Manual of Nephrology: Diagnosis and Therapy 5th edition (October 1999): By Robert W Schrier MD By Lippincott Williams & Wilkins Publishers

Manual of Nephrology

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Preface

The fifth edition of the *Manual of Nephrology* has been substantially updated with new authors in 10 of the 15 chapters. The focus of the manual continues to be primary care physicians, medical students, nephrology fellows, and house staff. The manual provides a practical approach to the diagnosis and treatment of acute and chronic renal diseases; fluid, electrolyte, and acid-base disorders; urinary tract infections; renal stones; and hypertensive disorders. Renal imaging approaches and recommendations for different renal disorders are discussed by Ronald R. Townsend and Robert A. Older. The diagnostic value of a careful urinalysis is again presented by Sharon G. Adler and Kenneth Fairley.

David H. Ellison has coauthored the chapter on edematous disorders and brings his expertise in diuretics to this important area. Similarly, Tomas Berl has strengthened the chapter on hyponatremia and hypernatremia with his vast experience in disorders of renal water excretion. William D. Kaehny and Stuart L. Linas have lent their extraordinary teaching talents to the respective chapters on disorders of acid-base and potassium. Robert F. Reilly has expertly dealt with disorders of calcium and phosphorus metabolism as well as renal calculi in a practical, elegant, and up-to-date manner. Jay Redington has joined L. Barth Reller to present the most recent information about the diagnosis of and preferred anti-biotic regimens for treatment of infection of the upper and lower urinary tract. Charles L. Edelstein has joined Robert E. Cronin in writing the chapter on acute renal failure. They have applied their substantial experience and knowledge in elucidating this important area. Bruce J. Fisch and David M. Spiegel have presented excellent chapters on chronic renal failure and renal rep lacement therapy, respectively. The general approach to drug dosing patients with renal failure, including specific recommendations for some 500 medications, has been expertly presented by George R. Aronoff. Phyllis August has updated her chapter on kidney disease and pregnancy, along with Adrian I. Katz and Marshall D. Lindheimer, and Charles R. Nolan has expertly dealt with the diagnosis and treatment of hypertensive disorders, including both primary and secondary hypertension.

All of these contributing authors were selected for their ability to use their extraordinary scientific knowledge in a practical way, allowing for focused and cost-effective plans of diagnosis and treatment in the best interest of patients. In this same spirit, the *Manual of Nephrology* is dedicated to Professor Hugh de Wardener, physician, scientist, and educator, who has made remarkable contributions to medical science and to his patients for more than 50 years.

Robert W. Schrier, M.D.

Chapter 1 The Edematous Patient: Cardiac Failure, Cirrhosis, and Nephrotic Syndrome

David H. Ellison and Robert W. Schrier

Body fluid distribution
Body fluid volume regulation
Dietary and diuretic treatment of edema: general principles
Congestive heart failure
Hepatic cirrhosis
Nephrotic syndrome

I. Body fluid distribution Of the total fluid in the human body, two-thirds resides inside the cell (i.e., intracellular fluid), and one-third resides outside the cell [i.e., extracellular fluid (ECF)]. The patient with generalized edema has an excess of ECF. ECF resides in two locations: in the vascular compartment (plasma fluid) and between the cells of the body but outside of the vascular compartment (interstitial fluid). In the vascular compartment, approximately 85% of the fluid resides on the venous side of the circulation and 15% on the arterial side (Table 1-1). An excess of interstitial fluid constitutes edema. On applying digital pressure, interstitial fluid can generally be moved from the area of pressure, leaving an indentation; this is described as *pitting*. This demonstrates that the excess interstitial fluid can move freely within its space between the body's cells. If digital pressure does not cause pitting in the edematous patient, then free movement of the interstitial fluid is not present. Such nonpitting edema can occur with lymphatic obstruction (i.e., lymphedema) or regional fibrosis of subcutaneous tissue, which may occur with chronic venous stasis.

Compartment	Amount	Volume in 70-kg man
Total body fluid	60% of body weight	42 L
Intracellular fluid	40% of body weight	28 L
Extracellular fluid (ECF)	20% of body weight	14 L
Interstitial fluid	Two-thirds of ECF	9.4 L
Plasma fluid	One-third of ECF	4.6 L
Venous fluid	85% of plasma fluid	3.9 L
Arterial fluid	15% of plasma fluid	0.7 L

Table 1-1. Body fluid distribution

Although generalized edema always signifies an excess of ECF, specifically in the interstitial compartment, the intravascular volume may be decreased, normal, or increased. Because two-thirds of ECF resides in the interstitial space and only one-third in the intravascular compartment, a rise in total ECF volume may occur as a consequence of excess interstitial fluid (i.e., generalized edema) even though intravascular volume is decreased.

A. **Starling's law** states that the rate of fluid movement across a capillary wall is proportional to the hydraulic permeability of the capillary, the transcapillary hydrostatic pressure difference, and the transcapillary oncotic pressure difference. As shown in Figure 1-1, under normal conditions fluid leaves the capillary at the arterial end, because the transcapillary hydrostatic pressure difference favoring transudation exceeds the transcapillary oncotic pressure difference, which favors fluid reabsorption. In contrast, fluid returns to the capillary at the venous end because the transcapillary oncotic pressure difference exceeds the hydrostatic pressure difference. Because serum albumin is the major determinant of capillary oncotic pressure, which acts to maintain fluid in the capillary, hypoalbuminemia can lead to excess transudation of fluid from the vascular to the interstitial compartment. Although hypoalbuminemia might be expected to lead commonly to edema, several factors act to buffer the effects of hypoalbuminemia on fluid transudation. First, an increase in transudation tends to dilute interstitial fluid, reducing the interstitial protein concentration. Second, increases in interstitial fluid volume increase interstitial hydrostatic pressure. Third, the lymphatic flow into the jugular veins, which return transudated fluid to the circulation, increases. In fact, in cirrhosis, where hepatic fibrosis causes high capillary hydrostatic pressures in association with hypoalbuminemia, the lymphatic flow can increase 20-fold, to 20 L per day, attenuating the tendency to accumulate interstitial fluid. When these safety factors are overwhelmed, interstitial fluid accumulation can lead to edema. Another factor that must be borne in mind as a cause of edema is an increase in fluid permeability of the capillary wall (an increase in hydraulic conductivity). This increase is the cause of edema associated with hypersensitivity reactions and angioneurotic edema, and it may be a factor in edema associated with diabetes mellitus and in idiopathic cyclic edema.

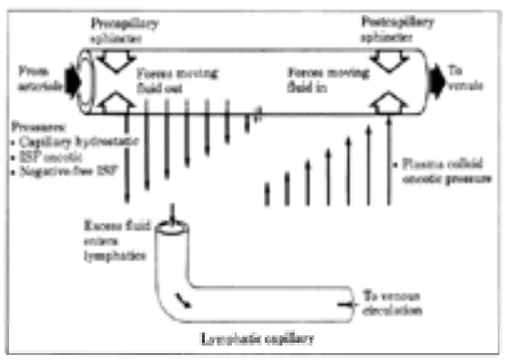

Figure 1-1. Effect of Starling forces on fluid movement across capillary wall. (ISF, interstitial fluid.)

B. These comments refer to **generalized edema** (i.e., an increase in total body interstitial fluid), but it should be noted that such edema may have a **predilection for specific areas** of the body for various reasons. The formation of ascites because of portal hypertension has already been mentioned. With the normal hours of upright posture, accumulation of the edema fluid in the dependent parts of the body should be expected, whereas excessive hours at bed rest in the supine position will predispose to edema accumulation in the sacral and periorbital areas of the body. The physician must also be aware of the potential presence of localized edema, which must be differentiated from generalized edema.
C. Although generalized edema may have a predilection for certain body sites, it is nevertheless a **total-body phenomenon** of excessive interstitial fluid. Localized edema, on the other hand, is caused by local factors and therefore is not a total-body phenomenon. Venous obstruction, as can occur with thrombophlebitis, may cause localized edema of one lower extremity. Lymphatic obstruction (e.g., from malignancy) can also cause excessive accumulation of interstitial fluid and, thus, edema. The physical examination of a patient with ankle edema should, therefore, include a search for venous incompetence (e.g., varicose veins) and for evidence of lymphatic disease. It should be recognized, however, that deep venous disease may not be detectable on physical examination and therefore may necessitate other diagnostic approaches (e.g., venography). Thus, if the venous disease is bilateral, the physician may mistakenly search for causes of generalized edema (e.g., cardiac failure and cirrhosis), when indeed the bilateral ankle edema is caused by local factors. Pelvic lymphatic obstruction (e.g., malignancy) can also cause bilateral lower-extremity edema and thereby mimic generalized edema. Trauma, burns, inflammation, cellulitis, and angioedema are other causes of localized edema.

II. Body fluid volume regulation The edematous patient has long presented a challenge in the understanding of body fluid volume regulation. In the normal subject, if ECF is expanded by the administration of isotonic saline, the kidney excretes the excess amount of sodium and water in the urine, thus returning ECF volume to normal. The important role of the kidney in volume regulation has been recognized for many years. What has not been understood, however, is why the

kidneys continue to retain sodium and water in the edematous patient. It is understandable that when kidney disease is present and renal function is markedly impaired (i.e., in acute or chronic renal failure), the kidney continues to retain sodium and water, even to a degree causing hypertension and pulmonary edema. Much more perplexing are those circumstances in which the kidneys are known to be normal and yet continue to retain sodium and water in spite of expansion of ECF and edema formation (e.g., cirrhosis, congestive heart failure). For example, if the kidneys of a cirrhotic patient are transplanted to a patient without liver disease, excessive renal sodium and water retention no longer occur. The conclusion has emerged, therefore, that neither total ECF nor its interstitial component, both of which are expanded in the patient with generalized edema, is the modulator of renal sodium and water excretion. Rather, as Peters suggested in the 1950s, some body fluid compartment other than total ECF or interstitial fluid volume must be the regulator of renal sodium and water excretion.

A. The term **effective blood volume** was coined to describe this undefined, enigmatic body fluid compartment that signals the kidney, through unknown pathways, to retain sodium and water in spite of expansion of total ECF. That the kidney must be responding to cardiac output was suggested, providing an explanation for sodium and water retention in low-output cardiac failure. This idea, however, did not provide a universal explanation for generalized edema, because many patients with decompensated cirrhosis who were avidly retaining sodium and water were found to have normal or elevated cardiac outputs.
B. **Total plasma or blood volume** was then considered as a possible candidate for the effective modulator of renal sodium and water excretion. However, it was soon apparent that expanded plasma and blood volumes were frequently present in renal sodium- and water-retaining states such as congestive heart failure and cirrhosis. The venous component of plasma in the circulation has also been proposed as the modulator of renal sodium and water excretion and thus of volume regulation, because a rise in the left atrial pressure is known to cause a water diuresis and natriuresis, mediated in part by a suppression of vasopressin and a decrease in neurally mediated renal vascular resistance. A rise in right and left atrial pressure has also been found to cause a rise in atrial natriuretic peptide. However, in spite of these effects on the low-pressure venous side of the circulation, renal sodium and water retention are hallmarks of congestive heart failure, a situation in which pressures in the atria and venous component of the circulation are routinely increased.
C. The **arterial portion of body fluids** (see Table 1-1) is the remaining compartment that may be pivotal in regulation of renal sodium and water excretion. More recently, the relationship between cardiac output and peripheral arterial resistance [the effective arterial blood volume (EABV)] has been proposed as a regulator of renal sodium and water reabsorption. This relationship establishes the “fullness” of the arterial vascular tree. In this context, a primary decrease in cardiac output, peripheral arterial vasodilation, or a combination thereof may cause arterial underfilling and thereby initiate and sustain a sodium- and water-retaining state, which leads to edema. The sodium- and water-retaining states that are initiated by a fall in cardiac output are shown in Figure 1-2 and include (a) ECF volume depletion (e.g., diarrhea, vomiting, hemorrhage); (b) low-output cardiac failure, pericardial tamponade, and constrictive pericarditis; and (c) intravascular volume depletion secondary to protein loss and hypoalbuminemia (e.g., nephrotic syndrome, burns or other protein-losing dermopathies, protein-losing enteropathy); and increased capillary permeability (capillary leak syndrome). The causes of increased renal sodium and water retention leading to edema that are initiated by primary peripheral arterial vasodilation are equally numerous and are shown in Figure 1-3. Severe anemia, beri-beri, Paget's disease, and thyrotoxicosis are causes of high-output cardiac failure that may lead to sodium and water retention. A wide-open arteriovenous fistula, hepatic cirrhosis, sepsis, pregnancy, and vasodilating drugs (e.g., minoxidil, hydralazine, and prazosin) are other causes of peripheral arterial vasodilation that decrease renal sodium and water excretion.

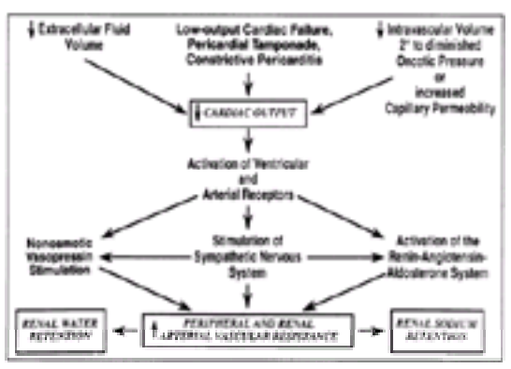

Figure 1-2. Decreased cardiac output as the initiator of arterial underfilling. (From Schrier RW. A unifying hypothesis of body fluid volume regulation. *J R Coll Physicians Lond* 1992;26:296. Reprinted with permission.)

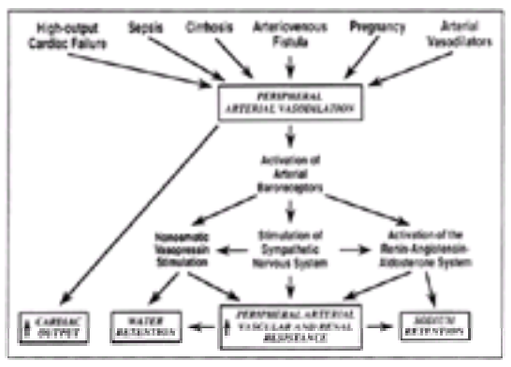

Figure 1-3. Peripheral arterial vasodilation as the initiator of arterial underfilling. (From Schrier RW. A unifying hypothesis of body fluid volume regulation. *J R Coll Physicians Lond* 1992;26:297. Reprinted with permission.)

D. Two major **compensatory processes** protect against arterial underfilling, as defined by the interrelationship of cardiac output and peripheral arterial vascular resistance. One compensatory process is very rapid and consists of a neurohumoral and systemic hemodynamic response, whereas the other is slower and involves renal sodium and water retention. In edematous patients, these compensatory responses occur to varying degrees depending on the point in the clinical course at which the patient is seen. Because of the occurrence of these compensatory processes, mean arterial pressure is a poor index of the integrity of the arterial circulation. Whether a primary fall in cardiac output or peripheral arterial vasodilation is the initiator of arterial underfilling, the compensatory responses are quite similar. As depicted in Figure 1-2 and Figure 1-3, the common neurohumoral response to arterial underfilling involves the stimulation of three vasoconstrictor pathways, namely, the sympathetic nervous system, angiotensin, and vasopressin. In addition to direct effects, the sympathetic nervous system increases angiotensin and vasopressin because increases in central sympathetic hypothalamic input and beta-adrenergic stimulation via renal nerves are important components of increased nonosmotic vasopressin release and stimulation of renin secretion, respectively. With a primary fall in cardiac output or with peripheral arterial vasodilation, increases in peripheral arterial vascular resistance or cardiac output, respectively, occur to maintain arterial pressure acutely. This rapid compensation allows time for the slower renal sodium and water retention to occur and further restore arterial circulatory integrity. With a decrease in ECF volume such as occurs with acute gastrointestinal losses, sufficient sodium and water can be retained to restore cardiac output to normal and terminate renal sodium and water retention before edema forms. Such may not be the case with low-output cardiac failure, because even these compensatory responses may not restore cardiac output to normal.
    1. Thus, the **neurohumoral** and **renal sodium- and water-retaining mechanisms** persist as important compensatory processes in maintaining arterial circulatory integrity. Specifically, neither the acute nor the chronic compensatory mechanisms are successful in restoring cardiac contractility or in reversing cardiac tamponade or constrictive pericardial tamponade. Compensatory renal sodium and water retention occurs with expansion of the venous side of the circulation as arterial vascular filling improves but does not return to normal. The resultant rise in venous pressure enhances capillary hydrostatic pressure and thus transudation of fluid into the interstitial fluid with resultant edema formation. With hypoalbuminemia and the capillary leak syndrome, excessive transudation of fluid occurs across the capillary bed and also prevents restoration of cardiac output; thus, continuous renal sodium and water retention occurs and causes edema formation.
    2. **Peripheral arterial vasodilation,** the other major initiator of arterial underfilling, also generally cannot be totally reversed by compensatory mechanisms and thus may lead to edema formation. Peripheral arterial vasodilation results in dilatation of precapillary arteriolar sphincters, increasing capillary hydrostatic pressure and probably capillary surface area. A larger proportion of retained sodium and water is transudated across the capillary bed into the interstitium in these edematous disorders (see Fig. 1-3).
E. Another reason that low cardiac output or peripheral arterial vasodilation may lead to edema formation is the inability of patients with these disorders, as compared with normal subjects, to escape from the **sodium-retaining effect of aldosterone** (Fig. 1-4). In the normal subject receiving large exogenous doses

of aldosterone or another mineralocorticoid hormone, a rise in glomerular filtration rate and a decrease in proximal tubular sodium and water reabsorption lead to an increase in sodium and water delivery to the distal nephron site of aldosterone action. This increase in distal sodium delivery is the major mediator of escape from the sodium-retaining effect of mineralocorticoids in normal subjects, thus avoiding edema formation. In contrast, the renal vasoconstriction that accompanies the compensatory neurohumoral response to arterial underfilling is associated with a decrease in sodium and water delivery to the distal nephron site of aldosterone action. This diminution in distal delivery, which occurs primarily because of a fall in glomerular filtration rate and an increase in proximal tubular sodium reabsorption, results in a failure to escape from aldosterone and, therefore, causes edema formation. The importance of renal hemodynamics, particularly glomerular filtration rate, in the aldosterone escape phenomenon is emphasized by the observation that in pregnancy, a state of primary arterial vasodilation, aldosterone escape occurs in spite of arterial underfilling because of an associated 30% to 50% increase in glomerular filtration rate. It still remains to be determined why pregnancy is associated with this large increase in glomerular filtration rate, which occurs within 2 to 4 weeks of conception. The increase in filtration rate cannot be due to plasma volume expansion, because this does not occur until several weeks after conception. The higher filtered load of sodium, and thus distal sodium load in pregnancy, no doubt allows the escape from the sodium-retaining effect of aldosterone. The occurrence of aldosterone escape in pregnancy attenuates edema formation compared with other edematous disorders.

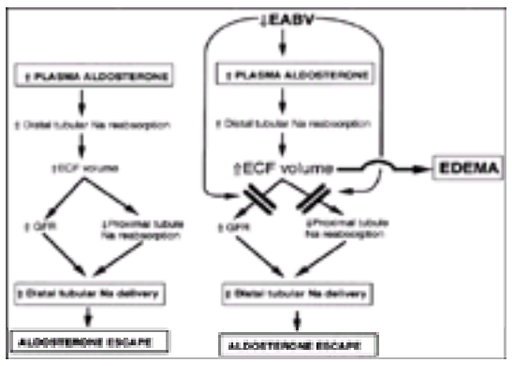

Figure 1-4. Aldosterone escape in a normal subject (left side) and failure of aldosterone escape in patients with arterial underfilling (right side). (EABV, effective arterial blood volume; ECF, extracellular fluid; GFR, glomerular filtration rate.) (From Schrier RW. Body fluid regulation in health and disease: a unifying hypothesis. *Ann Intern Med* 1990;113:155–159. Adapted with permission.)

III. Dietary and diuretic treatment of edema: general principles The daily intake of sodium in this country is typically 4 to 6 g [1 g of sodium contains 43 mEq; 1 g of sodium chloride (NaCl) contains 17 mEq of sodium]. By not using added salt at meals, the daily sodium intake can be reduced to 4 g (172 mEq), whereas a typical “low-salt” diet contains 2 g (86 mEq). Diets that are lower in NaCl content can be prescribed, but many individuals find them unpalatable. If salt substitutes are used, it is important to remember that these contain potassium chloride; therefore, potassium-sparing diuretics (i.e., spironolactone, triamterene, amiloride) should not be used with salt substitutes. Other drugs that increase serum potassium concentration must also be used with caution in the presence of salt substitute intake [e.g., converting enzyme inhibitors, beta blockers, and nonsteroidal antiinflammatory drugs (NSAIDs)]. When prescribing dietary therapy for an edematous patient it is important to emphasize that NaCl restriction is required, even if diuretic drugs are used. The therapeutic potency of diuretic drugs varies inversely with dietary salt intake.

All commonly used **diuretic drugs** act by increasing urinary sodium excretion. They can be divided into five classes, based on the predominant site of action along the nephron (Table 1-2). Osmotic diuretics (e.g., mannitol) and proximal diuretics (e.g., acetazolamide) are not employed as primary agents to treat edematous disorders. Loop diuretics (e.g., furosemide), distal convoluted tubule (DCT) diuretics (e.g., hydrochlorothiazide), and collecting duct diuretics (e.g., spironolactone), however, all play important but distinct roles in treating edematous patients. The goal of diuretic treatment of edema is to reduce ECF volume and maintain it at the reduced level. This requires an initial period of natriuresis, but, at steady state, urinary NaCl excretion returns close to baseline despite continued diuretic administration. Importantly, the presence of an initial natriuresis does *not* establish therapeutic efficacy if ECF volume does not decline. Conversely, the return to “basal” levels of urinary sodium excretion does not indicate diuretic resistance. The continued efficacy of diuretic therapy is documented by the rapid return to ECF volume expansion that occurs if the diuretic is discontinued.

