44t
Thrombocytosis, 301
Thrombosis, 300
Thrush, 221
diaper dermatitis, 230
Thymus, 202, 387, 387f
Thyroglossal duct cyst, 361
Thyroid dysgenesis, 185
Thyroid dyshormonogenesis, 185
Thyroid gland
development of, 360
disorders of, 185–188.e1
embryology of, 185
physiology of, 185
Thyroid hormones, 185, 186f
in surfactant production, 71
Thyrotoxicosis, neonatal, 187
Tinea versicolor, 231
Tobacco, in pregnancy, 16
Tobramycin, 403
Tongue, development of, 360
Tonic neck reflex, 315
Tonic seizures, 329
TORCH infections
in ear, 358
in eye, 354
Torsades de pointes, 63, 63f
Total anomalous pulmonary venous return (TAPVR), 53–54, 53f
chest imaging in, 381, 381f
Total body water (TBW), 156, 156f
Toxoplasmosis, 235–236
congenital defects and, 121
in newborn, 276t
prevention of, 241–242, 242t
T-piece resuscitator, for asphyxia, 28
Trace minerals, 143–144
potential toxicities of, 143–144
Trachea, development of, 360
Tracheal perforation, intubation and, 363
Tracheal stenosis, 91–92
acquired, 364
congenital, 364
Tracheoesophageal fistula (TEF), 247, 248f
Tracheomalacia, 92, 364
Tracheostomy, 363
Transfer RNA (tRNA), 106
Transfusion associated cardiac overload (TACO), 306
Transfusion related acute lung injury (TRALI), 306
Transfusion therapy, in neonates, 304–306.e1
fresh frozen plasma, 305
packed red blood cells, 304–305
platelets, 305
rare blood products, 305–306
Transient abnormal myelopoiesis (TAM), 307, 308t
Transient hypogammaglobulinemia of infancy, 214t
Transient hypothyroidism, 186
Transient hypothyroxinemia of prematurity (THOP), 186
Transient myeloproliferative disorder (TMD). *see also* Transient abnormal myelopoiesis.
Down syndrome and, 112
Transient neonatal diabetes, 191
Transient neurologic abnormalities, 347
Transient tachypnea of the newborn (TTN), 82
chest imaging in, 375, 376f
Translocations, 107–108, 111
balanced, 107–108
unbalanced, 108
Transport defects, 256
Transport system, components of, 408
Transport team, responsibilities of, 409
Transposition of the great arteries (TGA), chest imaging in, 381, 381f
d-Transposition of the great arteries, 52, 52f
l-Transposition of the great arteries, 54
Trauma
cranial and neurologic, 326–328.e1
in pregnancy, 12
Treacher Collins syndrome, 359
congenital heart disease with, 42t–44t
Treponema pallidum, 227–228, 229f
Tricuspid atresia, 51, 51f
Trimethadione syndrome, congenital heart disease with, 42t–44t
Trinucleotide repeat expansion, 108
Triploidy, 111, 115
Trisomy 13, 113–114. *see also* Patau syndrome.
Trisomy 18, 112–113. *see also* Edward syndrome.
Trisomy 21, 111. *see also* Down syndrome.
Trophoblast, 6
Truncus arteriosus, 53, 53f
Tryptophan, prenatal nutrition, 344
Tuberculosis, 228
Tuberous sclerosis (TS), 282t, 312
congenital heart disease with, 42t–44t
Tuberous sclerosis complex (TSC), 338
Tubular reabsorption, 396
Tubular secretion, 396
Tufting enteropathy, 256
Turner syndrome, 114–115, 178
congenital heart disease with, 42t–44t
Tuskegee syphilis study, 440
22q.11.2 deletion, 360
syndrome, 116
Twin anemia-polycythemia sequence (TAPS), 14
Twin reversed arterial perfusion (TRAP), 14
Twins, complications of, 14
Twin-twin transfusion syndrome (TTTS), 14, 341
treatment of, 20
Two-tailed test, 420
Tympanic membrane, 357
Type I error, 419
Type II error, 419