Osmotic diuretics
Proximal diuretics
Carbonic anhydrase inhibitors
Acetazolamide
Loop diuretics (maximal FE_{Na} = 30%)
Na-K-2Cl inhibitors
Furosemide
Bumetanide
Torsemide
Ethacrynic acid
Distal convoluted tubule diuretics (maximal FE_{Na} = 9%)
Na-Cl inhibitors
Chlorothiazide
Hydrochlorothiazide
Metolazone
Chlorthalidone
Indapamide*
Many others
Collecting duct diuretics (maximal FE_{Na} = 3%)
Na channel blockers
Amiloride
Triamterene
Aldosterone antagonists
Spironolactone

FE_{Na}, fractional sodium excretion.
*Indapamide may have other antihypertensive effects.

Table 1-2. Physiologic classification of diuretic drugs

A. When a **diuretic drug is administered by mouth,** the magnitude of the natriuretic response is determined by the intrinsic potency of the drug, its bioavailability, the dose, the amount delivered to the kidney, the amount that enters the tubule fluid (most diuretics act from the luminal side), and the physiologic state of the individual. Except for proximal diuretics, the maximal natriuretic potency of a diuretic can be predicted from its site of action. Table 1-2 shows that loop diuretics can increase fractional sodium excretion to 30%, DCT diuretics can increase it to 9%, and sodium channel blockers can increase it to 3%. The intrinsic potency of a diuretic is defined by its dose response curve, which is generally sigmoid. The steep sigmoid relation is the reason that loop diuretic drugs are often described as “threshold drugs.” When starting loop diuretic treatment, ensuring that each dose reaches the steep part of the dose-response curve before the dose frequency is adjusted is important. Recommended maximum doses of loop diuretics are given in Table 1-3. Because loop diuretics are rapid-acting, many patients note an increase in urine output within several hours of taking the drug; this can be helpful in establishing that an adequate dose has been reached. Because loop diuretics are short-acting, any increase in urine output more than 6 hours after a dose is unrelated to drug effects. Using diuretic drugs b.i.d. or t.i.d. is rational only if each dose exceeds the diuretic threshold.

	Drug					
	Furosemide (mg)		Bumetanide (mg)		Torsemide (mg)	
Condition	i.v.	p.o.	i.v.	p.o.	i.v.	p.o.
Renal insufficiency						
GFR 26–50 mL/min	80	80–160	2–3	2–3	50	50
GFR <25 mL/min	200	240	8–10	8–10	100	100
Severe acute renal failure	500	NA	32	NA		
Nephrotic syndrome with normal GFR	120	240	3	3	50	50
Cirrhosis with normal GFR	40–80	80–160	1	1	10–20	10–20
Congestive heart failure with normal GFR	40–80	160–240	2–3	2–3	20–50	50

GFR, glomerular filtration rate.
Note: Ceiling dose indicates the dose that produces the maximal increase in fractional sodium excretion. Larger doses may increase net daily natriuresis by increasing the duration of natriuresis without increasing the maximal rate.

Table 1-3. Ceiling doses of loop diuretics

B. The **bioavailability of diuretic drugs** varies widely between classes of drugs, between different drugs of the same class, and even within drugs. The bioavailability of loop diuretics ranges from 10% to 100% (mean, 50% for furosemide; 80% to 100% for bumetanide and torsemide). Limited bioavailability can usually be overcome by appropriate dosing, but some drugs, such as furosemide, are variably absorbed by the same patient on different days, making precise titration difficult. Doubling the furosemide dose when changing from intravenous to oral therapy is customary, but the relation between intravenous and oral dose may vary. For example, the amount of sodium excreted during 24 hours is similar whether furosemide is administered to a normal individual by mouth or by vein, despite its 50% bioavailability. This paradox results from the fact that oral furosemide absorption is slower than its clearance, leading to "absorption-limited" kinetics. Thus, effective serum furosemide concentrations persist longer when the drug is given by mouth, because a reservoir in the gastrointestinal tract continues to supply furosemide to the body. This relation holds for a normal individual, but it is frequently altered in the edematous patient. Predicting the precise relation between oral and intravenous doses, therefore, is difficult. These considerations are less important for bumetanide and torsemide because of their higher bioavailability.

C. Another factor that determines the maximal natriuresis after diuretic drug administration is **drug delivery to its active site**. Most diuretics, including loop diuretics, DCT diuretics, and amiloride, act from the luminal surface. Loop and DCT diuretics are organic anions that circulate bound to albumin and reach tubule fluid primarily via the organic anion secretory pathway in the proximal tubule. When serum albumin concentrations are very low, diuretic resistance results because the volume of distribution of diuretic increases, decreasing drug delivery to the kidney. Most studies suggest that this effect is observed only when the serum albumin concentration declines below 2 g per L. Endogenous and exogenous substances may compete with diuretics for secretion into tubule fluid and affect diuretic response. Uremic anions, NSAIDs, probenecid, and penicillins all inhibit loop and DCT diuretic secretion into tubule fluid. Under some conditions, this may predispose to diuretic resistance because the concentration of drug achieved in tubule fluid does not exceed the diuretic threshold. For example, chronic renal failure shifts the loop diuretic dose response curve to the right, requiring a higher dose to achieve maximal effect. These considerations explain the higher doses of loop diuretic that are necessary in patients with renal failure (see Table 1-3).

D. Diuretic effectiveness also may be affected by **protein binding in tubule fluid**. Diuretic drugs are normally bound to proteins in the plasma, but not once they are secreted into tubule fluid. This reflects the normally low protein concentrations in tubule fluid. In contrast, when serum proteins such as albumin are filtered in appreciable quantities, as in nephrotic syndrome, diuretic drugs will interact with them and lose effectiveness.

E. When starting a loop diuretic as treatment for edema, it is important to establish a **therapeutic goal,** usually a target weight. If a low dose does not lead to natriuresis, it can be doubled repeatedly until the maximum recommended dose is reached (see Table 1-3). Patients are considered to be resistant to diuretics when an inadequate reduction in ECF volume is observed despite near-maximum doses of loop diuretics. Several causes of apparent resistance can be understood by considering the factors that affect diuretic efficacy, as discussed earlier. One cause of pseudoresistance is excessive dietary NaCl intake. When NaCl dietary intake is high, intense renal NaCl retention after the natriuretic period has ceased can maintain expansion of the ECF volume. Measuring the sodium excretion over 24 hours can be useful in diagnosing excessive intake. If the patient is at steady state (the weight is stable), the 24-hour urinary sodium excretion is equal to intake. If it exceeds 100 to 120 mM (2.3 to 2.8 g of sodium), then dietary NaCl consumption is too high, and the patient is *not* resistant to the diuretic. True diuretic resistance is confirmed by an inadequate daily natriuretic response.

1. Not uncommonly, simple approaches to **diuretic resistance** fail. Several strategies are available to achieve effective control of ECF volume in such patients. First, loop diuretics should be administered more frequently than once a day. Second, a diuretic of another class may be added to a regimen that contains a loop diuretic. This strategy produces true synergism; the combination of agents is more effective than the sum of the responses to each agent alone. DCT diuretics are the class of drug most commonly combined with loop diuretics. DCT diuretics inhibit adaptive changes in the distal nephron that serve to limit the potency of loop diuretics. Additionally, DCT diuretics have longer half-lives than loop diuretics. These drugs therefore prevent or attenuate NaCl retention during periods between doses of loop diuretics, increasing natriuresis.
2. When **two diuretics are combined**, the DCT diuretic is generally administered some time before the loop diuretic (1 hour is reasonable) to ensure that NaCl transport in the distal nephron is blocked when it is flooded with solute (Table 1-4). When intravenous therapy is indicated, chlorothiazide may be employed. Metolazone is the DCT diuretic most frequently combined with loop diuretics, because its half-life is relatively long (as formulated in Zaroxolyn) and because it has been reported to be effective even when renal failure is present. Other thiazide and thiazidelike diuretics, however, appear to be equally effective, even in severe renal failure. The dramatic effectiveness of combination diuretic therapy is accompanied by complications in a significant number of patients. Massive fluid and electrolyte losses have led to circulatory collapse during combination therapy, and patients must be followed carefully (Table 1-5). The lowest effective dose of DCT diuretic should be added to the loop diuretic regimen unless ECF contraction is urgent; patients can frequently be treated with combination therapy for only a few days and then placed back on a single-drug regimen. When continuous combination therapy is needed, low doses of DCT diuretic (metolazone, 2.5 mg, or hydrochlorothiazide, 25 mg) administered only two or three times per week may be sufficient. As an alternative, a collecting duct diuretic can be added to a loop diuretic. Although collecting duct diuretics are not usually as potent as DCT diuretics, some studies suggest other beneficial effects (see section **IV**).

Distal convoluted tubule diuretics
Metolazone, 2.5–10.0 mg p.o. daily*
Hydrochlorothiazide (or equivalent), 25–100 mg p.o. daily
Chlorothiazide, 500–1000 mg i.v.
Proximal tubule diuretics
Acetazolamide, 250–375 mg p.o. daily or up to 500 mg i.v.
Collecting duct diuretics
Spironolactone, 100–200 mg p.o. daily
Amiloride, 5–10 mg p.o. daily

*Metolazone is generally best given for a limited period (3 to 5 days) or should be reduced in frequency to three times per week once extracellular fluid volume has declined to the target level. Only in patients who remain volume expanded should full doses be continued indefinitely, based on the target weight.

Table 1-4. Combination diuretic therapy (to add to a ceiling dose of a loop diuretic)

Contraction of the vascular volume (from overzealous diuresis)
Orthostatic hypotension (from volume depletion)
Hypokalemia
Hyperkalemia (spironolactone, triamterene, and amiloride)
Hyperuricemia
Hypercalcemia (thiazides)
Hypercholesterolemia (beta-adrenergic blocker or thiazides)
Hyponatremia
Metabolic alkalosis
Skin rash
Gastrointestinal upset
Hyperglycemia
Pancreatitis (thiazides)
Acute interstitial nephritis (thiazides, furosemide, and triamterene)

Table 1-5. Complications of diuretics

3. For **hospitalized patients who are resistant** to diuretic therapy, a different approach is to infuse loop diuretics continuously. Continuous diuretic infusions have several advantages over bolus diuretic administration. First, because they avoid peaks and troughs of diuretic concentration, continuous infusions prevent periods of positive NaCl balance (postdiuretic NaCl retention) from occurring. Second, continuous infusions are more efficient than bolus therapy (the amount of NaCl excreted per milligram of drug administered is greater). Third, some patients who are resistant to large doses of diuretics given by bolus have responded to continuous infusion. Fourth, diuretic response can be titrated; when obligate fluid administration must be balanced by fluid excretion, excellent control of NaCl and water excretion can be obtained in the intensive care unit. Finally, complications associated with high doses of loop diuretics, such as ototoxicity, appear to be less common when large doses are administered as continuous infusion. Total daily furosemide doses exceeding 1 g have been tolerated well when administered over 24 hours. Recommended doses are given in Table 1-6. In patients with preserved renal function, therapy at the lower dose range should be sufficient. When renal failure is present, higher doses may be used, but patients should be monitored carefully for side effects, such as ECF volume depletion and ototoxicity.

Diuretic	Starting bolus (mg)	Infusion rate (mg/h) GFR <15 mL/min	GFR 15–75 mL/min	GFR >75 mL/min
Furosemide	40	20 then 40	10 then 20	10
Bumetanide	1	1 then 2	0.5 then 1	0.5
Torsemide	20	10 then 20	5 then 10	5

GFR, glomerular filtration rate.

Table 1-6. Continuous infusion of loop diuretics

F. When therapy with diuretics fails, **ultrafiltration** using hemodialysis equipment has been used. Although this approach is not recommended for routine use, in one controlled study, the response to volume removal via ultrafiltration was more sustained than after an equivalent volume removal via diuretics. In that study, loop diuretics induced a large rise in renin and angiotensin secretion, probably by stimulating the macula densa mechanism directly.

IV. Congestive heart failure

A. Early **clinical symptoms** of cardiac failure occur before overt physical findings of pedal edema and pulmonary congestion. These symptoms relate to the compensatory renal sodium and water retention that accompanies arterial underfilling. The patient may present with a history of weight gain, weakness, dyspnea on exertion, decreased exercise tolerance, paroxysmal nocturnal dyspnea, and orthopnea. Nocturia may occur because cardiac output and therefore renal perfusion may be enhanced by the supine position. This is also why patients with congestive heart failure may lose considerable weight during the first few days of hospitalization without the administration of diuretics. Although overt edema is not detectable early in the course of congestive heart failure, the patient may complain of swollen eyes on awakening and tight rings and shoes, particularly at the end of the day. With incipient edema, as much as 3 to 4 L of fluid can be retained before the occurrence of overt edema.

   The period of incipient edema is followed by more overt symptoms and physical findings: basilar pulmonary rales, ankle edema, distended neck veins at 30 degrees, tachycardia, and a gallop rhythm with a third heart sound. Although the chest x-ray may only show cephalization of pulmonary markings early in cardiac failure, increased hilar markings, Kerley's B lines, and pleural effusions occur later, generally accompanied by an enlarged heart.

B. **Etiology.** Two mechanisms by which cardiac output is reduced are now recognized to cause congestive heart failure: systolic dysfunction and diastolic dysfunction. Because specific, lifesaving therapy is available for systolic dysfunction, determining whether systolic dysfunction is present when a patient presents with symptoms and signs of heart failure is essential. Although physical examination, chest x-ray, and electrocardiography are useful in this regard, additional diagnostic tests are usually indicated. An echocardiogram provides information about systolic function (the ejection fraction), diastolic function, and valvular disease, which may require surgery. Occult hypo- or hyperthyroidism and alcoholic cardiomyopathy may present as congestive heart failure and are treatable. Uncontrolled hypertension may contribute to congestive heart failure, but disease of the coronary arteries is now the most common cause. In one study, severe coronary artery disease was found in 9 of 38 patients undergoing cardiac transplantation for presumed idiopathic dilatated cardiomyopathy, and in 3 of 4 patients with presumed alcoholic cardiomyopathy. These data suggest that cardiac catheterization (or noninvasive testing) may be indicated in virtually all patients who present with new-onset congestive heart failure. Cardiac arrhythmia, pulmonary embolus, cessation of medicines, severe anemia or fever, dietary sodium indiscretion, and worsening of chronic obstructive lung disease are examples of potentially treatable precipitants of worsening of heart failure in patients with preexisting cardiac disease. Some drugs may also precipitate or worsen congestive heart failure in a patient with underlying heart disease: beta-adrenergic blockers or verapamil by decreasing cardiac output (see Treatment section, next, however), and NSAIDs by causing sodium retention or worsening control of hypertension. A trial of cessation of these drugs is the best means to determine their role in worsening congestive heart failure. Control of blood pressure in heart failure secondary to hypertension or atherosclerosis is extremely important, as is cessation of smoking.

C. **Treatment.** When none of these specific primary or precipitating causes of congestive heart failure is detectable, general principles of treatment must be considered.

   Every patient with symptomatic systolic dysfunction or, if asymptomatic, an ejection fraction less than 40% should be started on angiotensin-converting enzyme (ACE) inhibitors, unless specific contraindications exist. These agents should be started at low doses (enalapril, 2.5 mg b.i.d., or captopril, 6.25 mg t.i.d.) but increased, if tolerated, to 10 mg b.i.d. of enalapril or 50 mg t.i.d. of captopril, unless side effects occur. If cough or angioedema limits ACE inhibitor use, then an angiotensin receptor blocker may be tried (angioedema may develop with angiotensin receptor blockers, but the incidence is lower with this class of drugs). If neither class of drug can be employed safely, then therapy with hydralazine and isosorbide dinitrate or mononitrate should be used. The role of digitalis glycosides has been clarified by controlled studies. Digoxin significantly improves symptoms and reduces the incidence of hospitalization in patients with impaired left ventricular function, but it does not appear to prolong life. Thus, the drug is indicated for symptomatic treatment when combined with ACE inhibitors and diuretics. In certain clinical states of heart failure, however, cardiac glycosides have been shown to be of little therapeutic value (e.g., in association with thyrotoxicosis, chronic obstructive pulmonary disease, and cor pulmonale). Cardiac glycosides may actually worsen symptoms in patients with hypertrophic obstructive cardiomyopathy and subaortic stenosis, pericardial tamponade, and constrictive pericarditis. It should also be remembered that digoxin is excreted by the kidneys; therefore the dose or dosage interval should be increased in the patient with chronic renal disease (see Chapter 12). Also, the elderly patient should receive a decreased dose (e.g., 0.125 mg q.o.d.), even if the serum creatinine level is not increased. As renal function deteriorates with age, serum creatinine may not rise because of a concomitant loss of muscle mass. Although phosphodiesterase inhibitors, such as milrinone, which also increase cardiac output, are potentially useful acute therapy, they have been shown to increase mortality when used chronially and should be avoided.

   If symptomatic pulmonary congestion or peripheral edema is present, diuretic therapy is indicated. Patients with mild congestive heart failure may respond to a DCT diuretic, such as hydrochlorothiazide. If symptoms are more severe, however, a loop diuretic is usually used, according to the principles discussed earlier. In patients with congestive heart failure, diuretic therapy must be instituted with full knowledge of the Starling-Frank curve of myocardial contractility (Fig. 1-5). The patient with congestive heart failure who responds to a diuretic will exhibit improved symptomatology as end-diastolic volume and pulmonary congestion decrease. However, because there is no descending limb of the Starling-Frank curve, an improvement in cardiac output should not be expected. Rather, no change (flat part of curve) or a decrease (ascending limb of curve) occurs with diuretic treatment. If during the diuretic treatment of a patient with congestive heart failure the serum creatinine and blood urea nitrogen levels begin to rise, the cardiac output has likely fallen. This situation is especially pronounced in patients who receive ACE inhibitor therapy. ACE inhibitors impair renal autoregulation and predispose to prerenal azotemia. When mild azotemia develops in a patient treated with diuretics and an ACE inhibitor, usually reducing the diuretic dose or liberalizing dietary salt intake is advisable, as long as pulmonary congestion is not present simultaneously. This approach has been shown to permit continued administration of ACE inhibitors in many patients, which is important because of their ability to prolong life. Some pedal edema may be preferable to a diuretic-induced fall in cardiac output as estimated by the occurrence or worsening of prerenal azotemia. These patients are especially sensitive to renal functional deterioration if NSAIDs are used with diuretics and ACE inhibitors. Thus, NSAIDs should be diligently avoided in this patient population.

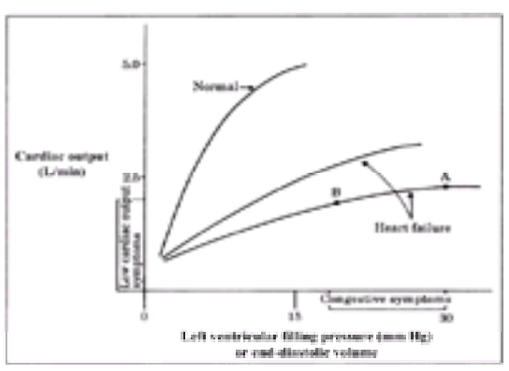

Figure 1-5. Relationship between cardiac output and left ventricular filling pressure under normal circumstances (*upper curve*) and low-output congestive heart failure (*lower curve*). Reduction of the afterload (e.g., angiotensin-converting enzyme inhibitor, hydralazine, prazosin, or nitroprusside) or improved contractility

(inotropic agents) may shift the lower curve to the middle curve. Diuretic-induced preload reduction or other causes of volume depletion may decrease cardiac output (e.g., shift from point A to point B on the lower curve). (From Schrier RW, ed. *Renal and electrolyte disorders*, 4th ed. Boston: Little, Brown, 1990. Reprinted with permission.)

The other major complications of diuretic therapy of congestive heart failure are electrolyte abnormalities (see Table 1-5). The combination of ACE inhibitors and furosemide was shown to ameliorate hyponatremia in some patients with congestive heart failure, probably by improving cardiac output and blocking the urinary concentrating mechanism. Yet hypokalemia and hypomagnesemia are frequent complications of diuretic treatment. This is particularly true of heart failure patients because they frequently have secondary hyperaldosteronism. Loop diuretics increase sodium delivery to the collecting duct site of aldosterone action where potassium secretion occurs. Severe renal magnesium wasting may also occur in the setting of secondary hyperaldosteronism and loop diuretic administration. Because both magnesium and potassium depletion cause similar deleterious effects on the heart, and potassium repletion is very difficult in the presence of magnesium depletion, supplemental replacement of both of these cations is frequently necessary in patients with cardiac failure. Table 1-5 lists some of the other major complications of diuretic therapy.

Another approach to preventing hypokalemia is the use of the aldosterone antagonist spironolactone. Interest in the possibility that aldosterone blockade with spironolactone may be useful in patients with congestive heart failure has revived. This interest has been driven by the observation that serum aldosterone concentrations frequently rise in patients treated with ACE inhibitors, despite continued suppression of angiotensin II production. Small preliminary studies suggested that adding spironolactone to a regimen that included ACE inhibitors and loop diuretics improves symptoms and reduces arrhythmias. Preliminary results of a large, multicenter, randomized trial [the Randomized Aldactone Evaluation Study (RALES) trial] support and extend these findings. The addition of spironolactone (12.5 to 75.0 mg per day) to a regimen that included an ACE inhibitor and a diuretic (with or without digoxin) decreased blood pressure and serum atrial natriuretic peptide levels and reduced the incidence of hypokalemia. Hyperkalemia occurred frequently, however (24% of patients experienced levels higher than 5.5 mM, versus 5% in controls). The study was stopped prematurely at 24 months because of a 27% reduction in mortality in the spironolactone group. It seems likely that this reflects both an improvement in ECF volume control and higher serum concentrations of potassium and magnesium. Because these data derive from a single study and because clinical experience with spironolactone in the setting of ACE inhibition remains modest, spironolactone is not currently recommended as routine therapy. But the dramatic results of the RALES trial suggest that cautious use of spironolactone may be indicated in patients with severe systolic dysfunction. Risk factors identified in the RALES study for the development of hyperkalemia included renal dysfunction, a pre-drug potassium concentration higher than 4.2 mM, and a dose of spironolactone greater than 50 mg per day.