U

Ultrasound
in germinal matrix and intraventricular hemorrhage, 366
in periventricular leukomalacia, 366
screening, fetal, 18–19
in urinary tract dilation, 389
Ultrasound Doppler velocimetry, fetal, 19
Umbilical artery
blood, asphyxia and, 27
Doppler, fetal, 19
end-diastolic velocities, 39, 39f–40f
Umbilical cord, disorders of, 278, 278t

Umbilical venous blood, asphyxia and, 27
Unbalanced translocations, 108
Unconjugated bilirubin, 262
  levels, 267
Undue inducement, 442
Undue influence, 442
Uniparental disomy (UPD), 106–107, 117
Urea cycle defects, 128–130, 129b
Ureaplasma infection
  bronchopulmonary dysplasia and, 83
  genital, 230
Ureaplasma urealyticum, 230
  neonatal pneumonia and, 86
Urethra, developmental anomalies of, 179–180
Urinalysis, 166
Urinary acidification process, 162
Urinary ascites, 259
Urinary tract dilation, posterior urethral valves, 389, 390f
Urinary tract infection (UTI)
  ascending, 222
  candidiasis, 230
Urine organic acid analysis, 127
Usher syndrome, 358
Uterine blood flow, in labor, 21

V

Vancomycin, 404
Variables, in biostatistics, 418, 418f
Varicella, in newborn, 276t
Varicella zoster virus (VZV), 233
  prevention of, 241
Vasa previa, 14
Vascular anomalies, in newborns, 277
Vascular compression, 92
Vascular injury, 322–325.e1
  cerebellar hemorrhage, 323–324
  echodensities, 323
  epidural hematoma, 322
  intraparenchymal cysts, 323
  intraventricular hemorrhage, 322–323
  perinatal cerebral infarction, 324–325
  periventricular leukomalacia, 323
  prenatal, 324
  subarachnoid hemorrhage, 322
  subdural hemorrhage, 322
Vascular malformations, 277, 277t, 337
Vascular redistribution, asphyxia and, 26
Vascular ring, 92
Vascular steal phenomenon, 337
Vasoactive drugs, 404, 405t
VATER association, congenital heart disease with, 42t–44t
Vein of Galen malformation, 337
Velocardiofacial syndrome, congenital heart disease with, 42t–44t
Venous return, to fetal heart, 38
Ventilation, 75
  management of, in asphyxia, 28
Ventilation-perfusion, pulmonary function and, 75
Ventilation-perfusion ratio, 75
  pathologic change, 75
  physiologic change, 75, 75f
Ventilator-associated pneumonia (VAP), 86
Ventricular output
  of fetal heart, 38
  in transition of circulation with birth, 39
Ventricular septal defect, 45–46, 46f
Ventricular septum, development of, 32, 36f
Ventricular tachycardia, 63
Veracity, in personalized decision making models, 412
Very late-onset sepsis, 218
Vesicoureteral reflux (VUR), 390f–391f, 391
Villous architecture, disorders of, 256–257
Viral infection, 231–233, 231t
  cytomegalovirus, 231–232, 232f
  enterovirus, 234
  hepatitis B virus, 235
  hepatitis C virus, 235
  herpes simplex virus, 232–233
  human immunodeficiency virus, 234–235
  human parvovirus B19, 234
  prevention of, 239–241, 240f
  rubella virus, 234
  varicella zoster virus, 233
Vision, in developmental influences, 346
Visual function, 352
Visual tracking, 314
Vitamin A, 142–143
  supplementation, for bronchopulmonary dysplasia, 83
Vitamin B, 142
Vitamin B_1, 141
Vitamin B_2, 141
Vitamin B_3, 141
Vitamin B_4, 142
Vitamin B_6, 142
Vitamin B_9, 142
Vitamin B_{12}, 142
  prenatal nutrition, 344
Vitamin C, deficiency in, 142
Vitamin D, 142–143
  bone mineral metabolism and, 195
  deficiency rickets, treatment/monitoring for, 197
Vitamin E, 142–143
Vitamin K, 142–143
  deficiency bleeding, 302
Vitamins, 141–143, 142t
  requirements for, in newborn infants, 141
Vocal cord paralysis, 91, 364
Voiding cystourethrogram (VCUG), in urinary tract dilation, 389
Volume of distribution (V_d), 394, 398
Volume targeted ventilation, 98
Volvulus, of small intestine, 249–250
von Recklinghausen disease, congenital heart disease with, 42t–44t
von Willebrand disease (VWD), 302
Vulnerable populations, research ethics in, 442–443

W

Waardenburg syndrome, 282t, 358–359
Warfarin
  fetal syndrome, congenital heart disease with, 42t–44t
  teratogenic effects in pregnancy, 401t
Water metabolism, 156, 157t
  disorders of, 157–166
Water-electrolyte metabolism, 155–167.e2
Water-soluble vitamin deficiencies, manifestations of, 141–142
White blood cells (WBCs), 296–298, 297f
  neutrophil maturation, 298f
White matter injury (WMI), 323
Whole-exome sequencing (WES), 109, 415
Whole-genome sequencing (WGS), 415
Wilcoxon rank-sum test, 420

Williams syndrome, 195
  congenital heart disease with, 42t–44t
Wilms tumor, 308t, 312
Wiskott-Aldrich syndrome, 213t, 301
Wolf-Hirschhorn syndrome, 115–116
Wolff-Parkinson-White syndrome, 61

X

X-linked agammaglobulinemia, 214t
X-linked dominant disorders, 107
X-linked hyper IgM, 214t
X-linked ichthyosis, 284
X-linked recessive disorders, 107

Z

Zellweger syndrome, congenital heart disease with, 42t–44t
Zero-order elimination, 397–398
Zinc
  deficiency in, 143
  postnatal nutrition, 344
  prenatal nutrition, 344
  toxicity of, 143
Zona fasciculata, 181
Zona glomerulosa, 181
Zona reticularis, 181
Zygosity, 7

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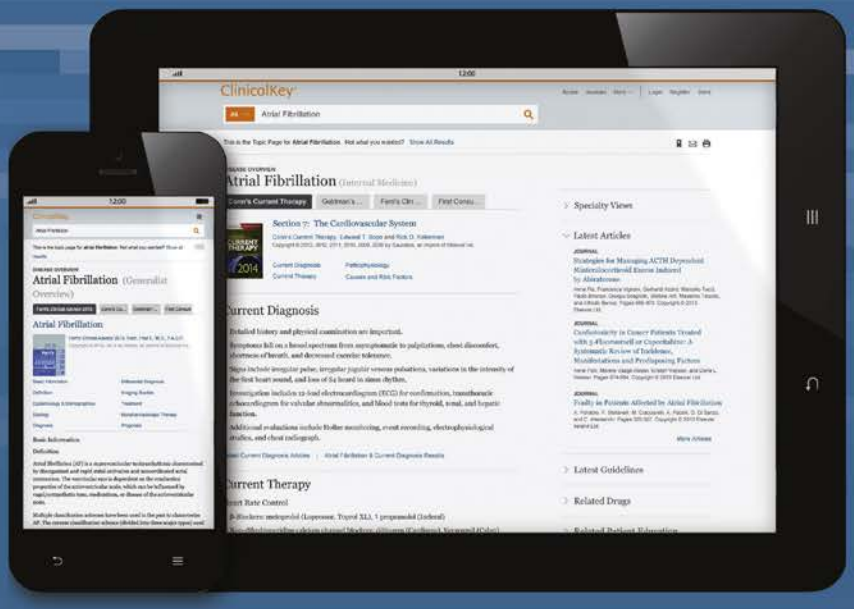

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