Beta blockers have been shown to improve symptoms and mortality in patients with systolic dysfunction. Carvedilol, a nonselective beta blocker with alpha-blocking properties was recently approved by the U.S. Food and Drug Administration for the treatment of congestive heart failure. It is usually used for patients who have been stabilized on an ACE inhibitor, digoxin, and a diuretic, but, like other beta blockers, it can lead to acute symptomatic exacerbations of heart failure and should be used cautiously.

Treatment of patients with diastolic dysfunction is less clearly defined. Beta blockers and verapamil are usually considered to be the agents of choice. Diuretics have the potential to induce hypotension and syncope because these patients may be highly preload dependent, but their use may be necessary if congestive symptoms predominate. Although afterload reduction therapy has theoretical drawbacks in these patients, preliminary studies suggest that ACE inhibitors may also be useful in this group of patients.

V. Hepatic cirrhosis may be caused by several etiologies. It seems likely that the pathogenesis of renal sodium and water retention is similar in all varieties of cirrhosis, including alcoholic, viral, and biliary cirrhosis. Studies in both humans and animals indicate that renal sodium and water retention precedes the formation of ascites in cirrhosis. Thus, the classic “underfill” theory, which attributes renal sodium and water retention of cirrhosis to ascites formation with resultant hypovolemia, seems untenable as a primary mechanism. Because plasma volume expansion secondary to renal sodium and water excretion occurs before ascites formation, the overflow theory of ascites formation was proposed. This theory postulated that an undefined process, triggered by the diseased liver (e.g., increased intrahepatic pressure), causes renal sodium and water retention that overflows into the abdomen because of portal hypertension. The overflow theory, however, implies that renal salt retention and ascites formation would be associated with decreased levels of vasopressin, renin, aldosterone, and norepinephrine. Because these hormones rise progressively as cirrhosis advances from the states of compensation (no ascites) to decompensation (ascites) to hepatorenal syndrome, the overflow hypothesis also does not seem to explain the renal sodium and water retention associated with advanced cirrhosis. More recently, the peripheral arterial vasodilation hypothesis has been proposed This hypothesis, summarized in Figure 1-6, is compatible with virtually all known observations in patients during the various stages of cirrhosis. According to this hypothesis, cirrhosis causes arterial vasodilation and a decline in blood pressure with resultant renal NaCl retention. The cause of the primary arterial vasodilation in cirrhosis is not clear, but it is known to occur early in the course of the disease, before ascites formation. Although several mediators, including substance P, vasoactive intestinal peptide, endotoxin, and glucagon have been proposed to play a role in this primary arterial vasodilation, recent information indicates that nitric oxide may be a crucial participant. The opening of existing splanchnic arteriovenous shunts may account for some early arterial vasodilation. Later, anatomically new portosystemic and arteriovenous shunting secondary to the portal hypertension may also occur.

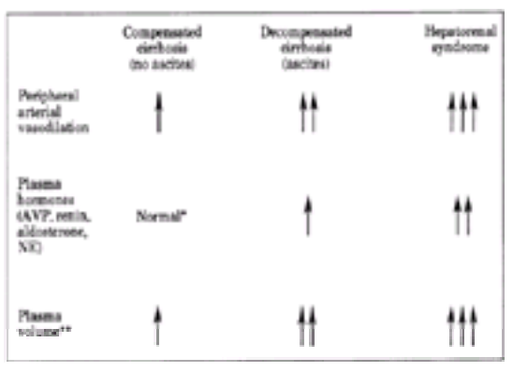

Figure 1-6. Peripheral arterial vasodilation hypothesis. Stages of progression of cirrhosis. (AVP, arginine vasopressin; NE, norepinephrine.)
*Given the positive sodium and water balance that has occurred, these plasma hormones would be suppressed in normal subjects without liver disease.
**The progressive renal sodium and water retention increases extracellular fluid, interstitial fluid, and plasma volume. However, the concomitant occurrence of hypoalbuminemia in decompensated cirrhosis and hepatorenal syndrome may attenuate the degree of plasma volume expansion.

A. **Options for treating cirrhotic ascites** and edema include dietary NaCl restriction, diuretic drugs, large-volume paracentesis, peritoneovenous shunting, portosystemic shunting [usually transjugular intrahepatic portosystemic shunting (TIPS)], and liver transplantation. Each of these approaches has a role in the treatment of cirrhotic ascites, but most patients can be treated successfully with dietary restriction, diuretics, and sometimes large-volume paracentesis.

   As discussed, the **initial therapy of cirrhotic ascites** is supportive, including dietary sodium restriction and cessation of alcohol intake. When these maneuvers prove inadequate, diuretic treatment should begin with spironolactone. Spironolactone has several advantages. First, a controlled trial showed that spironolactone is more effective than furosemide alone in reducing ascites in cirrhotic patients. Second, spironolactone is a long-acting diuretic that can be given once per day in doses ranging from 25 to 400 mg per day. Third, unlike most other diuretics, hypokalemia does not occur when spironolactone is administered. Hypokalemia increases renal ammonia production and can precipitate encephalopathy. The most common side effect of spironolactone is painful gynecomastia. Although amiloride, another potassium-sparing diuretic, can be used as an alternative, in one study spironolactone was shown to be more effective than amiloride in reducing ascites. For patients who do not respond to a low dose of spironolactone, spironolactone can be combined with furosemide, starting at 100 mg spironolactone per 40 mg furosemide (to a maximum of 400 mg spironolactone per 160 mg furosemide). This regimen has the advantages of once-per-day dosing and minimal hypokalemia and appears to be more effective than either drug alone.

   The appropriate **rate of diuresis** depends on the presence or absence of peripheral edema. Because the mobilization of ascitic fluid into the vascular compartment is slow (approximately 500 mL per day), the rate of daily diuresis should be limited to 0.5 kg per day if peripheral edema is absent. In the presence

of edema, most patients can tolerate up to 1 kg per day of fluid removal. Because ascites in the decompensated cirrhotic patient is associated with substantial complications including (a) spontaneous bacterial peritonitis (50% to 80% mortality), which does not occur in the absence of ascites; (b) impaired ambulation, decreased appetite, and back and abdominal pain; (c) elevated diaphragm with decreased ventilation predisposing to hypoventilation, atelectasis, and pulmonary infections; and (d) negative cosmetic and psychological effects, the gradual treatment of ascites with diuretics and sodium restriction is appropriate. The approach outlined above is successful in approximately 90% of patients. Early studies in which complications of diuretic therapy were high often exceeded 500 mL per day in volume losses.

B. An alternate approach to diuretics is **large-volume paracentesis**. Total paracentesis over 3 days or at one setting has been shown to have few complications; in some studies, paracentesis appeared to have a lower incidence of complications than did diuretic treatment. Many investigators favor infusing 6 g albumin for each liter of ascitic fluid removed, because albumin prevents hemodynamic compromise after the procedure (as indicated by elaboration of vasoregulatory hormones). Yet the use of albumin remains controversial, especially in patients with concomitant edema. Patients often favor large-volume paracentesis because the frequency and duration of hospitalizations are diminished, whereas some physicians in the United States continue to favor diuretics and salt restriction as the primary approach in the diuretic-sensitive individual.

   Interest in **portosystemic shunting** has increased because the use of TIPS is less invasive than surgical shunting. In two uncontrolled trials, TIPS led to an increase in urine output, a marked reduction in ascites, and a reduction in diuretic use. Renal function also improved. Yet in a controlled trial, mortality was *increased* in patients who received TIPS, as compared with control subjects. TIPS can also precipitate hepatic encephalopathy, especially in Child-Pugh C patients. In the absence of controlled trials supporting its use, TIPS is best reserved for truly refractory patients who will not receive a liver transplant. Similar considerations apply to peritoneovenous (LeVeen) shunting. In controlled trials, peritoneovenous shunting was shown to reduce ascites more effectively than paracentesis or diuretics, but this was associated with a high rate of complications (e.g., infections, clotting of shunt), and the shunt provided no survival advantage. Despite reports that the high complication rate can be reduced, most centers reserve this therapy for patients who are truly refractory to more conventional approaches and who are not candidates for liver transplantation.

   The development of ascites in a previously compensated cirrhotic patient is an indication to be listed for liver transplantation unless there is a reversible insult. In view of the morbidity and mortality associated with decompensated cirrhosis, liver transplantation has emerged as an important therapy for end-stage liver disease. Worsening of ascites in a previously stable individual is most often caused by progressive liver disease but should also compel the search for hepatocellular carcinoma and portal vein thrombosis.

C. Specific **treatment aimed at the peripheral arterial vasodilation of cirrhosis** has only been used in the acute setting of the patient with portal hypertension and bleeding esophageal varices. Evidence for an important role of nitric oxide in cirrhosis-associated vasodilation has been described. In a rat model of cirrhosis, blockade of chronic nitric oxide synthesis was shown to correct the hemodynamic and neurohumoral perturbations and to dramatically improve the sodium and water retention. Whether this approach will prove useful in human cirrhosis remains to be tested. Portal venous hypertension is caused not only by the intrahepatic capillary fibrosis that causes resistance to flow but also by increased splanchnic flow. The administration of vasopressin, which selectively constricts the splanchnic vasculature, has been shown to decrease portal venous pressure and thereby diminish esophageal variceal bleeding. A chronic oral vasopressin analogue that has selective V_1 (vascular) agonist activity but not V_2 (antidiuretic) activity and a reasonably long duration of action (hours) could be of value for the chronic treatment of portal hypertension and prevention of esophageal variceal bleeding. Such a compound, however, remains to be developed. Because there are fewer V_1 receptors on the renal than the splanchnic vascular bed, such an approach could also increase renal perfusion presure without causing further renal vasoconstriction.

VI. Nephrotic syndrome is another major cause of edema. Its clinical hallmarks include proteinuria (>3.5 g per day), hypoalbuminemia. hypercholesterolemia, and edema. The degree of the edema may range from pedal edema to total body anasarca, including ascites and pleural effusions. The lower the plasma albumin concentration, the more likely the occurrence of anasarca; the degree of sodium intake is, however, also a determinant of the degree of edema. Nephrotic syndrome has many causes (see Chapter 8). Systemic causes include diabetes mellitus, lupus erythematosus, drugs (e.g., phenytoin, heavy metals, NSAIDs), carcinomas, and Hodgkin's disease; and primary renal diseases such as minimal change nephropathy, membranous nephropathy, focal glomerulosclerosis, and membranoproliferative glomerulonephritis can also cause nephrotic syndrome.

A. The **pathogenesis** of ECF volume expansion in nephrotic syndrome appears to be more variable than the pathogenesis of edema in congestive heart failure or cirrhotic ascites. Traditionally, ECF volume expansion in nephrotic syndrome was believed to depend on hypoalbuminemia and a resulting underfilling of the arterial circulation. Several observations have raised questions about this hypothesis. First, the interstitial oncotic pressure in normal individuals is higher than previously appreciated. Transudation of fluid during ECF volume expansion reduces the interstitial oncotic pressure, minimizing change in transcapillary oncotic pressure. Second, patients recovering from minimal-change nephropathy frequently begin to excrete sodium before the serum albumin concentration rises. Third, volume-regulatory hormones frequently circulate in nephrotic patients at levels that are lower than in patients with cirrhosis or congestive heart failure. These and other observations have suggested a role for primary renal NaCl retention in the pathogenesis of nephrotic edema.

B. Although primary renal NaCl retention may contribute to nephrotic edema in many patients, it is usually not the only mechanism; some component of **"underfill"** often plays a role as well. Evidence against the overflow hypothesis includes the observation that primary renal NaCl retention usually does not by itself lead to edema. For example, as discussed earlier, chronic aldosterone infusion leads to escape from sodium retention before edema develops. Other causes of primary renal NaCl retention are associated with severe hypertension but not with edema. Further, levels of vasoactive hormones, although below levels commonly seen in cirrhosis and congestive heart failure, are often higher than would be expected based on the level of ECF volume expansion.

   It appears that different causes of nephrotic syndrome are associated with a preponderance either of "primary" renal salt retention or of underfill edema. In general, a normal or near-normal glomerular filtration rate is associated with hypovolemic, vasoconstrictor nephrotic syndrome. In the setting of a reduced glomerular filtration rate, primary renal sodium retention may play a larger role. In this setting, evidence of volume expansion (e.g., decreased plasma renin activity) may be observed.

C. **Treatment.** The initial focus of therapy must be aimed at treatable systemic causes of nephrotic syndrome, such as systemic lupus erythematosus or etiologic drugs (e.g., phenytoin, NSAIDs). Treatment of the primary renal causes of nephrotic syndrome is described in Chapter 8.

   The treatment of edema in nephrotic patients involves **dietary sodium restriction and diuretics**. Because these patients may not be as underfilled as patients with cirrhosis or congestive heart failure, diuresis is often tolerated well. In general, loop diuretics are used as initial therapy. For several reasons, however, nephrotic patients are relatively resistant to these drugs. First, as discussed above, loop diuretics circulate bound to albumin. When the serum albumin concentration declines below 2 g per L, the volume of distribution increases, and drug delivery to the kidney is reduced. Second, filtered albumin binds to loop diuretics in the tubule lumen, impairing its activity. Finally, many nephrotic patients have reduced glomerular filtration rates. In renal failure, endogenous organic anions impair secretion of diuretics to their active site within the tubule. Thus, higher doses of loop diuretics are often required to achieve natriuresis in nephrotic patients.

   Administration of large amounts of albumin to patients with the nephrotic syndrome is costly and can cause pulmonary edema. One report, however, suggested that mixing albumin with a loop diuretic (6.25 g albumin per 40 mg furosemide) may induce a diuresis in severely hypoalbuminemic patients by increasing drug delivery to the kidney. A double-blind, controlled study of nine nephrotic patients compared the effects of (a) 60 mg intravenous furosemide, (b) 60 mg intravenous furosemide plus 200 mL of a 20% solution of albumin, and (c) a sham infusion plus 200 mL of albumin. Coadministration of furosemide and albumin was significantly more effective than either albumin or furosemide alone. The authors noted, however, that the effect of the added albumin was relatively modest. Nevertheless, this study provides the strongest support to date for mixing albumin with loop diuretics in resistant hypoalbuminemic patients. In some anecdotal cases, patients with minimal change disease with severe hypoalbuminemia and anasarca were not responsive to prednisone therapy until a substantial diuretic-induced weight loss was achieved. The exact mechanism and the actual frequency of occurrence of this phenomenon remain to be examined.

Suggested Reading

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Chapter 2 The Patient with Hyponatremia or Hypernatremia

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Hyponatremia
Interpretation of the serum sodium
Approach to the hypo-osmolar hyponatremic patient
Signs and symptoms
Therapy
Hypernatremia
Approach to the hypernatremic patient
Signs and symptoms
Therapy

Control of serum sodium and osmolality. Under physiologic conditions, the concentration of sodium in plasma is kept in a very narrow range between 138 and 142 mEq per L, despite great variations in water intake. Because sodium is the predominant cation in extracellular fluid (ECF), this reflects the equally narrow range in which the tonicity (osmolality) of body fluids is regulated between 280 and 290 mOsm per kg. Thus, calculated plasma osmolality can be expressed as follows:

$$P_{osm} = 2[Na^+] + \frac{\text{blood urea nitrogen (mg/dL)}}{2.8} + \frac{\text{glucose (mg/dL)}}{18}$$

Serum sodium (concentration) and plasma osmolality are maintained in these normal ranges by the function of a very sensitive osmoreceptor that controls the secretion of the antidiuretic hormone arginine vasopressin. This hormone, in turn, is critical in determining water excretion by allowing urinary dilution in its absence and urinary concentration in its presence. Hyponatremic disorders supervene when the water intake exceeds the patient's renal diluting capacity. Conversely, hypernatremia supervenes in settings associated with renal concentrating defects accompanied by inadequate water intake.

Hyponatremia

Hyponatremia, defined as a plasma sodium concentration of less than 135 mEq per L, is a frequent occurrence in the hospitalized patient. It has been suggested that approximately 10% to 15% of patients in hospitals have a low plasma sodium concentration at some time during their stay. Hyponatremia in the ambulatory outpatient is a much less frequent occurrence and is usually associated with a chronic disease state.

I. Interpretation of the serum sodium Under most clinical circumstances, a decrement in serum sodium reflects a hypo-osmolar state. However, recognizing the settings in which a normal or even a low sodium level does not reflect a normal osmotic or a hypo-osmotic state is important. The addition to the ECF of osmotically active solutes that do not readily penetrate into cells, such as glucose, mannitol, or glycine, causes water to move from cells to ECF, thereby leading to cellular dehydration and a decrement in serum Na concentration. This has been designated *translocational hyponatremia*, a name that does not reflect changes in total body water but rather the movement of water from the intracellular to the extracellular compartment.

With hyperglycemia, for each 100 mg per dL rise in blood glucose, a 1.6 mEq per L fall in plasma sodium concentration will occur as water moves out of cells into the ECF. For example, as blood glucose rises from 200 to 1200 mg per dL in an untreated diabetic patient, the plasma sodium concentration would be expected to fall from 140 to 124 mEq per L (1.6 mEq/L × 10 = 16 mEq) without a change in total body water and electrolytes. Conversely, treatment with insulin and lowering of the blood sugar from 1200 to 200 mg per dL in this diabetic patient would result in comparable osmotic water movement from the ECF into cells and a return of plasma sodium concentration to 140 mEq per L without any change in total body water or electrolytes.

Another setting in which hyponatremia can occur without a change in plasma osmolality is pseudohyponatremia. This occurs when the solid phase of plasma, primarily lipids and proteins (usually 6% to 8%), is greatly increased, as in severe hypertriglyceridemia and paraproteinemic disorders. This falsely low reading is a consequence of the flow photometry methods that measure the concentration of Na^+ in whole plasma and not only in the liquid phase. It is estimated that a rise in plasma lipids by 4.6 g per L or in plasma proteins of 10 g per dL lowers serum Na concentration by 1 mEq per L. This is not a problem when undiluted serum is analyzed with an ion-specific electrode that measures the concentration of sodium in serum water.

II. Approach to the hypo-osmolar hyponatremic patient In the absence of pseudohyponatremia or an excess of osmotically active solute in the ECF, the most important initial step in the diagnosis of hyponatremia is an assessment of the ECF volume status. The hyponatremic patient can then be classified in one of three categories: (a) hyponatremia in the presence of an excess of total body sodium, (b) hyponatremia in the presence of a deficit of total body sodium, and (c) hyponatremia with a near normal total body sodium.

Sodium is the primary cation in the ECF compartment, and therefore sodium, with its accompanying anions, dictates ECF osmolality and fluid volume. Thus, ECF volume provides the best index of total body exchangeable sodium. A careful physical examination focused on the evaluation of ECF volume status therefore allows for the classification of the hyponatremic patient into one of these categories. For example, the edematous patient is classified as having hyponatremia with an excess of total body sodium. The volume-depleted patient with flat neck veins, decreased skin turgor, dry mucous membranes, and orthostatic hypotension and tachycardia is classified as having hyponatremia with a deficit of total body sodium. The patient with neither edema nor evidence of ECF volume depletion is classified as having hyponatremia with near-normal total body sodium (Fig. 2-1).

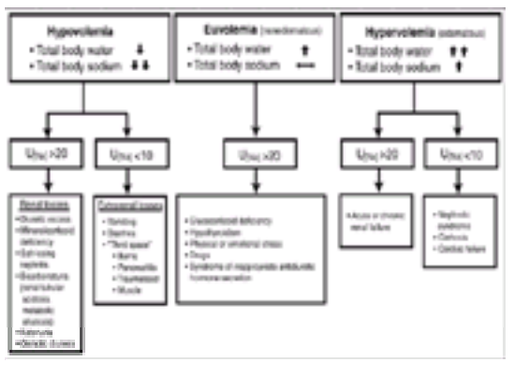

Figure 2-1. Diagnostic approach to hyponatremia. (↑, increased; ↑↑, greatly increased; ¯, decreased; ¯¯, greatly decreased; «, not increased or decreased; $U_{[Na]}$ = urinary sodium concentration, in mEq per L.)

A. In the **hypervolemic (edematous) hyponatremic patient,** both total body sodium and total body water are increased, water more so than sodium. These patients have cardiac failure, cirrhosis, nephrotic syndrome, or renal failure. When hyponatremia is secondary to cardiac and hepatic disease, the disease is advanced and readily evident on clinical examination. In the absence of the use of diuretics, the urinary sodium concentration in the hyponatremic edematous patient should be quite low (<10 mEq per L) because of avid tubular sodium reabsorption. The exception is in the presence of acute or chronic renal failure, in which, because of tubular dysfunction, the urinary sodium concentration is higher (>20 mEq per L).

B. The diagnostic possibilities in the **hypovolemic hyponatremic patient** are entirely different. Again, a spot urinary sodium concentration is of value. If the volume-depleted hyponatremic patient has a low (<10 mEq per L) sodium concentration, the kidney is functioning normally by conserving sodium in response to ECF volume depletion. On the other hand, if the urinary sodium concentration is greater than 20 mEq per L in a hypovolemic hyponatremic patient, the kidney is not responding appropriately to the ECF volume depletion, and renal losses of sodium and water must he considered as the likely cause of the hyponatremia.
   1. In a hypovolemic hyponatremic patient with **urinary sodium concentration less than 10 mEq per L,** a gastrointestinal (or "third space") source of sodium and water losses must be sought. The source may be readily apparent if the patient presents with a history of vomiting or diarrhea, or both. In the absence of an obvious history of gastrointestinal fluid losses, several other diagnostic possibilities must be considered. Substantial ECF losses may occur into the abdominal cavity with peritonitis or pancreatitis and into the bowel lumen with ileus or pseudomembranous colitis. The surreptitious cathartic abuser may present with evidence of ECF volume depletion and no history of gastrointestinal losses. A clue to this diagnosis may be the presence of hypokalemic metabolic acidosis and phenolphthalein in the urine. Loss of haustra on barium enema and melanosis coli on endoscopy are other clues to cathartic abuse. Burns or muscle damage may also lead to a state of hypovolemia and hyponatremia secondary to substantial fluid and electrolyte losses from skin or into muscle.
   2. In a hypovolemic hyponatremic patient with a **urinary sodium level greater than 20 mEq per L**, renal losses are occurring, and several different diagnostic possibilities must be considered.
      a. **Excessive use of diuretics** is foremost among these diagnoses. It occurs almost exclusively with thiazide diuretics, because these agents, unlike loop diuretics, alter only urinary diluting ability, and urinary concentration remains unimpaired. A fall in plasma sodium concentration in a patient receiving diuretics may be the first clue to the need to adjust the dosage of the diuretic. In some patients with diuretic abuse, ECF volume depletion is not readily apparent from clinical examination. An important clue, however, to the diagnosis of diuretic-induced hyponatremia is that virtually all of these patients have an associated hypokalemic alkalosis if they are receiving potassium-losing diuretics. If, however, a potassium-sparing diuretic is involved (e.g., triamterene, amiloride, or spironolactone), neither hypokalemia nor metabolic alkalosis may be present. Cessation of use of the diuretic is the best means of confirming the diagnosis of diuretic-induced hyponatremia. However, it must be remembered that restoration of ECF volume is also necessary to correct the hyponatremia. In the hypokalemic patient, potassium replacement may also be necessary for complete correction of the plasma sodium concentration imbalance.

         Surreptitious diuretic abuse occurs among premenopausal women who use diuretics for weight loss or other cosmetic reasons (e.g., thick ankles or calves, "puffy" face). These patients may be difficult to distinguish from patients with surreptitious vomiting, because both may present with evidence of ECF volume depletion and hypokalemic metabolic alkalosis. The presence or absence of hyponatremia depends on the patient's water intake. The pivotal diagnostic test to distinguish between the hypovolemic hyponatremic patient with metabolic alkalosis who is a diuretic abuser and the patient who is a surreptitious vomiter is the urinary chloride concentration. Surreptitious vomiters have low (<10 mEq per L) concentrations and surreptitious diuretic abusers high (>20 mEq per L) concentrations.
      b. **Salt-losing nephritis.** Patients with medullary cystic disease, chronic interstitial nephritis, polycystic kidney disease, analgesic nephropathy, partial urinary tract obstruction, and, rarely, chronic glomerulonephritis may present with hypovolemic hyponatremia secondary to salt-losing nephritis. These patients generally have moderately advanced renal impairment with serum creatinine levels greater than 3 to 4 mg per dL. This diagnosis should virtually never be considered in patients with renal disease that is not associated with elevated serum creatinine. Patients with salt-losing nephritis may need supplemental NaCl intake to avoid ECF volume depletion or may be very susceptible to ECF volume depletion in association with either decreased intake or extrarenal (e.g., gastrointestinal) sodium and water losses. Because these patients may be pigmented secondary to uremic dermatitis and exhibit hyponatremia and volume depletion, their disease was initially described as mimicking Addison's disease.
      c. **Mineralocorticoid deficiency.** The patient with Addison's disease (i.e., primary adrenal insufficiency) generally has associated hyperkalemia, and prerenal azotemia generally does not increase serum creatinine to concentrations greater than 3 mg per dL. In patients with mineralocorticoid deficiency, ECF volume repletion may correct both the hyponatremia and the hyperkalemia. The plasma cortisol during periods of stress may fall within the normal range. Thus, if adrenal insufficiency is suspected, a 2-hour cosyntropin (Cortrosyn) stimulation test should be performed. In addition to a urinary sodium concentration greater than 20 mEq per L, a urinary potassium concentration of less than 20 mEq per L may be another clue to mineralocorticoid deficiency. If fluid intake has been restricted, the patient with Addison's disease may not present with hyponatremia, and hyperkalemia may not be present if the ECF volume depletion is not severe. Thus, a high index of suspicion is necessary to make the diagnosis of adrenal insufficiency. These patients may present with nonspecific symptoms such as weight loss, anorexia, abdominal pain, nausea, vomiting, diarrhea, and fever.
      d. **Osmotic diuresis obligating anion excretion** is another major diagnostic consideration in the hypovolemic hyponatremic patient with a urinary sodium concentration greater than 20 mEq per L.
         1. **Glucose, urea, or mannitol diuresis.** The uncontrolled diabetic patient may have substantial glucosuria, causing water and electrolyte losses and, thus, ECF volume depletion. The urea diuresis after relief of urinary tract obstruction is another example of an osmotic diuresis that can cause ECF volume depletion. A chronic mannitol infusion without electrolyte replacement can produce a similar situation.
         2. **Bicarbonaturia.** Increased anion excretion also can obligate renal water and electrolyte losses. The most frequently encountered example of this is metabolic alkalosis with bicarbonaturia. The bicarbonate anion in the urine is accompanied by cations, including sodium and potassium, which maintain electrical neutrality. Bicarbonaturia may accompany the early development of metabolic alkalosis with postoperative nasogastric suction or vomiting. Proximal renal tubular acidosis (e.g., in Fanconi's syndrome) is another condition in which bicarbonaturia causes renal electrolyte loss. In the absence of a urinary tract infection with urease-producing organisms, a urinary pH (measured by a pH meter) greater than 6.1 indicates the presence of bicarbonate in the urine.
         3. **Ketonuria.** Ketoacids are other anions that can obligate renal electrolyte losses in spite of ECF volume depletion; this may contribute to urinary electrolyte losses in diabetic or alcoholic ketoacidosis or starvation.

C. **Euvolemic hyponatremia** is a commonly encountered form of hyponatremia in hospitalized patients. The urinary sodium concentration in euvolemic hyponatremia is generally greater than 20 mEq per L. However, if the patient is on a sodium-restricted diet or is volume depleted, the urinary sodium concentration may be less than 10 mEq per L. Refeeding with a normal salt intake or expansion of ECF volume with saline increases urinary sodium concentration to more than 20 mEq per L, but the hyponatremia will persist in the patient with euvolemic hyponatremia. These patients show no signs of either an increase or a decrease in total body sodium. Although the water retention leads to an excess in total body water, no edema is detected because two-thirds of the water is inside the cell. There are a limited number of diagnostic possibilities with hyponatremic patients who exhibit neither edema nor ECF volume depletion (i.e., euvolemic hyponatremic patients) (see Fig. 2-1). Two endocrine disorders must be considered—hypothyroidism and secondary adrenal insufficiency associated with pituitary or hypothalamic disease.
   1. The occurrence of hyponatremia with **hypothyroidism** generally suggests severe disease, including myxedema coma. In some patients, particularly the elderly, the diagnosis may not be readily apparent. Thus, thyroid function must be assessed in the euvolemic hyponatremic patient.
   2. **Glucocorticoid deficiency.** An intact renin-angiotensin-aldosterone system avoids ECF volume depletion in patients with secondary adrenal insufficiency, but it is clear that glucocorticoid deficiency alone can impair water excretion and cause hyponatremia. Although skull films and computed tomographic scans should always be obtained in the euvolemic hyponatremic patient when the cause of the hyponatremia is not obvious, normal skull films or computed tomographic scans do not exclude secondary adrenal insufficiency. A low plasma cortisol level associated with a low adrenocorticotropic hormone level supports the diagnosis of secondary adrenal insufficiency. In this setting, both secondary adrenal insufficiency and secondary hypothyroidism may contribute to the hyponatremia accompanying pituitary insufficiency.
   3. **Emotional or physical stress** must be considered in the euvolemic hyponatremic patient before invoking the diagnosis of the syndrome of inappropriate antidiuretic hormone (SIADH). Acute pain or severe emotional stress (e.g., decompensated psychosis associated with continued water ingestion) may lead to acute and severe hyponatremia. It is likely that a combination of emotional shock and physical pain accounts for the frequently encountered secretion of vasopressin in the postoperative state, which in turn leads to hyponatremia in the face of hypotonic fluid administration.
   4. A number of **pharmacologic agents** either stimulate the release of vasopressin or enhance its action. These include
      a. Nicotine
      b. Chlorpropamide
      c. Tolbutamide
      d. Clofibrate
      e. Cyclophosphamide
      f. Morphine
      g. Barbiturates
      h. Vincristine
      i. Carbamazepine (Tegretol)
      j. Acetaminophen
      k. Nonsteroidal antiinflammatory drugs
      l. Antipsychotics
      m. Antidepressants

Thus, determining whether the euvolemic hyponatremic patient is receiving such drugs is an important diagnostic step.

5. **SIADH** should be considered after exclusion of the diagnoses given above in the euvolemic hyponatremic patient. In general, the causes of SIADH include
   a. **Carcinomas,** most frequently but not exclusively of the
      1. Lung
      2. Duodenum
      3. Pancreas
   b. **Pulmonary disorders,** including but not limited to
      1. Viral pneumonia
      2. Bacterial pneumonia
      3. Pulmonary abscess
      4. Tuberculosis
      5. Aspergillosis
   c. **Central nervous system (CNS) disorders:**
      1. Encephalitis (viral or bacterial)
      2. Meningitis (viral, bacterial, or tubercular)
      3. Acute psychosis
      4. Stroke (cerebral thrombosis or hemorrhage)
      5. Acute intermittent porphyria
      6. Brain tumor
      7. Brain abscess
      8. Subdural or subarachnoid hematoma or hemorrhage
      9. Guillain-Barré syndrome
      10. Head trauma
   d. **Acquired immunodeficiency syndrome**

Thus, SIADH occurs primarily in association with infections and with vascular and neoplastic processes in the CNS or lung.

III. Signs and symptoms. The level of hyponatremia that may cause signs and symptoms varies with the rate of decline in the plasma sodium concentration and the age of the patient. In general, the young-adult patient appears to tolerate a specific level of hyponatremia better than does the older patient. However, the acute (i.e., within a few hours) development of hyponatremia in a previously asymptomatic young patient may cause severe CNS signs and symptoms, such as depressed sensorium, seizures, and even death, when the plasma sodium concentration has reached only a level between 125 and 130 mEq per L. This is because the capacity of brain cells to extrude osmotically active particles, thus relieving the brain swelling that accompanies hyponatremia, requires a longer time to be invoked at the beginning of the condition. On the other hand, this protective mechanism against brain swelling becomes very effective with the chronic development of hyponatremia over days or weeks, so that an elderly person may present without overt signs or symptoms even with a plasma sodium concentration below 110 mEq per L.

Gastrointestinal symptoms, including anorexia and nausea, may occur early with hyponatremia; however, the more severe later signs and symptoms relate to the CNS, because the cell swelling that occurs with hyponatremia is tolerated worst within the rigid encasement of the skull. Severe hyponatremia of rapid onset may lead to brain edema and herniation and, thus, requires rapid treatment. Cheyne-Stokes respiration may be a hallmark of severe acute hyponatremia. In addition to exposure, uremia, and hypothyroidism, hyponatremia also should be considered in the differential diagnosis of the hypothermic patient.

In summary, **symptoms** that may be associated with hyponatremia include

A. Lethargy, apathy
B. Disorientation
C. Muscle cramps
D. Anorexia, nausea
E. Agitation

Signs that may be associated with hyponatremia include

F. Abnormal sensorium
G. Depressed deep tendon reflexes
H. Cheyne-Stokes respiration
I. Hypothermia
J. Pathologic reflexes
K. Pseudobulbar palsy
L. Seizures

IV. Therapy

A. **Factors affecting the approach to treatment.** The presence or absence of the symptoms described earlier and the duration of the hyponatremia are the primary guides to treatment strategy. Different time-dependent processes are involved in the adaptation to changes in tonicity, and the presence of cerebral symptoms reflects a failure of the adaptive response. In this regard, hyponatremia developing within 48 hours carries a greater risk of permanent neurologic sequelae from cerebral edema if the Na^+ is not corrected expeditiously. On the other hand, patients with chronic hyponatremia are at risk of osmotic demyelination if the correction is excessive or too rapid.
B. **Cerebral adaptation to hypotonicity.** Decreases in extracellular osmolality cause movement of water into cells, increasing intracellular volume and causing tissue edema. Edema within the cranium raises intracranial pressure, leading to neurologic syndromes. To prevent this complication, a volume-regulatory adaptation occurs. Early in the course of hyponatremia, within 1 to 3 hours, cerebral ECF volume decreases by movement of fluid into the cerebrospinal fluid, which is then shunted into the systemic circulation. Thereafter, the brain adapts by losing cellular potassium and organic solutes, which tend to lower the intracellular osmolality without substantial gain of water. If hyponatremia persists, other organic osmolytes, such as phosphocreatine, myoinositol, and amino acids (e.g., glutamine and taurine) are lost. The loss of these solutes greatly decreases cerebral swelling. Patients in whom this adaptive response fails are prone to severe cerebral edema when they develop hyponatremia. Postoperative menstruant females, elderly women on thiazide, psychiatric polydipsic patients, and hypoxemic patients seem to be particularly prone to hyponatremia-related encephalopathy. Conversely, as noted earlier, patients who have had the adaptive response are at risk of osmotic demyelination syndrome if the hyponatremia is excessively or too rapidly corrected. For example, a rapid increase in plasma osmolality may cause excessive cerebral water loss in previously adapted brains. Alcoholic subjects, burn victims, and severely hypokalemic patients are at risk for this complication.
C. **Acute symptomatic hyponatremia**, developing in less than 48 hours, is almost inevitable in hospital patients receiving hypotonic fluids. Treatment should be prompt, because the risk of acute cerebral edema exceeds the risk of osmotic demyelination. The aim should be to raise the serum Na^+ by 2 mmol per L per hour until symptoms resolve. Complete correction is unnecessary, although it is not unsafe. Hypertonic saline (3% NaCl) is infused at the rate of 1 to 2 mL per kg per hour, and a loop diuretic, such as furosemide, enhances solute-free water excretion and hastens the return to a normal serum Na^+. If severe neurologic symptoms (seizures, obtundation, or coma) are present, 3% NaCl may be infused at 4 to 6 mL per kg per hour. Even 29.2% NaCl (50 mL) has been used safely. Serum electrolytes should be carefully monitored.
D. **Chronic symptomatic hyponatremia.** If hyponatremia has been present for more than 48 hours or the duration is unknown, correction needs to be handled carefully. Whether it is the rate of correction of hyponatremia or the magnitude that predisposes to osmotic demyelination is unknown, but in practice dissociating the two is difficult, because a rapid correction rate usually means a greater correction over a given period of time.

   The following guidelines are fundamental to successful therapy:

   1. Because cerebral water is increased only by approximately 10% in severe chronic hyponatremia, promptly increase the serum Na^+ level by 10%, or by approximately 10 mEq per L.

2. After the initial correction, do not exceed a correction rate of 1.0 to 1.5 mEq per L per hour.
3. Do not increase the serum Na^+ by more than 15 mEq per L per 24 hours.

It is important to take into account the rate of infusion and the electrolyte content of infused fluids and the rate of production and electrolyte content of the urine.

Once the desired increment in serum Na^+ concentration is obtained, the treatment should consist of water restriction.

E. The approach to the **chronic asymptomatic patient with hyponatremia** is different. Initial bedside evaluation includes searching for an underlying disorder. Hypothyroidism and adrenal insufficiency should be sought as possible etiologies and hormones replaced if these deficiencies are found. A careful analysis of the patient's medications should be made and necessary adjustments undertaken.

For patients with SIADH, if the etiology is not identifiable or cannot be treated, the approach should be conservative, because rapid changes in serum tonicity lead to a greater degree of cerebral water loss and possible demyelination. Various approaches can be considered.

1. **Fluid restriction** is the easy and usually successful option, if the patient complies. It involves calculation of the fluid restriction that will maintain a specific serum Na^+. The daily osmolar load ingested divided by the minimal urinary osmolality (a function of the severity of the diluting disorder) determines a patient's maximal urine volume. On a normal North American diet, the daily osmolar load is about 10 mOsm per kilogram of body weight, and in a healthy person, the minimum urinary osmolality (given no circulating ADH) can be as low as 50 mOsm per kg. Thus, the daily urine volume in a 70-kg man can be as high as 14 L (700 mOsm per 50 mOsm per L). If the patient has SIADH and the urinary osmolality cannot be lowered below 500 mOsm per kg, the same osmolar load of 700 mOsm per day allows for only 1.4 L of urine. Thus, if the patient drinks more than 1.4 L per day, the serum Na^+ will fall.
2. **Pharmacologic agents.** Lithium was the first drug used to antagonize the action of vasopressin in hyponatremic disorders. Lithium may be neurotoxic, and its effects are unpredictable. Therefore, demeclocycline has become the agent of choice. This drug inhibits the formation and action of cyclic adenosine monophosphate in the renal collecting duct. The onset of action is 3 to 6 days after treatment is started. The dose needs to be decreased to the lowest level that keeps the serum Na^+ within the desired range, with unrestricted water intake; this dose is usually 300 to 900 mg daily. The drug should be given 1 to 2 hours after meals, and calcium-, aluminum-, and magnesium-containing antacids should be avoided. However, polyuria tends to make patients noncompliant. Skin photosensitivity may occur, and in children, tooth or bone abnormalities may result. Nephrotoxicity also limits the drug's use, especially in patients with underlying liver disease, in whom the hepatic metabolism of demeclocycline may be impaired.
3. **Vasopressin antagonists.** Specific antagonists of vasopressin action on the collecting duct may soon supplement these pharmacologic agents. Orally active, nonpeptide vasopressin type 2 (V_2)–receptor antagonists that have shown encouraging results in animal models and humans with hyponatremia are undergoing clinical studies, but these “aquaretic” agents have not yet been approved by the U.S. Food and Drug Administration.
4. **Increase in solute excretion.** Because urine flow can be significantly increased by obligating the excretion of solutes, thereby allowing a greater intake of water, maneuvers to increase solute excretion have been used. A loop diuretic, when combined with high sodium intake (2 to 3 g additional NaCl), is effective. A single diuretic dose (40 mg furosemide) is usually sufficient. The dose should be doubled if the diuresis induced in the first 8 hours is less than 60% of the total daily urine output. Administration of urea to increase the solute load increases urine flow by causing an osmotic diuresis. This permits a more liberal water intake without worsening the hyponatremia and without altering urinary concentration. The dose is usually 30 to 60 g of urea daily. The major limitations are gastrointestinal distress and unpalatability.

F. **Hypovolemic and hypervolemic hyponatremia.** Symptoms directly related to hyponatremia are unusual in hypovolemic hyponatremia, because loss of both sodium and water limits osmotic shifts in the brain. Restoration of ECF volume with crystalloids or colloids interrupts the nonosmotic release of vasopressin. In patients with hypovolemic hyponatremia from diuretics, the drug must be discontinued and potassium repletion ensured.

The treatment of hyponatremia in hypervolemic states is more difficult because it requires attention to the underlying disorder, heart failure or chronic liver disease. In congestive heart failure, both sodium and water restriction are critical. Refractory patients may be treated with a combination of an angiotensin-converting enzyme (ACE) inhibitor and a diuretic. The resultant increase in cardiac output with ACE inhibitors may increase solute-free water excretion and correct hyponatremia. Loop diuretics diminish the action of vasopressin on the collecting tubules, thereby increasing water excretion. Thiazide diuretics impair urinary dilution and may worsen hyponatremia. Water and salt restriction are also the mainstay of therapy in cirrhotic patients. For both disorders, V_2-receptor antagonists are under investigation, and these aquaretics may be clinically available to treat hyponatremia in the near future.

Hypernatremia

Hypernatremia, defined as a plasma sodium concentration greater than 150 mEq per L, is less common than hyponatremia. This is probably not due to a more frequent occurrence of disorders of renal dilution than of renal concentration, but rather to drinking behavior. Specifically, if an inability to dilute the urine is present, water intake of 1 to 2 L per day may cause hyponatremia. This amount of fluid intake may be ingested as routine behavior in spite of a hypo-osmolar stimulus to suppress thirst, which may explain the frequency of hyponatremia On the other hand, renal concentrating defects that cause renal water losses generally do not cause hypernatremia unless a disturbance in thirst is also present or the patient cannot drink or obtain adequate fluid to drink. The very young, the very old, and the very sick are, therefore, the populations that develop hypernatremia most frequently. In the absence of an inability to drink (e.g., with coma, nausea, and vomiting) or to obtain water (e.g., in infants or severely ill adults), the thirst mechanism is very effective in preventing hypernatremia. Although, as noted, hyponatremia does not always reflect a hypotonic state (i.e., pseudo- or translocation hyponatremia), hypernatremia always denotes a hypertonic state.

I. Approach to the hypernatremic patient As is the case with hyponatremia, hypernatremic patients may have low, high, or normal total body sodium (Fig. 2-2). Such a classification allows the clinician to focus on the most likely diagnosis in each category.

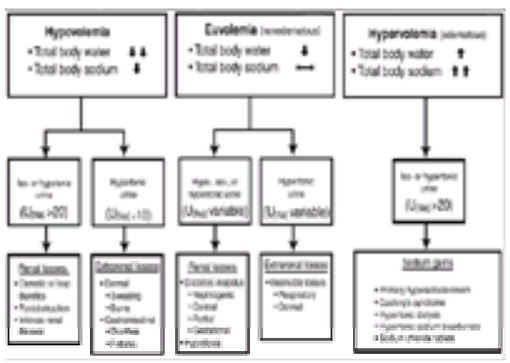

Figure 2-2. Diagnostic approach to hypernatremia. (↑, increased; ↑↑, greatly increased; ↓, decreased; ↓↓, greatly decreased; «, not increased or decreased; $U_{[Na]}$ = urinary sodium concentration, in mEq per L.)

A. **Hypovolemic hypernatremic patient.** The hypernatremic patient may have evidence of ECF volume depletion that has occurred secondary to either renal or extrarenal losses. These patients have sustained water losses that are greater than the sodium losses.
   1. **Extrarenal losses.** If the losses have been from an extrarenal site (e.g., in diarrhea), then sodium and water conservation by the kidney should be readily apparent. In such patients, the urine sodium concentration is less than 10 mEq per L, and the urine is hypertonic. In fact, hypotonic diarrhea losses are among the most common causes of hypernatremia in both children and adults, especially in those who are on lactulose for underlying liver disease.
   2. **Renal losses.** In contrast, hypotonic electrolyte losses may occur in the urine during osmotic diuresis or use of loop diuretics. In these patients, evidence of renal sodium and water conservation is, of course, not present, because the urine is the source of the losses. Thus, the urine is not hypertonic, and urine sodium concentration is generally greater than 20 mEq per L. In the hyperglycemic diabetic patient with good renal function and profound glucosuria, hypernatremia may be a presenting feature, because hypotonic renal losses may obscure any effect of hyperglycemia to shift water osmotically from cells to ECF. This is particularly true if the patient does not have access to water or is incapable of ingesting fluids (e.g., a comatose, ketoacidotic diabetic patient).
B. **Hypervolemic hypernatremic patient.** Patients with hypernatremia also may have evidence of ECF volume expansion. Generally, these are patients who have

received excessive amounts of hypertonic NaCl or sodium bicarbonate. In such an acute setting, the incidence of ECF volume expansion is most likely to be associated with pulmonary congestion, elevated neck veins, or both, rather than with peripheral edema. This variety of hypervolemic hypernatremia is rather infrequent.

C. **Euvolemic hypernatremia.** Most patients with hypernatremia secondary to water loss appear euvolemic with normal total body sodium, because loss of water without sodium does not lead to overt volume contraction. Water loss in and of itself need not culminate in hypernatremia unless it is unaccompanied by water intake. Because such hypodipsia is uncommon, hypernatremia usually supervenes only in those who have no access to water or who have a neurologic deficit that does not allow them to seek it. Extrarenal water loss occurs from the skin and respiratory tract in febrile or other hypermetabolic states. Urine osmolality is very high, reflecting an intact osmoreceptor-vasopressin-renal response. Thus, the defense against hyperosmolality requires both stimulation of thirst and the ability to respond by drinking water. The urine Na^+ varies with the sodium intake.

   The renal losses of water that lead to euvolemic hypernatremia are a consequence of a defect in vasopressin production or release (central diabetes insipidus), a failure of the collecting duct to respond to the hormone (nephrogenic), or excessive rapid degradation of vasopressin (gestational).

   1. Approximately 50% of instances of **central diabetes insipidus** have no detectable underlying cause and thus are classified as idiopathic. Trauma, surgical procedures in the area of the pituitary or hypothalamus, and brain neoplasms, either primary or secondary (e.g., from metastatic breast cancer), constitute the majority of the remaining causes of central diabetes insipidus. In addition, encephalitis, sarcoidosis, or eosinophilic granuloma may cause central diabetes insipidus. Central diabetes insipidus can be partial with some preservation of vasopressin release. When the central diabetes is associated with hypothalamic lesions and hypodipsia, these patients present with hypernatremia and a concentrated urine. A congenital form of central diabetes insipidus has also been described.
   2. **Nephrogenic diabetes insipidus.** In addition to well-characterized X-linked and autosomal recessive forms of congenital nephrogenic diabetes insipidus, a number of **acquired causes** have been described:
      a. **Secondary to renal diseases.** Medullary or interstitial renal diseases are particularly likely to be accompanied by vasopressin-resistant renal concentrating defects; the most frequent of these diseases are medullary cystic disease, chronic interstitial nephritis (e.g., analgesic nephropathy), polycystic kidney disease, and partial bilateral urinary tract obstruction. Far-advanced renal disease of any cause is uniformly associated with a renal concentrating defect. However, because of the very low glomerular filtration rate, the renal water loss (i.e., polyuria) is modest (2 to 4 L per day).
      b. **Secondary to hypercalcemia and hypokalemia.** Hypercalcemia secondary to any cause, including primary hyperparathyroidism, vitamin D intoxication, milk-alkali syndrome, hyperthyroidism, and tumor, may also cause nephrogenic diabetes insipidus. Similarly, hypokalemia secondary to any cause, including primary aldosteronism, diarrhea, and chronic diuretic use, may cause nephrogenic diabetes insipidus; however, some of the polyuria with hypercalcemia or hypokalemia may be due to stimulation of thirst and the resultant increase in water intake.
      c. **Drugs, dietary abnormalities, and other causes.** Various drugs impair the end-organ response to vasopressin and thus cause a renal concentrating defect (see section **I.C.2.d**). Excess water intake and dietary sodium and protein restriction also have been shown to impair urinary concentration. Other unique causes of nephrogenic diabetes insipidus include multiple myeloma, amyloidosis, Sjögren's syndrome, and sarcoidosis.
      d. **Summary** of acquired causes of nephrogenic diabetes insipidus
         1. Chronic renal disease
            Polycystic kidney disease
            Medullary cystic disease
            Pyelonephritis
            Ureteral obstruction
            Far-advanced renal failure
            Analgesic nephropathy
         2. Electrolyte disorders
            Hypokalemia
            Hypercalcemia
         3. Drugs
            Lithium
            Demeclocycline
            Acetohexamide
            Tolazamide
            Glyburide
            Propoxyphene
            Amphotericin
            Methoxyflurane
            Vinblastine
            Colchicine
         4. Dietary abnormalities
            Excessive water intake
            Decreased sodium chloride intake
            Decreased protein intake
         5. Miscellaneous
            Multiple myeloma
            Amyloidosis
            Sjögren's syndrome
            Sarcoidosis
            Sickle cell disease
   3. **Diabetes insipidus secondary to vasopressinase.** Central diabetes insipidus and nephrogenic diabetes are not the only causes of polyuria during pregnancy. Vasopressinase is an enzyme that is produced in the placenta that causes *in vivo* degradation of arginine vasopressin during pregnancy. Normally, an increase in vasopressin synthesis and release during pregnancy compensates for the increased degradation of the hormone. In rare cases, however, excessive vasopressinase has been incriminated in causing polyuria during pregnancy. Because vasopressinase cannot degrade deamino-8-D-arginine vasopressin, this is the treatment of choice for pregnancy-related polyuria.
   4. **Response to fluid deprivation and arginine vasopressin in the diagnosis of polyuric disorder.** The various forms of diabetes insipidus must be differentiated from primary polydipsia in patients who present with polyuria. Table 2-1 summarizes the procedure and interpretation of a water deprivation test.

Cause of polyuria	Urinary osmolality with water deprivation (mOsm/kg of water)	Plasma arginine vasopressin (AVP) after dehydration	Increase in urinary osmolality with exogenous AVP
Normal	>800	>2 pg/mL	Little or no increase
Complete central diabetes insipidus	<300	Undetectable	Substantially increased
Partial central diabetes insipidus	300–800	<1.5 pg/mL	Increase of more than 10% after water deprivation
Nephrogenic diabetes insipidus	<300–500	>5 pg/mL	Little or no increase
Primary polydipsia	>500	<5 pg/mL	Little or no increase

Note: Water intake is restricted until the patient loses 3% to 5% of his or her body weight or until three consecutive hourly determinations of urinary osmolality are within 10% of each other. Caution must be exercised to ensure that the patient does not become excessively dehydrated. Aqueous AVP (5 units subcutaneously in grams, and urinary osmolality is measured after 60 minutes. The expected responses are given above.

From Greene D, Tolefsrud J: Hypernatremia. In: Jacobson HR, Striker GE, Klahr S, eds. *The principles and practice of nephrology*. 2nd ed. St. Louis: Mosby, 1995:608–616. Reprinted with permission.

Table 2-1. Procedure and interpretation of a water deprivation test

Patients with compulsive water drinking may present with polyuria and a blunted response to the fluid deprivation test; on cessation of fluid intake, hypernatremia does not develop in these patients and their renal concentration defect is primarily due to a resistance of the kidney to vasopressin. However, because patients with central or nephrogenic diabetes insipidus may present with polyuria and polydipsia in the absence of hypernatremia, awareness of the diagnosis of compulsive (psychogenic) water drinking is quite important. Menopausal women with previous psychiatric problems are particularly prone to

compulsive water drinking. Psychoneurosis and psychosis are also frequently associated with increased water intake. Last, the patient with nephrogenic diabetes insipidus may occasionally have vasopressin-resistant hypotonic urine (e.g., hypercalcemic or hypokalemic nephropathy); thus, the temporary absence of fluid intake because of an intercurrent illness can be associated with hypernatremia. In all hypernatremic patients who have primarily water losses without electrolyte losses, the urine sodium concentration merely reflects sodium intake.

II. Signs and symptoms. Polyuria and polydipsia may be prominent symptoms in the patient who subsequently develops hypernatremia in association with inadequate water intake.

A. **CNS dysfunction.** Neurologic abnormalities constitute the most prominent manifestations of hypernatremic states. These neurologic manifestations appear to be due primarily to cellular dehydration and shrinkage of brain cells that are associated with tearing of cerebral vessels. Capillary and venous congestion, subcortical and subarachnoid bleeding, and venous sinus thrombosis all have been described with hypernatremia.
B. **Prognosis of acute versus chronic hypernatremia.** The signs and symptoms of hypernatremia are more severe with acute than with chronic hypernatremia. Indeed, 75% mortality has been reported in association with acute hypernatremia in adults with acute elevations of plasma sodium concentration above 160 mEq per L. These adults, however, frequently have severe primary diseases associated with their hypernatremia, and these primary diseases may largely account for the high mortality. A 45% mortality has been reported in children with acute hypernatremia, and as many as two-thirds of the surviving children may have neurologic sequelae.
C. **Idiogenic osmoles with chronic hypernatremia.** The more benign course of chronic hypernatremia appears to be related to cellular mechanisms that protect against severe brain dehydration. The brain, however, requires some period of time, perhaps days, to adapt. With chronic hypernatremia, brain cells generate idiogenic osmoles, some of which appear to be amino acids; these idiogenic osmoles are osmotically active and restore brain water to near-control levels in spite of persistent hypernatremia. The presence of these idiogenic anions with chronic hypernatremia, although protective against brain dehydration and shrinkage, may predispose to brain edema if the hypernatremia is corrected too rapidly.
D. **Correlation of CNS dysfunction with degree of hyperosmolality.** The earliest manifestations of hypernatremia are restlessness, increased irritability, and lethargy. These symptoms may be followed by muscular twitching, hyperflexia, tremulousness, and ataxia. The level of hyperosmolality at which these signs and symptoms occur depends not only on the rapidity of the change in the plasma sodium concentration but also on the age of the patient; the very young and the very old exhibit the most severe manifestations. In general, however, these signs and symptoms may occur progressively with plasma osmolality in the range of 325 to 375 mOsm per kg of water. At plasma osmolalities above this level, tonic muscular spasticity, focal and grand mal seizures, and death may occur. The elderly patient with dementia or severe cerebrovascular disease may demonstrate these life-threatening signs and symptoms at a lower level of plasma hyperosmolality.

III. Therapy. In most cases, hypernatremia can be treated by judicious administration of water to patients with water-losing disorders who cannot obtain water. The treatment of hypernatremia depends on two important factors: ECF volume status and the rate of development of the hypernatremia.

A. **Correction of ECF volume depletion.** When hypernatremia is associated with ECF volume depletion, the primary therapeutic goal is to administer isotonic saline until restoration of ECF volume is achieved, as assessed by normal neck veins and absence of orthostatic hypotension and tachycardia. Hypotonic (0.45%) NaCl or 5% glucose solutions can then be used to correct plasma osmolality.
B. **Correction of ECF volume expansion.** In contrast, if hypernatremia is associated with ECF volume expansion, diuretics (e.g., furosemide) can be used to treat the hypernatremia. In the presence of advanced renal failure, the patient with hypernatremia and fluid overload may need to be dialyzed to treat the hypernatremia.
C. **Water-replacement method of calculation.** Last, the patient with euvolemic hypernatremia can be treated primarily with water replacement either orally or parenterally with 5% glucose in water. The method of calculation of the necessary water replacement for a 75-kg man with a plasma sodium of 154 mEq per L is as follows:

$$\text{Total body water (TBW)} = \text{body weight} \times 60\% \text{ or}$$

$$\text{TBW} = 75 \times 0.6 = 45 \text{ L}$$

Then,

$$\frac{\text{Actual plasma sodium}}{\text{Desired plasma sodium}} \times \text{TBW} = \frac{154 \text{ mEq/L}}{40 \text{ mEq/L}} \times 45 \text{ L} = 49.$$

Therefore, 4.5 L (49.5 L – 45 L) positive water balance will correct the plasma sodium concentration. Ongoing water losses should not be overlooked.

D. **Rate of correction.** The recommended rate of correction of hypernatremia depends on the rate of development of the hypernatremia and the symptoms. More neurologic signs and symptoms are associated with acute hypernatremia; therefore, this biochemical abnormality should be corrected rapidly over a few hours.

   On the other hand, idiogenic osmoles appear to accumulate in brain cells during periods of chronic hypernatremia, a mechanism that protects against brain shrinkage, Thus, rapid correction of chronic hypernatremia can create an osmotic gradient between the ECF and intracellular compartments with osmotic water movement into cells and brain edema. In general, therefore, chronic hypernatremia is best corrected gradually at a rate not to exceed 2 mOsm per hour. One-half of the correction can be achieved in 24 hours and the other half in the next 24 hours or longer.

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Chapter 3 The Patient with Hypokalemia or Hyperkalemia

Stuart L. Linas

Overview of potassium physiology
Hypokalemia
Hyperkalemia

Potassium, the most abundant cation in the human body, regulates intracellular enzyme function and neuromuscular and cardiovascular tissue excitability. Because potassium is normally tightly maintained within the narrow range of 3.5 to 5.5 mEq per L, the intracellular-to-extracellular potassium ratio determines tissue excitability and underlies the clinical findings caused by disorders of potassium metabolism.

I. Overview of potassium physiology

The usual Western diet contains approximately 100 mEq of potassium per day. Renal excretion accounts for approximately 90% of daily potassium intake, the remainder being excreted in very small quantities in stool and sweat. About 90% of total body potassium is located in intracellular fluid, the majority in muscle. Extracellular fluid contains approximately 10% of total body potassium, but less than 1% is in plasma.

A. **Internal balance.** After a potassium meal, potassium is rapidly redistributed between the plasma and intracellular compartments. Over time, increases in renal potassium excretion occur, so that external potassium balance is maintained. A number of factors regulate the transcellular movement of potassium:
   1. **Insulin.** Binding of the hormone to insulin receptors results in hyperpolarization of cell membranes, thereby facilitating potassium uptake. In addition, insulin activates sodium-potassium adenosine triphosphatase (ATPase) pumps, resulting in cellular uptake of potassium.
   2. **Catecholamines.** Activation of the $beta_2$ adrenoreceptor results in cellular potassium uptake. These effects are transduced by cyclic adenosine monophosphate (cAMP) activation of sodium-potassium ATPase pumps, causing influx of potassium in exchange for sodium. Therapeutic agents such as theophylline potentiate $beta_2$ adrenoreceptor-mediated potassium uptake by inhibiting the degradation of cAMP.
   3. **Aldosterone.** Although this mineralocorticoid facilitates potassium uptake into muscle, clear proof of the clinical significance of this effect is lacking.
   4. **Acid-base.** Inorganic acidosis (e.g., hydrochloric acid) facilitates potassium movement from intracellular to extracellular fluid. Protons enter cells, whereas impermeant inorganic ions do not. The resulting increases in intracellular fluid positive charge favor outward movement of potassium. Organic ions (lactate, ketoacids) are less restricted from entering cells, so increases in serum potassium may not occur in organic acidosis.
   5. **Tonicity.** Hyperglycemia results in bulk flow of potassium-rich fluid from the cell, thereby increasing extracellular fluid potassium. Under most conditions, increases in insulin modulate and reverse the effect of increased extracellular tonicity. However, when insulin cannot be increased (as in diabetes mellitus) or hyperglycemia occurs rapidly (as with administration of 50% glucose), hyperkalemia occurs. Rapid infusions of mannitol may also cause hyperkalemia.

B. **External balance.** Potassium is almost freely filtered at the glomerulus. More than 50% of filtered potassium is reabsorbed by the end of the proximal convoluted tubule. Potassium is added to tubular fluid in the descending limb of Henle's loop, especially in deep nephrons. Along the course of the ascending limb of the loop of Henle, potassium is reabsorbed. The Na-K-2Cl cotransporter is responsible for potassium reabsorption, so that by the time tubular fluid reaches the early distal convoluted tubule, only 10% to 15% of filtered potassium remains. Potassium is secreted by principal cells of the cortical collecting and outer-medullar collecting duct. Potassium is reabsorbed in the collecting tubule, an effect mediated by intercalated cells. Urinary potassium excretion, therefore, is the result of differences between potassium secreted and potassium reabsorbed in the distal nephron. For the most part, decreases in glomerular filtration rate (GFR) do not cause changes in potassium excretion unless the GFR is less than 20 mL per minute. The major factors regulating potassium excretion are as follows:
   1. **Distal nephron flow rate and sodium delivery.** Principal cells of the cortical collecting duct contain apical sodium channels. Under normal conditions, sodium delivered to the cortical collecting tubule is reabsorbed through these apical sodium channels. This results in increases in cell sodium and secondary increases in basolateral sodium-potassium ATPase. The resultant increases in cellular potassium lead to enhanced apical potassium transport through specific potassium channels. Increases in sodium delivery facilitate this mechanism of potassium secretion; furthermore, increases in flow rate maintain urinary potassium concentration at a level sufficiently low to drive continued potassium movement from cells into tubular fluid.
   2. **Mineralocorticoids.** Aldosterone is the major mineralocorticoid and acts to increase potassium secretion by
      a. Increasing the number and activity of apical sodium channels
      b. Increasing basolateral sodium-potassium ATPase activity
      c. Increasing the number of apical potassium channels
   3. Increases or decreases in **dietary potassium** increase or decrease urinary potassium, respectively. Renal adaptation to high potassium intake is mediated by potassium-induced increases in aldosterone secretion and by increases in distal nephron sodium-potassium ATPase activity. In response to potassium restriction, mineralocorticoid activity decreases, an effect that facilitates potassium retention by the kidney.
   4. Increases in relatively nonresorbable **anions** (e.g., bicarbonate, penicillins) trap secreted potassium in the tubular lumen, thereby rendering potassium reabsorption in the medullary collecting duct more difficult. The resulting renal potassium losses may lead to severe potassium depletion.

II. Hypokalemia

A. The **initial approach** to hypokalemia is to determine whether decreases in serum potassium concentration are spurious, are caused by shifts of potassium from extracellular to intracellular compartments, or are due to decreases in total body potassium (Fig. 3-1).

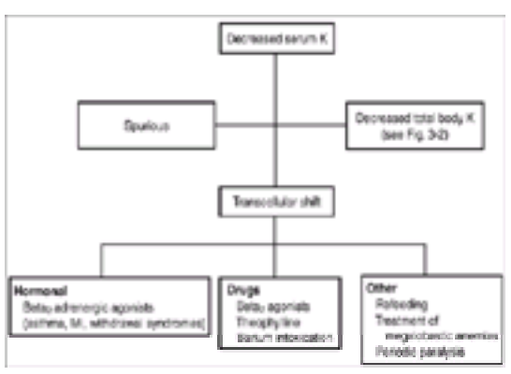

Figure 3-1. Diagnostic approach to hypokalemia. (K, potassium; MI, myocardial infarction.)

   1. **Spurious hypokalemia** occurs in the setting of extreme leukocytosis (*in vitro* white blood cell uptake potassium in the test tube) and, therefore, is not associated with changes in either internal or external potassium balance.
   2. **Cell shifts of potassium** occur acutely in a number of conditions associated with increases in endogenous hormones, including catecholamines. For example, hypokalemia due to catecholamine-mediated cell shift occurs during shortness of breath caused by asthma; chronic obstructive pulmonary disease exacerbations; heart failure; chest pain syndromes (myocardial infarction or angina); or drug withdrawal syndromes such as after use of alcohol, narcotics, or barbiturates. Additionally, the administration of some drugs causes hypokalemia: for example, insulin (correction of diabetic ketoacidosis, postresuscitation for hyperkalemia) or $beta_2$-adrenoreceptor mimetics ($beta_2$ agonists, theophylline). Other common causes of decreases in serum potassium without decreases in total body potassium include hypokalemic periodic paralysis (familial and hyperthyroid types), refeeding syndromes (probably insulin mediated), and treatment of megaloblastic anemias.
   3. **Decreases in total body potassium** (Fig. 3-2) are caused by decreases in potassium intake or increases in potassium excretion through renal or extrarenal sites. Urinary potassium excretion levels (taken by 24-hour measurements or “spot” potassium concentrations) are initially used as a guide in distinguishing causes of decreases in total body potassium. Urinary potassium concentrations less than 20 mEq per L or less than 20 mEq per day suggest extrarenal causes of potassium depletion. Serum acid-base status is often helpful in distinguishing various causes of hypokalemia: for example, metabolic acidosis indicates gastrointestinal (GI) losses (diarrhea of any cause, e.g., infectious, toxic, laxative abuse). Conversely, a normal serum pH is less helpful, because hypokalemia can be secondary to decreases in intake as well as GI losses. Metabolic alkalosis with urinary potassium less than 20 mEq per L is rare but can

be associated with laxative abuse, villous adenoma, or congenital chloride-losing diarrhea. Hypokalemia in the setting of urinary potassium excretion greater than 20 mEq per L or 20 mEq per day indicates renal causes of potassium wasting. The serum pH is again used to further evaluate etiologies. Metabolic acidosis suggests renal tubular acidosis (type 1 or type 2), diabetic ketoacidosis (osmolal diuresis), ureterosigmoidostomy, or carbonic anhydrase inhibitor use.

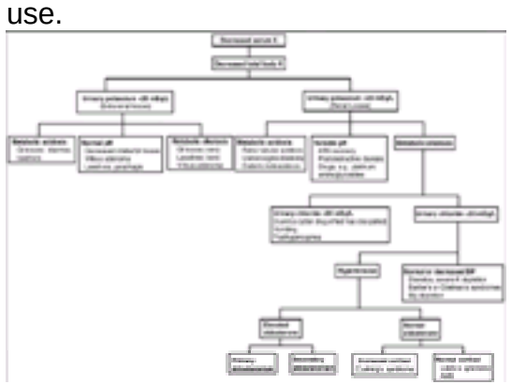

Figure 3-2. Diagnostic approach to hypokalemia. (AME, aseptic meningo-encephalitis; ATN, acute tubular necroses; BP, blood pressure; GI, gastrointestinal; K, potassium.)

More commonly, renal potassium losses are associated with **metabolic alkalosis.** The urinary chloride concentration is used to differentiate between various causes. A low urinary chloride concentration (less than 20 mEq per L or 20 mEq per day) suggests that renal potassium losses are related to vomiting or other upper GI causes; diuretic use, after diuretic effects are dissipated; or a post-hypercapnic syndrome. Hypokalemia in the setting of a high urinary chloride concentration is further distinguished on the basis of the presence or absence of hypertension. Hypokalemia with metabolic alkalosis and a high urinary chloride in normotensive individuals occurs in the setting of diuretic use (loop or distal convoluted tubule-acting diuretics); in a number of unusual syndromes, including Bartter's and Gitelman's; and with severe decreases in total body magnesium or potassium. Hypokalemia with renal potassium wasting, renal chloride wasting, and hypertension is further distinguished on the basis of serum or urinary aldosterone concentrations: a high aldosterone level suggests primary (from adenoma, hyperplasia, glucocorticoid remedial) or secondary (from renovascular or accelerated hypertension, diuretic use) aldosteronism. On the other hand, in the presence of normal aldosterone levels, increases in cortisol suggest Cushing's syndrome or exogenous steroid use. Normal cortisol levels indicate Liddle's syndrome (caused by increases in activity of the cortical collecting tubule sodium channel) or apparent mineralocorticoid excess syndrome [decreases in 11b hydroxy-steroid dehydrogenase activity in kidney tissue (congenital, licorice) causing the mineralocorticoid receptor to respond to glucocorticoid]. Finally, increases in urinary potassium excretion without a significant acid-base disorder is seen during the recovery phase of acute tubular necroses, postobstructive diuresis, and magnesium depletion, in association with drugs such as aminoglycosides and cis-platinum, or in myelomonocytic leukemia (secondary to lysozymuria).

4. Although **cell-shift hypokalemia** and **decreases in total body potassium** do occur as isolated problems, they frequently occur **simultaneously**. Decreases in total body potassium potentiate the effects of drugs and hormones to shift potassium into cells. For example, small changes in potassium during insulin therapy may not cause hypokalemia if total body potassium is normal, but in the setting of total body potassium depletion (e.g., during the treatment of diabetic ketoacidosis or diuretic use), cellular shifts of potassium during insulin therapy can result in profound hypokalemia.

B. The **manifestations** of hypokalemia are mainly cardiac and neuromuscular (Table 3-1). The most dramatic neuromuscular symptoms are paresis, paralysis, and respiratory failure. Potassium depletion causes supraventricular and ventricular arrhythmias, especially in patients on digitalis therapy. Although severe hypokalemia is more likely to cause complications, even minimal decreases in serum or total body potassium can be arrhythmogenic in patients with underlying heart disease or who are on digitalis therapy.

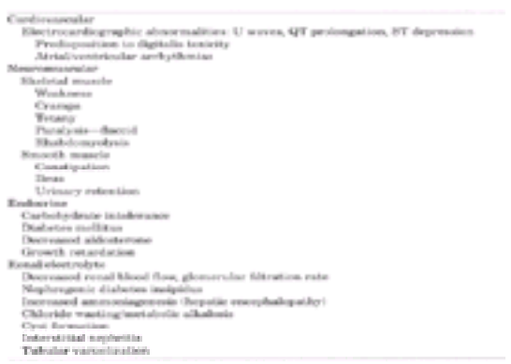

Table 3-1. Clinical manifestations of hypokalemia

C. The **treatment** of hypokalemia depends on the underlying cause, the degree of potassium depletion, and the risk of potassium depletion to the patient. In general, hypokalemia secondary to cell shift is managed by treating underlying conditions. For example, hypokalemia in the setting of increases in catecholamines, as in chest pain syndromes, is managed with appropriate treatments for the pain. However, when cell-shift hypokalemia is associated with life-threatening conditions such as paresis, paralysis, or hypokalemia in the setting of myocardial infarction, the administration of potassium is indicated. With potassium depletion, replacement therapy depends on the estimated degree of decreases in total body potassium. For example, in the presence of decreases in total body potassium when the serum potassium falls from 3.5 to 3.0 mEq per L, the potassium deficit is 150 to 200 mEq. Decreases in serum potassium from 3 to 2 mEq per L are associated with 200- to 400-mEq additional decreases in total body potassium. Potassium can be administered intravenously, but in limited quantities (10 mEq per hour into a peripheral vein; 15 to 20 mEq per hour into a central vein). Larger potassium requirements can only be accomplished by oral therapy or with dialysis.

III. Hyperkalemia

A. The **approach** to hyperkalemia (Fig. 3-3) is to first determine whether increases in serum potassium are spurious or caused by shifts of potassium from cellular to extracellular spaces, or whether increases in total body potassium are present.

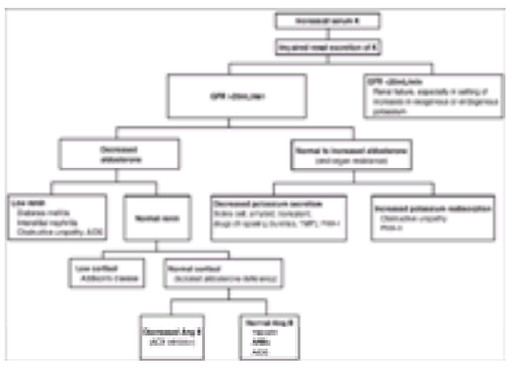

Figure 3-3. Diagnostic approach to hyperkalemia. (ACE, angiotensin-converting enzyme; AIDS, acquired immunodeficiency syndrome; ARBs, adrenergic receptor binders; GFR, glomerular filtration rate; K, potassium; PHA, pseudohypoaldosteronism; TMP, trimethoprim-sulfa.)

1. **Spurious** hyperkalemia is caused by red blood cell hemolysis *in vitro* in test tubes, ischemic blood draws, or extreme thrombocytosis (greater than 1 million mL) or leukocytosis (greater than 50,000 mL). Spurious hyperkalemia is distinguished from true hyperkalemia by the absence of electrocardiographic (ECG)

abnormalities in the former. Hyperkalemia caused by **cell shifts** of potassium occurs acutely and results from decreased potassium transfer into cells (with decreases in insulin or beta-adrenergic blocker therapy), increased potassium movement from cells to the extracellular space (with metabolic acidosis), hypertonicity (with hyperglycemia or administration of mannitol), exercise, muscle breakdown (with rhabdomyolysis), or drug intoxications from digitalis or succinylcholine.

2. **Sustained hyperkalemia** is caused by decreases in renal potassium excretion, especially in the setting of reduced GFR (less than 20 mL per minute). In the setting of decreases in GFR, increases in exogenous potassium (e.g., due to diet, salt substitutes, or drugs, including potassium chloride and potassium citrate), increases in endogenous potassium production (e.g., due to GI bleed, resolving hematoma, rhabdomyolysis, catabolic states, tumor lysis), and drugs that alter potassium excretion (e.g., potassium-sparing diuretics, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, nonsteroidal antiinflammatory drugs) frequently precipitate hyperkalemia.
3. Hyperkalemia also occurs in the **setting of a relatively well preserved GFR**. The causes of hyperkalemia in this setting are distinguished on the basis of plasma or urinary aldosterone levels. Decreases in aldosterone occur in the setting of normal, increased, or decreased plasma renin activity. The latter (hyporeninemic hypoaldosteronism) is associated with a number of renal diseases, including diabetes, interstitial nephritis (e.g., sickle cell anemia, analgesic use, heavy metal toxicity), obstructive uropathy, systemic lupus erythematosus, amyloid, and acquired immunodeficiency syndrome nephropathy, and with transplantation and drugs, including cyclosporine and nonsteroidal antiinflammatory agents. Hyperreninemic hypoaldosteronism occurs in the setting of decreases in cortisol (in Addison's disease) or with normal cortisol (drugs such as angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, heparin). Finally, increases in serum potassium can be associated with normal to high levels of aldosterone and end-organ resistance to aldosterone. Aldosterone resistance is caused by decreases in potassium secretion (drugs such as potassium-sparing diuretics, trimethoprim, and pentamidine), interstitial renal diseases (systemic lupus erythematosus, sickle cell anemia), obstructive uropathy, or transplantation. It also occurs as an unusual hereditary disease called *pseudohypoaldosteronism type 1*. Hyperkalemia in association with normal potassium secretion and increased potassium reabsorption occurs in pseudohypoaldosteronism type 2 and obstructive uropathy.
4. The **urinary potassium excretion rate** or **transtubular potassium gradient (TTKG)** (urine potassium divided by serum potassium divided by the ratio of urine osmolality to plasma osmolality) is used to distinguish renal from extrarenal causes of hyperkalemia (Table 3-2). Extrarenal causes of hyperkalemia (e.g., diet) are associated with increases in potassium excretion (24-hour urinary potassium excretion greater than 80 mEq per day and TTKG greater than 10). In contrast, renal causes of hyperkalemia (for example, Addison's disease) are associated with decreases in urinary potassium excretion (less than 20 mEq per day) and TTKG (less than 3). Administration of mineralocorticoid (0.05 mg fludrocortisone) results in increases in urinary potassium excretion (greater than 40 mEq per day) and TTKG (greater than 7) in patients with aldosterone deficiency (Addison's disease) but no increases in urinary potassium excretion or in TTKG in patients with aldosterone resistance (e.g., sickle cell anemia).

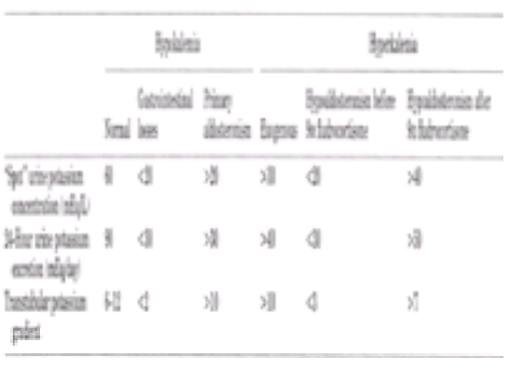

Table 3-2. Laboratory findings in potassium disorders

B. The **clinical manifestations** of hyperkalemia are predominantly cardiac and neuromuscular. It is important to note that patients with hyperkalemia often present with vague GI complaints and nonspecific feelings of not feeling well. ECG abnormalities include peak T waves, widened QRS interval, and asystole. Neuromuscular abnormalities include weakness, constipation, and paralysis.
C. The **treatment** of hyperkalemia (Fig. 3-4) depends on the presence or absence of ECG and neuromuscular abnormalities. In the absence of symptoms, paralysis, or ECG abnormalities, hyperkalemia is treated conservatively—for example, by decreasing dietary potassium or withdrawing offending drugs. In the presence of ECG abnormalities or paralysis, treatment consists of calcium gluconate, 10 to 30 mL as a 10% solution (onset 1 or 2 minutes); sodium bicarbonate, 50 to 150 mEq (onset 15 to 30 minutes); glucose, 25 g intravenously, and insulin, 5 to 10 units intravenously (onset 5 to 10 minutes); or albuterol nebulizer, 20 mg in 4 mL normal saline (onset 15 to 30 minutes). Additional therapy includes reductions in total body potassium by potassium exchange resin, 30 to 60 g orally (onset 2 hours) or by enema (onset 30 to 60 minutes), and hemodialysis (once started, 25 to 30 mEq per hour).

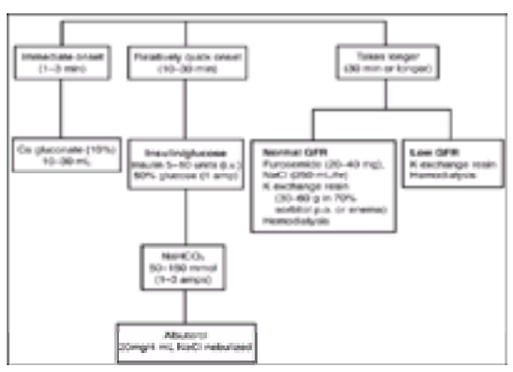

Figure 3-4. Treatment of hyperkalemia. (GFR, glomerular filtration rate; K, potassium.)

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Chapter 4 The Patient with an Acid-Base Disorder

William D. Kaehny

Acid-base disorders
When to suspect acid-base disorders
Identifying the major acid-base disorders
Judging whether an acid-base disorder is simple or mixed
Identify the underlying cause of an acid-base disorder
Treating acid-base disorders

I. Acid-base disorders occur commonly in the very ill. They are important markers of underlying diseases. Occasionally, acid-base disorders disrupthomeostasis sufficiently to move the arterial pH out of a “safe” range (7.20 to 7.55). Depending on the overall status of the patient and the response of the cardiovascular system, the pH may require direct attention. After the physician is alerted to the possibility of an acid-base disorder by clinical and laboratory clues, a logical progression of analysis will lead to optimal management of the patient.

A. **Step 1.** Identify the **major** acid-base **disorder** from the pH, P_{CO_2}, and HCO_3^- in an arterial blood or arterialized venous blood sample.
B. **Step 2.** Determine whether the disorder is **simple** or **mixed** based on the compensatory response of the P_{CO_2} or HCO_3^-.
C. **Step 3.** Calculate the serum **anion gap** and the **potential HCO_3^-** to screen for a **mixed** metabolic disorder.
D. **Step 4.** Use a thoughtful differential diagnosis and simple laboratory tests to establish the **cause** of the acid-base disorder.
E. **Step 5.** Direct **treatment** of the underlying disorder, unless the pH is in a dangerous range or the disorder is chronic and affects structure (such as bone in metabolic acidosis) or function (such as renal potassium wasting in metabolic alkalosis).

II. When to suspect acid-base disorders

A. **Clinical.** Most often the underlying cause of the acid-base disorder is responsible for the patient's symptoms and signs. Certain findings and clinical settings should alert the physician to the likelihood of an acid-base disorder (Table 4-1). Marked changes in pH and P_{CO_2} may cause direct clinical manifestations on occasion (Table 4-2). Although central nervous system dysfunction occurs frequently with acid-base disorders, changes in pH do not seem to be responsible. Rather, altered plasma osmolality and blood P_{CO_2} appear to be causative.

Clues to possible acid-base disorder	Types of acid-base disorders often seen
Central nervous system	
Coma	Respiratory acidosis or alkalosis
Seizures	Metabolic acidosis
Cardiovascular system	
Congestive heart failure	Respiratory alkalosis
Shock	Metabolic acidosis, respiratory alkalosis
Respiratory system	
Tachypnea, hyperpnea	Respiratory alkalosis
Bradypnea, hypopnea	Respiratory acidosis
Gastrointestinal system	
Vomiting	Metabolic alkalosis
Diarrhea	Metabolic acidosis
Abdominal pain	Respiratory alkalosis, metabolic acidosis
Renal excretory system	
Oliguria, anuria	Metabolic acidosis
Polyuria	Metabolic acidosis (ketoacidosis) or alkalosis (diuretics)
Endocrine system	
Myxedema	Respiratory acidosis
Hypertension	Metabolic alkalosis

Table 4-1. Clinical manifestations of diseases that may cause acid-base disorders

Acidemia (pH <7.20)	Hypercapnia (PCO_2 >50)
Depressed sensorium	Headaches
Depressed myocardial “squeeze”	Papilledema
	Asterixis
Alkalemia (pH >7.55)	Hypocapnia (PCO_2 <30)
Seizures	Coronary spasm
Ventricular arrhythmias	Electrocardiogram ST elevation

Table 4-2. Clinical manifestations due to altered pH and P_{CO_2}

B. **Laboratory.** Routine determination of serum electrolytes is not good practice. However, selected thoughtful measurement of electrolytes in patients with evidence of abnormal losses or gains of body fluids is indicated. An abnormal serum total carbon dioxide content (tCO_2) is definite evidence of an acid-base disorder; an abnormal serum anion gap is very suggestive; an abnormal serum potassium is suspicious.
   1. **Serum tCO_2.** The HCO_3^- in blood can be estimated reasonably by measuring the tCO_2 in venous serum. The sample need not be kept anaerobic or cold, but it should not be bubbled or shaken in air or left at room temperature for more than 30 minutes. Acid is added to the serum to release carbon dioxide from bicarbonate, dissolved carbon dioxide, carbonic acid, and carbonate. The carbon dioxide causes a change in pH and P_{CO_2} in either the test or a reference solution. This change is translated into serum tCO_2 in mmol per L. This is 1 to 3 mmol per L greater than the HCO_3^- derived from arterial blood gas measurements, because it includes HCO_3^- *plus* other compounds and is a *venous* serum constituent. Normal sea-level values of tCO_2 range around 26 mmol per L. A change by more than 3 units from normal indicates a high likelihood of an acid-base disorder. However, a normal value does not exclude an acid-base disorder that has mixed metabolic and respiratory components. Throughout the remainder of this chapter, *serum tCO_2* represents the base content of venous serum.
   2. The **serum anion gap** (AG) is calculated from the serum electrolytes as sodium (Na^+) minus chloride (Cl^-) and tCO_2:
      $AG = Na^+ – (Cl^- + tCO_2)$

      The units are mEq per L, because this calculation estimates the charge difference between the so-called unmeasured anions (total anions $–Cl^- – HCO_3^-$) and unmeasured cations (total cations $–Na^+$) The mean normal value varies from laboratory to laboratory, but averages 9 ± 3 mEq per L. Albumin is the major unmeasured anion. A fall in serum albumin of 1 g per dL from normal of 4.5 g per dL decreases the anion gap by 2.5 mEq per L.

      a. **Metabolic acidosis** due to an organic acid such as lactic or ketoacid is indicated by an anion gap equal to or greater than 27 mEq per L or one-half the serum tCO_2 plus 12, irrespective of the blood pH. Values of the anion gap from 17 to 26 mEq per L are suggestive, albeit not diagnostic, of organic acidosis. The anion of the organic acid replaces an HCO_3^- lost in the buffering of the hydrogen ion (H^+) part of the acid and thus raises the unmeasured anions. Importantly, a normal or slightly elevated anion gap does not rule out the presence of organic metabolic acidosis such as lactic or diabetic acidosis. This happens because a patient with good renal perfusion and urine flow may excrete the organic acid at a rate sufficient to keep the serum anion gap from rising markedly.
      b. **Metabolic alkalosis.** At times, a metabolic acidosis that increases anion gap and lowers HCO_3^- may occur with a metabolic alkalosis that raises the HCO_3^- (e.g., diabetic ketoacidosis and vomiting). In this case, serum tCO_2 (and arterial HCO_3^-) may be low or normal despite the elevating action of

metabolic alkalosis. The clue to the presence of such hidden metabolic alkalosis is derived in a holmesian fashion by adding the observed serum tCO_2 and the increment in anion gap (observed anion gap minus 9 mEq per L). If this sum is greater than 27 mEq per L (especially if it is less than 32), a hidden metabolic alkalosis is likely. The increment in anion gap is a marker of "lost" or potential bicarbonate, that which was titrated by the hydrogen ion of an organic acid. Metabolic alkalosis alone directly increases the anion gap by a maximum of 5 mEq per L due to effects on albumin concentration and charge.

3. **Serum potassium.** Potassium metabolism is linked to acid-base metabolism at the levels of cell shifts, renal tubular handling, and gastrointestinal transport. Therefore, an abnormal serum potassium concentration usually is a clue to the presence of an acid-base disorder. Table 4-3 contains an outline of these laboratory indicators of acid-base disorders.

Laboratory variable	Disorder
Serum total carbon dioxide content (tCO_2)	
Increased	Metabolic alkalosis or respiratory acidosis
Decreased	Metabolic acidosis or respiratory alkalosis
Serum potassium	
Increased	Hyperkalemic distal renal tubular acidosis
Decreased	Metabolic alkalosis, renal tubular acidosis
Serum anion gap (AG)	
Increased markedly	Organic metabolic acidosis
$AG - 9 + tCO_2 > 29$	Metabolic alkalosis

Table 4-3. Laboratory markers of acid-base disorders

III. Identifying the major acid-base disorders

When the suspicion of an acid-base disorder has been raised, and the management of the patient might be altered by such a disorder, a set of acid-base variables should be obtained: pH, P_{CO_2}, and HCO_3^-.

A. **Chemistry and physiology.** Cellular, tissue, and organ systems apparently function best at an extracellular fluid pH of 7.40. Intracellular pH is heterogeneous depending on organelles and changes with cell activity, but it averages about 7.00. Extracellular pH is a function of the state of body buffers, those molecules that respond to a fall in pH by binding (or buffering) H^+ and respond to an increase in pH by releasing H^+. These buffers prevent extreme shifts in pH in the face of gain or loss of acids or bases.

1. **Blood pH** is the mathematical expression of the intensity of acidity.It can be translated roughly into H^+ concentration in mol per L:

$$pH = -\log [H^+] \text{ or } [H^+] = 10^{-pH}$$

H^+ concentration usually is expressed in nmol per L. H^+ concentration is 100 nmol per L at pH 7.00 and 40 nmol per L at pH 7.40. Within the pH range of 7.26 to 7.45, H^+ concentration is estimated accurately as 80 minus the decimal of pH (e.g., at pH 7.32, H^+ concentration equals 80 minus 32, or 48 nmol per L). The pH is measured at body temperature with a glass flow-through electrode.

2. The **partial pressure of carbon dioxide in blood, P_{CO_2}** represents the respiratory component in the acid-base equation. The respiratory system determines the level at which the P_{CO_2} is set. Using mathematical corrections in the equation, P_{CO_2} substitutes for the buffer acid H_2CO_3 (carbonic acid). P_{CO_2} is determined in whole blood by machine calculation based on the change in pH caused by diffusion of carbondioxide from the unknown sample into a known buffer solution.

3. **HCO_3^-** is the metabolic component of the acid-base equation, serving as the base of the H^+-binding partner in the buffer pair. HCO_3^- concentration is controlled by the buffering state, metabolic processes, and the kidneys. HCO_3^- concentration is calculated from the pH and P_{CO_2} using the Henderson-Hasselbalch equation. The fact that it is calculated makes it no less reliable a value than the serum tCO_2.

4. The **acid-base equation** allows the state of extracellular fluid acid-base balance, the presence or absence of an acid-base disorder, the nature of the disorder, and the presence of a simple or mixed disorder to be determined:

$$pH = \text{constant} \times \frac{[HCO_3^-]}{Pco_2}$$

Thus, the pH depends on the ratio or mathematical relationship between HCO_3^- and P_{CO_2}. An acid-base disorder is generated by a change from normal in one of these two variables. This causes a change in pH that results in chemical shifts in buffers that keep pH from changing too drastically. Then, a physiologic response (of the respiratory system to a metabolic disorder or of metabolic-renal activities to a respiratory disorder) occurs. In a new steady state, the new pH is determined by the changes in HCO_3^- and P_{CO_2}.

B. **Measurement of acid-base variables.** The determination of the acid-base state does not require sampling of arterial blood, although this is traditional. The best reason to sample arterial blood is to determine the state of oxygenation. Arterialized venous blood is perfectly acceptable for acid-base determinations if oxygenation is not in question. Blood is obtained anaerobically into a heparinized syringe from a mid-forearm vein without use of a tourniquet after 15 minutes of external heating of the forearm. The syringe is sealed and placed on ice. Anaerobic, iced samples are required to prevent blood constituents or air from altering the acid-base variables *in vitro*.Excess dilution by heparin in the syringe should be avoided. The values of the acid-base variables are indistinguishable from those of true arterial blood. Therefore, arterial blood values are used for subsequent interpretations. Although experimental studies show that intracellular pH and mixed venous acid-base measurements correlate better with organ function, arterial blood measurements are useful as a readily accessible window to the metabolic state of organs and their function, keeping in mind that cardiopulmonary arrest or severe shock make tissue acidosis worse than is reflected by arterial blood acid-base values.

1. **Calculation of HCO_3^- from pH and P_{CO_2}.** Remember that arterial HCO_3^- is 1 to 3 mmol per L less than the venous serum tCO_2. At times, we may have to calculate the arterial HCO_3^- or verify the integrity of the reported values. This can be accomplished by converting pH to H^+, as in the earlier section on blood pH, and using the simplified Henderson equation:

$$[HCO_3^-] = 24 \times \frac{Pco_2}{[H^+]}$$

C. **Identification of a major acid-base disorder.** The basis of this approach is to determine the direction (up or down) in which the observed values differ from normal sea-level values for pH (7.40), P_{CO_2} (40 mm Hg), and HCO_3^- (24 mmol per L). The first step is to determine if acidemia (pH down) or alkalemia (pH up) is present. The two possibilities for each of these deviations are given in Table 4-4. The second step is to determine the directional change from normal of the HCO_3^-. The third step is to judge whether this could cause the observed change in pH. The last two steps should be repeated for P_{CO_2}. Usually, only one of these latter two variables can account for the change in pH. If both can, then a mixed disorder is present. The major component is the variable with the greatest percentage change from normal.

	Metabolic acidosis	Metabolic alkalosis	Respiratory acidosis	Respiratory alkalosis
Primary change	$\downarrow HCO_3^-$	$\uparrow HCO_3^-$	$\uparrow Pco_2$	$\downarrow Pco_2$
Compensation	$\downarrow Pco_2$	$\uparrow Pco_2$	$\uparrow HCO_3^-$	$\downarrow HCO_3^-$
Effect on pH	$\downarrow$pH	$\uparrow$pH	$\downarrow$pH	$\uparrow$pH

$\downarrow$, decreased; $\uparrow$, increased.

Table 4-4. Simple acid-base disorders

1. **Example of a simple disorder.** Sampling of arterialized venous blood yielded the following:

$$\text{pH (7.55)} = \text{constant} \times \frac{[HCO_3^-]\ (18\ \text{mmol/L})}{Pco_2\ (21\ \text{mm Hg})}$$

   a. **Step 1.** The pH is up. Thus, alkalemia is present, and metabolic or respiratory alkalosis is indicated.
   b. **Step 2.** The bicarbonate is down from the normal 24 mmol per L.
   c. **Step 3.** A low bicarbonate cannot raise pH, and, therefore, this cannot be *metabolic* alkalosis.
   d. **Step 4.** The PCO_2 is down from the normal of 40 mm Hg.
   e. **Step 5.** A low PCO_2 can increase the pH. These numbers indicate that *respiratory* alkalosis is present.
2. **Example of a mixed disorder.** Sampling of arterial blood yielded the following:

$$\text{pH (7.55)} = \text{constant} \times \frac{[HCO_3^-]\ (30\ \text{mmol/L})}{Pco_2\ (35\ \text{mm Hg})}$$

   a. **Step 1.** The pH is up; alkalemia is present.
   b. **Step 2.** HCO_3^- is up.
   c. **Step 3.** Elevated HCO_3^- can raise pH; thus, metabolic alkalosis is present.
   d. **Step 4.** The PCO_2 is down.
   e. **Step 5.** Lowered PCO_2 can raise pH; thus, respiratory alkalosis is also present. The major disorder is metabolic alkalosis, because the change in HCO_3^- from normal is 25% (30 – 24 = 6; 6/24 = 25%) whereas the change in PCO_2 is only 12.5% (40 – 35 = 5; 5/40 = 12.5%).

IV. Judging whether an acid-base disorder is simple or mixed

When an underlying process generates an acid-base disorder by perturbing one member of the HCO_3^--PCO_2 buffer pair (remember that PCO_2 represents H_2CO_3), the other member is adjusted by the physiologic response of the body to change in the same direction in order to reduce the magnitude of the change in pH. The time-honored term for the physiologic response is *compensation*; however, as will be seen, the physiologic responses may be activated by stimuli other than pH and may actually contribute to maintenance of the abnormal pH. Thus, these responses are not always compensatory. Note that these responses do *not* completely restore pH to the preexisting normal level.

A. **Steps in judging whether a disorder is simple.** After the major acid-base disorder is determined, whether the compensation for the primary (first) event is "appropriate" should be judged. Appropriate responses correspond to those observed in controlled or carefully defined settings of single (simple) acid-base disorders.
   1. **Check directions from normal of changes of the buffer pair.** The HCO_3^- and PCO_2 change from normal in the same direction in all simple acid-base disorders. If they change in opposite directions (up-down or down-up), the disorder must be mixed. This step has already been completed in the analysis for the major disorder (see section **III**.)
   2. **Compare the magnitude of the compensation of the buffer pair member with the primary change in the other buffer pair member.** For metabolic disorders, the primary change occurs in the HCO_3^-, with the physiologic response in the PCO_2. For respiratory disorders, the opposite is true. Table 4-5 contains guidelines that can help in judging whether the responses are appropriate. Note that the respiratory disorders have two phases of response: acute, when only buffering responds, and chronic, when the kidneys respond. If an observed response varies by more than 2 to 4 units from the rule, a mixed disorder is highly likely. Two methods of estimating whether compensation is appropriate are given in Table 4-5. One method uses the relationship between changes in HCO_3^- and PCO_2, and the other relates the primary change in HCO_3^- or PCO_2 to the change in pH.

	Change in Pco_2 per change in HCO_3^-	Change in pH per change in HCO_3^-
Metabolic acidosis	1.0–1.5 per 1	0.010 per 1
Metabolic alkalosis	0.25–1.00 per 1	0.015 per 1
	Change in HCO_3^- per change in Pco_2	Change in pH per change in Pco_2
Respiratory acidosis		
Acute	1 per 10	0.08 per 10
Chronic	4 per 10	0.03 per 10
Respiratory alkalosis		
Acute	1 per 10	0.08 per 10
Chronic	4 per 10	0.03 per 10

Table 4-5. Appropriate compensations in the acid-base disorders

   3. **Check the anion gap for evidence of a hidden metabolic disorder.** As noted in the discussion of the anion gap in section **II.B.2**, an anion gap greater than 17 mEq per L suggests organic acidosis; more than 27 mEq per L is almost diagnostic. Also, if the increase in anion gap over the normal 9 mEq per L is added to the observed serum tCO_2, the theoretical starting serum tCO_2 can be estimated. A value greater than 29 mmol per L suggests metabolic alkalosis.

B. **Application of the rules**
   1. The primary event in **metabolic acidosis** is a fall in HCO_3^-; the compensation is a fall in the PCO_2. This is due to the stimulation of central nervous system receptors by the low pH. Hyperventilation increases the excretion of CO_2, and PCO_2 falls. For example, if the HCO_3^- falls from 24 mmol per L by 10 to 14 mmol per L, the PCO_2 should fall by 1.0 to 1.5 times as much, or 10 to 15 mm Hg, to a level of 25 to 30 mm Hg (40 – 10 = 30; 40 – 15 = 25).
   2. The primary event in **metabolic alkalosis** is a rise in HCO_3^-. The respiratory system responds to the subsequent rise in pH with hypoventilation, which reduces carbon dioxide excretion and results in a rise in PCO_2. For example, if HCO_3^- rises by 16 mmol per L from 24 to 40 mmol per L, the PCO_2 should rise by 0.25 to 1.00 multiplied by 16, or 4 to 16 mm Hg, to a level of 44 to 56 mm Hg (40 + 4 = 44; 40 + 16 = 56). This response is tempered by the body's response to the concomitant hypoxemia resulting from hypoventilation.
   3. The primary event in **respiratory acidosis** is a rise in PCO_2. During the acute phase, up to 24 hours, only buffering contributes measurably to the response. The HCO_3^- should increase, but not to as high as 30 mmol per L. In contrast, the kidneys respond to chronic elevations of PCO_2 by generating sufficient HCO_3^- to prevent the pH from falling to less than 7.20, even in the most severe cases of chronic respiratory acidosis.
   4. The primary event in **respiratory alkalosis** is a fall in PCO_2. Initially, buffering occurs as a result of release of H^+ from cells; later (hours) the kidneys dump HCO_3^- into the urine, with resultant fall in blood HCO_3^- as defined in Table 4-5.

C. **Effects of respiratory responses to metabolic disorders.** The kidneys respond to changes in PCO_2 no matter what the pH. A fall in PCO_2 causes renal HCO_3^- loss; a rise in PCO_2 causes HCO_3^- neogenesis. Thus, in chronic metabolic acidosis (lasting days), some of the reduction in bicarbonate actually is due to the compensatory fall in PCO_2 and not directly to the process causing the metabolic acidosis. Similarly, the increase in PCO_2 in chronic metabolic alkalosis contributes to the hyperbicarbonatemia.

D. **Examples of mixed acid-base disorders.** Four combinations of the "double" mixed acid-base disorders are possible. Two are important because they cause drastic changes in pH: metabolic and respiratory acidosis and metabolic and respiratory alkalosis. The other two disorders—metabolic acidosis with respiratory alkalosis and metabolic alkalosis with respiratory acidosis—tend to be associated with pH values close to normal and are not dangerous per se; however, they are important markers of underlying disease. Two other mixed disorders, so-called triple disorders, also have been described. The anion gap points to both metabolic acidosis and alkalosis developing simultaneously or sequentially in these. Imposition of a respiratory disorder yields the infamous triple acid-base disorder.
   1. **Metabolic acidosis and respiratory acidosis.** A patient with emphysema with carbon dioxide retention (chronic respiratory acidosis) (develops diarrhea (metabolic acidosis).

Note how the reduction in HCO_3^- to normal results in severe acidemia (Table 4-6).

	Health	Emphysema	Emphysema and diarrhea
pH	7.40	7.52	7.10
P_{CO_2}	40	80	80
HCO_3^-	24	40	24

Table 4-6. Example of a mixed acid-base disorder

2. **Metabolic alkalosis and respiratory acidosis.** The same emphysematous patient is given a diuretic for cor pulmonale. The bicarbonate level rises from 40 to 48 mmol per L, which, with the P_{CO_2} at 80 mm Hg, sets the pH at 7.40. Although this is a normal pH, some believe it is better for carbon dioxide–retaining patients to be mildly acidemic to keep ventilation stimulated.
3. **Triple acid-base disorder.** The more common mixture involves metabolic acidosis developing in a patient with metabolic alkalosis and superimposed respiratory alkalosis. For example, Table 4-7 summarizes the condition of a patient with metabolic alkalosis from nasogastric suction who becomes septic, which generates both lactic acidosis and respiratory alkalosis due to endotoxin.

	Health	Nasogastric suction	Septic shock	Endotoxemia
pH	7.40	7.49	7.14	7.44
P_{CO_2}	40	44	24	12
HCO_3^-	24	32	8	8
Anion gap	9	11	33	35
Venous total carbon dioxide	26	35	9	9
Disorder		Metabolic alkalosis	Metabolic alkalosis Metabolic acidosis	Metabolic alkalosis Metabolic acidosis Respiratory alkalosis

Table 4-7. Example of a triple mixed acid-base disorder

Note that both the metabolic and respiratory alkaloses should cause only small increases in the anion gap. The lactic acidosis of septic shock results in a fall of 24 mmol per L in the HCO_3^-, with a reciprocal increase in anion gap. The anion gap above 27 is diagnostic of organic acidosis. The increase in the anion gap of 26 (35 – 9), added to the serum tCO_2 of 9, yields 35 mmol per L, an estimate of the value before acidosis, which indicated metabolic alkalosis. The evidence for the presence of respiratory alkalosis is the high pH and low P CO_2 due to the hyperventilation caused by endotoxemia.

V. Identify the underlying cause of an acid-base disorder. Usually, the cause of an acid-base disorder is obvious from the history, examination, and clinical course. However, on occasion, careful review of a thoughtful differential diagnosis is necessary to identify a remote causative disorder.

A. **Differential diagnosis of metabolic acidosis.** The anion gap is used to divide the causes of metabolic acidosis into those with influx of organic acid into plasma (increased anion gap) and those with external losses of bicarbonate (normal anion gap; hyperchloremic). Some disorders belong to both groups at different stages (diabetic ketoacidosis) or are generated by mechanisms other than those described above (renal failure). A list of these other causes is given in Table 4-8.

High anion gap type
Ketoacidosis
Diabetic
Alcoholic
Starvation
Lactic acidosis
Type A
Type B
Intoxications
Ethylene glycol
Methanol
Salicylate
Advanced renal failure
Normal anion gap type
Gastrointestinal HCO_3^- loss
Diarrhea
External fistulae
Renal HCO_3^- loss
Acetazolamide
Proximal renal tubular acidosis (RTA)
Distal RTA
Hyperkalemic RTA
Miscellaneous
NH_4Cl ingestion
Sulfur ingestion
Posturesmall dilution

Table 4-8. Differential diagnosis of metabolic acidosis

1. **Metabolic acidosis with increased anion gap.** Severe metabolic acidosis is caused by only three broad groups of disorders: ketoacidosis,lactic acidosis, and intoxications. In addition, renal failure may cause mild to moderate acidosis.
   a. **Ketoacidosis** arises when glucose is not available to cells because of insulin lack, cell dysfunction, or glucose depletion, and fatty acids are oxidized to yield energy, acetone (not an acid), and the two ketoacids (acetoacetic and beta-hydroxybutyric). The H^+ produced are consumed (buffered) by HCO_3^- producing carbonic acid, which dehydrates into water and carbon dioxide. The ketoanions accumulate in the serum in place of the HCO_3^-, increasing the anion gap. The diagnostic test for ketoacidosis consists of testing the serum with a nitroprusside reagent, which reacts with the acetoacetate only. In diabetic ketoacidosis, the beta-hydroxybutyrate–acetoacetate ratio averages 5 to 2, whereas in alcoholic ketoacidosis, it may reach as high as 20 to 1. In these latter cases, only urine, a concentrate of serum, may have a concentration of acetoacetate high enough to give a positive purple reaction with the reagent. Diabetic ketoacidosis occurs because of insulin deficiency. Hyperglycemia may be corrected by volume reexpansion, but insulin is needed to stop ketogenesis. Volume expansion enhances renal excretion of ketoanions, thus correcting the increased anion gap. However, the kidneys take time to generate new $HCO_3^-$to replace that lost earlier in buffering H^+. Thus, early in diabetic ketoacidosis, the anion gap usually is increased; during correction, the anion gap may return to normal despite a low HCO_3^-. Chloride replaces the ketoanions, and this stage is therefore called *hyperchloremic* or *normal anion gap metabolic acidosis*. Alcoholic ketoacidosis occurs because of altered cell metabolism. Usually the patient relates a story of cessation of recently increased alcohol intake and vomiting. Urine ketones are usually, albeit not always, positive. Blood glucose ranges between 50 and 250 mg per dL. Starvation ketoacidosis occurs after the use of fatty acids for energy maintenance. The degree of acidosis is mild, with arterial HCO_3^- not less than 18 mmol per L.
   b. **Lactic acidosis** arises when oxygen delivery to cells is inadequate (type A) or cell processes cannot use oxygen (type B). In this situation, glucose is metabolized via anaerobic glycolysis to pyruvate and then to the dead-end metabolite lactate. The H^+ produced from adenosine triphosphate (one per lactate) are buffered by HCO_3^-, which is replaced in the blood by lactate. Thus, the anion gap is increased. Common causes of type A lactic acidosis include hemorrhagic shock, mesenteric vascular occlusion, and severe pulmonary edema. Causes of type B lactic acidosis include hepatic fail ure, sepsis, and acute pancreatitis. The diagnosis is usually established by exclusion of ketoacidosis, intoxications, and advanced renal failure as causes for a high anion gap metabolic acidosis. Lactate can be measured by an enzyme-specific assay, but measurement is usually unnecessary.

c. Three modern **intoxications** cause high anion gap metabolic acidosis: ethylene glycol ingestion, methanol ingestion, and salicylate intoxication. Methanol and ethylene glycol are low-molecular-weight alcohols that readily enter cells. Metabolism generates H^+ that causes acidosis and formate (with methanol) or glycolate (with ethylene glycol) that causes a high anion gap. A clue to the presence of early stages with elevated alcohol levels is an increased osmolal gap. This gap is the difference between the measured serum osmolality and the calculated osmolality (calc Sosm).

$$\text{Calc Sosm} = 2 \times [Na^+] + [\text{glucose}]/18 + [\text{urea nitrogen}]/2.8 + [\text{ethanol}]/4.6$$

If this difference is greater than 15 to 20 mOsm per kg, the presence of a toxic alcohol is likely. Needlelike or envelope-shaped calcium oxalate crystals in the urine suggest ethylene glycolingestion. The combination of high anion gap metabolic acidosis and a high osmolal gap is an indication for specific analysis for methanol and ethylene glycol. The decision to measure levels of these alcohols, of course, must be tempered by the clinical setting. Salicylate intoxication may cause metabolic acidosis, respiratory alkalosis, or a mixed disorder. It should be suspected in the pediatric and geriatric populations.

d. **Renal failure.** Failure to excrete the daily acid load of 1 mmol per kilogram of body weight that is generated by metabolism results in metabolic acidosis. Bone buffers take up a large number of hydrogen ions during chronic renal failure, and, thus, the degree of acidosis is moderated until the end stages of disease. Arterial bicarbonate usually remains above 15 mmol per L. In acute failure, venous tCO_2 or arterial HCO_3^- falls by about 0.5 mmol per L per day unless hypercatabolism increases daily acid production. The anion gap increases more slowly than HCO_3^- decreases in acute and chronic renal failure. In chronic renal failure, the serum anion gap rises by about 0.5 mEq per L for each 1.0 mg per dL rise in serum creatinine. Retention of sulfate, phosphate, and organic anions causes the increase in anion gap.

2. **Metabolic acidosis with normal anion gap (hyperchloremic)** can be caused by three groups of disorders: gastrointestinal HCO_3^- loss, renal HCO_3^- loss, and inorganic acid intake.

a. **Gastrointestinal bicarbonate loss.** The gastrointestinal tract distal to the stomach is a chloride-absorbing, bicarbonate-secreting organ. Thus, diarrhea and external drainage of pancreatic, biliary, or small-bowel juices cause external losses of bicarbonate-rich fluid. Relatively chloride-rich fluid remains behind. This generates hyperchloremic metabolic acidosis (normal anion gap). An interesting variety of this disorder occurs when normal urine rich in sodium chloride from dietary sources is drained into the gut via ureterosigmoidostomy or ileal loop conduit (both bladder replacement constructions). If contact time with mucosa is excessive, the gut reabsorbs the chloride in exchange for bicarbonate, resulting in hyperchloremic metabolic acidosis.

b. **Renal bicarbonate loss.** The proximal renal tubule reabsorbs the bulk (85%) of filtered HCO_3^-. The carbonic anhydrase inhibitor acetazolamide blocks much of this reabsorption, resulting in urinary bicarbonate losses until arterial HCO_3^- falls to 16 to 18 mmol per L. The filtered load of HCO_3^- at this concentration can be completely reabsorbed by the distal nephron. Thus, the urine becomes bicarbonate-free, with an acidic pH, in this new steady state. Proximal renal tubular acidosis (RTA), a defect in proximal tubular HCO_3^- reabsorption, has identical features. Proximal RTA is unusual but may occur with Wilson's disease, multiple myeloma, transplant rejection, and other disease states. Distal RTA differs in that it is a defect of the collecting duct in which the daily metabolic acid load is not excreted totally and a small HCO_3^- leak occurs every day. This leads to a mild-to-moderate normal anion gap, hyperchloremic metabolic acidosis, and hypercalciuria with calcium stones or nephrocalcinosis. Two varieties occur: hypokalemic distal RTA and hyperkalemic distal RTA. Hypokalemic distal RTA occurs when collecting duct potassium secretion is intact and in fact enhanced by the small amount of bicarbonaturia. Hyperkalemic distal RTA occurs when collecting duct potassium secretion is impaired by either a tubular defect or hypoaldosteronism. Hypokalemic distal RTA occurs with amphotericin B toxicity, cirrhosis of the liver, medullary sponge kidney, and many other diseases. The postobstructed kidney, lupus erythematosus, and sickle cell disease can cause the tubular defect type of hyperkalemic distal RTA. Diabetes mellitus, mild chronic renal failure, and old age are associated with the hyporeninemic hypoaldosteronism type of hyperkalemic distal RTA. Diagnosis is made by eliminating nonrenal causes for a normal anion gap metabolic acidosis (e.g., diarrhea). Proximal RTA is characterized by urinary wasting of more than 5% to 15% of the filtered load of HCO_3^- when serum levels are maintained slightly below normal. Hypokalemic distal RTA is characterized by the inability to decrease urine pH to less than 5.4 with an oral acid load of ammonium chloride. Hyperkalemic normal ion gap metabolic acidosis almost always is due to distal RTA. The tubular defect type is marked by inability to acidify maximally (urine pH usually above 6.0), in contrast to the hypoaldosteronism type, in which the intensity of acidification is intact (urine pH can fall lower than 5.5). In both types, renal ammonium excretion is reduced, and the urine anion gap often is positive (see section **V.A.2.d**).

c. **Inorganic acid intake.** Ingestion of ammonium chloride to reduce appetite or acidify urine, and of sulfur, such as flowers of sulfur cathartic, produces hyperchloremic metabolic acidosi.

d. On occasion, the **urinary anion gap** (UAG) may help to distinguish gastrointestinal from renal loss of HCO_3^- as the cause of hyperchloremic metabolic acidosis: $UAG = (Na^+ + K^+) - Cl^-$. The UAG is an estimate of urinary ammonium that is elevated in gastrointestinal HCO_3^- loss but low in distal RTA. UAG is a negative value if urine ammonium is high (as in diarrhea; average, –20 mEq per L), whereas it is positive if urine ammonium is low (as in distal RTA; average, +23 mEq per L).

B. **Differential diagnosis of metabolic alkalosis.** Volume-depleted metabolic alkalosis is characterized by a low urine Cl^-, indicating the avidity of the kidney for solute, largely sodium chloride. During unsteady states of metabolic alkalosis, bicarbonaturia may occur and necessitate cation, dnamely Na^+ and K^+, excretion. Thus, urine Cl^- is a better marker than urine Na^+ of the stimulus of volume depletion on renal salt avidity. During the established steady state of maintenance, bicarbonaturia is minimal, urine pH is acid, and urine Na^+ is low. Volume-depleted metabolic alkalosis is due to external losses of hydrogen ion or chloride. Volume-replete metabolic alkalosis is characterized by spot urine Cl^- usually well over 20 mmol per L. The kidney is not avid for salt because of volume expansion (mild) and thus excretes the daily Na^+ and Cl^- load without difficulty. This group of disorders is due to hypermineralocorticoidism or profound potassium depletion.

1. **Metabolic alkaloses of the volume-depleted variety** have in common the external loss of fluids rich in H^+ or Cl^-. The stomach, kidney, D(or skin may be the culprit (Table 4-9).

Volume-depleted type
Gastric acid loss
Vomiting
Gastric suction
Renal chloride loss
Diuretics
Hypercapnia correction
Volume-replete type
Mineralocorticoid excess
Hyperaldosteronism
Bartter's syndrome
Cushing's syndrome
Licorice excess
Profound potassium depletion

Table 4-9. Differential diagnosis of metabolic alkalosis

2. **Metabolic alkaloses of the volume-replete variety** are characterized by enhanced renal hydrogen ion secretion despite normal or increased extracellular fluid volume. The stimulus for this sustained hydrogen ion secretion is aldosterone (or a relative) or major cellular potassium depletion (see Table 4-9).

C. **Differential diagnosis of respiratory acidosis.** Two ventilatory abnormalities allow carbon dioxide retention and increased P_{CO_2}—namely, alveolar hypoventilation and severe ventilation-perfusion mismatching. Hypoxemia occurs in both settings. Table 4-10 lists causes according to level of respiratory system affected.

Abnormal respiratory drive
Central alveolar hypoventilation
Sleep apnea
Brainstem infarcts
Myxedema
Abnormal nerve conduction
Poliomyelitis
Multiple sclerosis
Amyotrophic lateral sclerosis
Phrenic nerve injury
Guillain-Barré syndrome
Thoracic cage problems
Kyphoscoliosis
Ankylosing spondylitis
Muscular dystrophy
Polymyositis
Pleural disease
Fibrothorax
Hydrothorax
Pulmonary disease
Advanced interstitial fibrosis
Chronic obstructive lung disease

Table 4-10. Differential diagnosis of chronic respiratory acidosis

D. **Differential diagnosis of respiratory alkalosis.** Disorders that drive ventilation independent of P_{CO_2} can cause hyperventilation and hypocapnia. Inflammatory and mass lesions of the brain, psychiatric disorders, and certain central-acting drugs and chemicals increase central respiratory drive and produce hypocapnia. Importantly, salicylates, endotoxin, and progesterone are among this group. Disorders that cause hypoxemia are common causes of hyperventilation that causes hypocapnia. Disorders that reduce lung or chest compliance, such as mild pneumonia or pulmonary edema; vascular disorders, such as pulmonary emboli; and mixed disorders, such as hepatic cirrhosis or failure, can cause hypocapnia. Volume depletion appears to be a primary stimulus to hyperventilation and hypocapnia.

VI. Treating acid-base disorders As discussed, acid-base disorders are markers of underlying diseases, and these diseases should be the targets of treatment.

A. **Step 1.** Correct volume and electrolyte deficiencies.
B. **Step 2.** Direct specific treatment at the underlying cause.
C. **Step 3.** Manipulate the bicarbonate or P_{CO_2} only if the pH is adversely affecting organ function or if pH is less than 7.10 or greater than 7.60.
D. **Treatment of metabolic acidosis** with alkali has not been shown to be efficacious in many situations, including cardiopulmonary resuscitation. This may be because the HCO_3^- reaction with H^+ generates CO_2 at the tissue level and lowers cell pH. A mixture of carbonate and bicarbonate that produces less CO_2 and potentially may be useful, although clinical benefit is not supported by evidence at this time. At times, alkali therapy may be beneficial. In the acute setting, sodium bicarbonate, 50 mmol in 50-mL ampules, or 595 mmol per L of 5% solution in 500-mL containers, can be given as a bolus or continuous infusion, respectively. The space into which bicarbonate appears to distribute is a theoretical volume estimated to be 50% of body weight. However, for serious metabolic acidosis with arterial HCO_3^- less than 10 mmol per L, a distribution space of 80% of body weight is more accurate. The predicted change in arterial HCO_3^- is calculated as the amount of bicarbonate administered divided by 80% of body weight. For example, a 60-kg person with HCO_3^- of 4 mmol per L is given 200 mmol of sodium bicarbonate over 12 minutes. The HCO_3^- concentration should rise by (4×50 mmol)/(0.8×60), or about 4 mmol per L. If the initial pH was 7.05 and P_{CO_2} was 15 mm Hg, and the P_{CO_2} does not change, this doubling of HCO_3^- from 4 to 8 mmol per L will raise the pH to 7.35. Of course, in conditions with ongoing metabolic production of organic acids, bicarbonate continues to be consumed, and this calculation is less informative. In chronic metabolic acidosis, oral alkali can be given as sodium bicarbonate tablets, 500 mg or 6 mmol, or as sodium or potassium citrate solution, 1 mmol per mL. Usually 3 mmol per kilogram of body weight is the starting dose. HCO_3^- infusions produce hypernatremia with the potential for harm. Oral HCO_3^- also is accompanied by a sodium (or potassium load that must be watched.
    1. Insulin is the specific **treatment for diabetic ketoacidosis**. HCO_3^- and phosphate administration are usually unnecessary, but potassium repletion is important. Volume and electrolyte repletion plus glucose and thiamine suffice to correct alcoholic ketoacidosis. Starvation requires only calories. Note that metabolism of ketoanions, like all organic anions, produces HCO_3^- this metabolism corrects about half of the HCO_3^- deficit. If alkali is given unwisely, an overshoot metabolic alkalosis may result.
    2. In the **treatment of lactic acidosis**, restoration of tissue perfusion and oxygenation is optimal. On occasion, ongoing severe lactic acidosis requires bolus administration of sodium bicarbonate followed by early bicarbonate hemodialysis to provide alkali, to avoid the depressant effects of acetate dialysis, and to prevent hypernatremia. Other forms of treatment are unproved or experimental.
    3. **Treatment of intoxications.** Ethylene glycol and methanol poisoning require immediate ethanol infusion to retard metabolism of the alcohols, followed as soon as possible by hemodialysis to remove the toxins. Ethanol should be infused to maintain a blood level of 100 mg per dL. The loading dose of ethanol is 0.6 to 1.0 g per kilogram of body weight followed by a maintenance infusion of 10 to 20 g per hour. Other treatment, such as fomepizole, is experimental or not available in the United States. Salicylate intoxication should be treated with urinary alkalinization by infusing a 5% dextrose solution with 150 mmol sodium bicarbonate added per L, at a rate of 375 mL per hour for 4 to 6 hours. Hemodialysis should be used to remove salicylate in patients with prominent renal failure, worsening mental status, recalcitrant acidosis, or general deterioration.
E. **Correction of metabolic alkalosis** very rarely requires administration of acid. If renal failure prohibits renal excretion of bicarbonate, the patient usually requires dialysis for other reasons, and a low-bicarbonate dialysate can be used to correct hyperbicarbonatemia. If heart failure precludes use of sodium chloride, then dilute hydrochloric acid, 150 mmol per L, can be infused at 250 mL per hour into a central venous line or, preferably, in parenteral nutrition solution. Acid infusion is fraught with the potential complications of hemolysis and vascular necrosis and is best avoided. Ammonium chloride can be substituted for hydrochloric acid, but it causes gastric distress even when given intravenously and may cause ammonia intoxication. Often, acetazolamide, 500 mg intravenously, suffices in the sodium chloride–intolerant patient, but vigorous potassium repletion will be needed.
    1. **Volume-depleted metabolic alkalosis is corrected** by provision of ample chloride with sodium or potassium. Prevention, however, is preferable. Proton pump inhibitors minimize gastric acid loss in patients with gastric suction. Use of the potassium-sparing diuretics spironolactone, triamterene, and amiloride reduces diuretic-induced alkalosis.
    2. **Treatment of volume-replete metabolic alkalosis.** If possible, the cause of hypermineralocorticoidism should be removed (e.g., surgical excision of adrenal adenoma). In the interim, the use of spironolactone in doses up to 400 mg daily with large amounts of potassium chloride may suffice. Care should be taken to avoid hyperkalemia. Indomethacin may be effective in Bartter's syndrome.
F. **Respiratory acidosis does not require direct treatment**, because even at chronic P_{CO_2} levels above 100 mm Hg, renal bicarbonate generation keeps pH above 7.20. Adequate oxygenation in both the acute and the chronic setting must be ensured and monitored.
G. **In treatment of respiratory alkalosis** ,again, correction of the causative disorder is the key. Provision of oxygen to seriously hypoxemic patients is essential.
H. **Treatment of mixed acid-base disorders**
    1. **Metabolic acidosis and respiratory acidosis.** If the situation is life-threatening, the most rapid treatment is to give 200 mmol of sodium bicarbonate rapidly and to provide mechanical ventilation. Then the cause of the metabolic acidosis should be treated.
    2. In **metabolic alkalosis and respiratory acidosis**, the pH is often alkalemic. Use of acetazolamide, 250 mg b.i.d. by mouth 3 days a week, plus potassium chloride, usually keeps pH near 7.30, a better level for enhancement of respiratory drive in a patient with chronic hypercapnia. Dosing may need adjustment.
    3. **Metabolic alkalosis and respiratory alkalosis** in combination may produce severe alkalemia with dangerous ventricular arrhythmias. The most expedient treatment consists of intravenous morphine and benzodiazepine with immediate access to airway intubation and mechanical ventilation. Then the cause of the metabolic alkalosis should be treated.

Suggested Reading

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Chapter 5 The Patient with Disorders of Serum Calcium and Phosphate

Robert F. Reilly

Disorders of Serum Calcium
Calcium regulation
Hypercalcemia
Hypocalcemia
Disorders of Serum Phosphorus
Overview
Phosphate regulation
Hyperphosphatemia
Hypophosphatemia

Disorders of Serum Calcium

The majority of calcium in the body is in the form of hydroxyapatite in bone (99%). Although a small fraction of total body calcium is contained in the extracellular fluid (ECF), only the concentration of ionized calcium in the ECF is physiologically active and regulated. Approximately 60% of calcium in the ECF is ultrafiltrable and exists either free in solution as ionized calcium (50%) or complexed to anions such as citrate, phosphate, sulfate, and bicarbonate (10%). The remaining 40% is bound to protein primarily albumin).

Figure 5-1 shows the calcium fluxes between the ECF, intestine, kidney, and bone. Net intestinal absorption of calcium amounts to about 200 mg of the normal dietary intake of 800 to 1,000 mg. In the steady state, this net intestinal absorption is matched by urinary excretion. As a result, 10,600 mg of the approximately 10,800 mg (98%) of calcium that is filtered daily is reabsorbed.

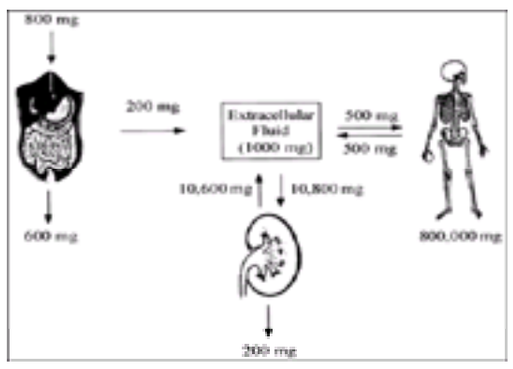

Figure 5-1. Calcium homeostasis.

I. Calcium regulation. Plasma ionized calcium is regulated by a complex and coordinated interplay of parathyroid hormone (PTH) and 1,25(OH) $_2$ vitamin D_3 (calcitriol) in intestine, bone, and kidney. The parathyroid gland senses the ECF ionized calcium concentration via a calcium-sensing receptor. High concentrations of ECF calcium stimulate the receptor and cause a transient rise in intracellular calcium concentration that, in turn, inhibits the release of PTH. Low concentrations of ECF calcium stimulate PTH secretion and production and increase parathyroid gland mass. This system responds quickly (within minutes) to alterations in ionized calcium concentration. An inverse sigmoid relationship exists between ECF calcium concentration and PTH secretion, with a nonsuppressible component present even at high plasma calcium concentration. The parathyroid gland does not contain excess storage granules, and the amount of the hormone stored is enough to support basal secretion for 6 hours and stimulated secretion for 2 hours.

In bone, PTH in the presence of permissive amounts of calcitriol stimulates reabsorption by increasing osteoclast number and activity. In intestine,PTH enhances calcium and phosphorus absorption indirectly by promoting the formation of calcitriol. In kidney, it augments distal tubular reabsorption of calcium, stimulates the formation of calcitriol in the proximal tubule, and decreases proximal tubular reabsorption of phosphate and bicarbonate.

Calcitriol is generated in the proximal tubule via 1-a hydroxylation of 25OH vitamin D $_3$ (calcidiol). The calcitriol biosynthetic pathway is illustrated in Figure 5-2. The main stimulators of this process are PTH and hypophosphatemia. The major function of calcitriol is to enhance the availability of calcium and phosphate for new bone formation and the prevention of symptomatic hypocalcemia and hypophosphatemia. In intestine and kidney, calcitriol increases the production of calcium-binding proteins that aid in the transcellular movement of calcium, which may be the rate-limiting step in transepithelial calcium flux. In bone, calcitriol potentiates the actions of PTH, stimulates osteoclastic reabsorption, and induces the differentiation of monocytes into osteoclasts.

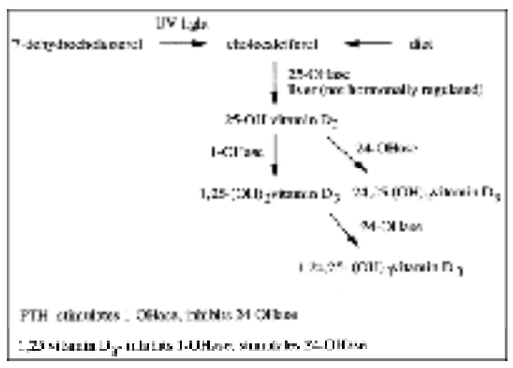

Figure 5-2. Vitamin D metabolism. (PTH, parathyroid hormone; UV, ultraviolet.)

In the parathyroid gland, calcitriol binds to its receptor, leading to a decrease in PTH production. The promoter of the PTH gene contains regions that bind the calcitriol receptor. Binding to these regions results in a dramatic decrease in PTH expression. Calcitriol is the most potent suppressor of PTH gene transcription.

II. Hypercalcemia

A. **Etiology.** Three basic pathophysiologic mechanisms contribute to hypercalcemia: increased calcium absorption from the gastrointestinal tract, decreased renal excretion of calcium, and increased bone reabsorption of calcium. The most common etiologies of hypercalcemia are listed in Table 5-1.

Hyperparathyroidism
Malignancy
Vitamin A and D intoxication
Milk-alkali syndrome
Thyrotoxicosis
Granulomatous disease
Immobilization
Paget's disease
Thiazide diuretic intake
Addison's disease
Pheochromocytoma
Lithium intake
Renal failure
Complications from renal transplant
Familial hypocalciuric hypercalcemia

Table 5-1. Etiologies of hypercalcemia

1. **Increased calcium absorption from the gastrointestinal tract** plays a primary role in the hypercalcemia of the milk-alkali syndrome, vitamin D intoxication, and granulomatous disorders. Milk-alkali syndrome is the result of ingestion of excess amounts of calcium and alkali. In the past, the most common sources of calcium and alkali were milk and sodium bicarbonate, respectively. This syndrome most often occurs in elderly women who consume excess amounts of calcium carbonate for the treatment of osteoporosis. Patients present with the classic triad of hypercalcemia, metabolic alkalosis, and renal insufficiency. Treatment of the hypercalcemia in these patients is often complicated by hypocalcemia resulting from sustained PTH suppression.
2. **Hypercalcemia in renal failure** is uncommon, except in patients treated with calcium and vitamin D supplements. This disorder and the milk-alkali syndrome both illustrate the important concept that an increase in plasma calcium concentration from ingestion of excessive amounts of dietary calcium alone does not occur in the absence of renal impairment.

   Vitamin D intoxication also results in hypercalcemia. Calcium is absorbed primarily in the small intestine, and this process is stimulated by calcitriol. Hypercalcemia may also be secondary to granulomatous disorders, such as sarcoidosis. Activated macrophages produce calcitriol, which leads to increased absorption of dietary calcium. This results more commonly in hypercalciuria than in hypercalcemia. Lymphomas occasionally produce hypercalcemia via the same mechanism.
3. **Increased reabsorption of calcium from bone** plays a primary role in hypercalcemia that occurs as a result of primary and secondary hyperparathyroidism, malignancy, hyperthyroidism, immobilization, Paget's disease, and vitamin A toxicity.
   a. **Primary hyperparathyroidism** is the most frequent cause of hypercalcemia, with an estimated prevalence of 1 per 10,000. The underlying pathology is most often a solitary adenoma (80%). Among the rest of these patients, 15% to 20% have diffuse hyperplasia, and approximately one-half of these have a familial syndrome [multiple endocrine neoplasia (MEN) type I, associated with pituitary adenomas and islet cell tumors, or MEN type II, associated with medullary carcinoma of the thyroid and pheochromocytoma]. Multiple adenomas are uncommon, and parathyroid carcinoma is rare (occurring in less than 1%). Hypercalcemia is a result of increased calcium reabsorption from bone, increased calcium absorption from intestine mediated by calcitriol, and increased distal tubular renal calcium reabsorption. In primary hyperparathyroidism, the hypercalcemia is often mild, asymptomatic, and identified on routine blood chemistries in the outpatient setting. Patients present most commonly in the fifth and sixth decades. Women are affected two to three times more frequently than men, and two-thirds of all cases occur in postmenopausal women.
   b. **Secondary hyperparathyroidism** results in hypercalcemia after renal transplantation when plasma phosphorus, vitamin D metabolism, and renal function improve, but PTH secretion remains high secondary to increased parathyroid mass. In most patients, the hypercalcemia resolves within the first year after transplantation.
   c. **Malignancy** is the second most common cause of hypercalcemia. Hypercalcemia of malignancy can be a result of several pathophysiologic mechanisms: the overproduction of PTH-related peptide (PTHrP), local reabsorption of bone around sites of tumor infiltration (mediated via a variety of cytokines and osteolytic prostaglandins), and the production of calcitriol (e.g., with lymphomas). Patients with squamous cell cancer of the lung, breast cancer, multiple myeloma, and renal cell carcinoma are at highest risk. Hypercalcemia due to tumoral production of PTHrP is often referred to as *humoral hypercalcemia of malignancy* (HHM). PTHrP has 70% amino acid identity to the first 13 amino acids of PTH, binds to the PTH receptor, and has biological activity similar, but not identical, to PTH. HHM often presents with severe hypercalcemia (calcium level higher than 14 mg per dL) in a patient with either a known history of malignancy or evidence of malignancy at initial presentation. PTHrP is immunologically distinct from PTH and is not detected by standard PTH assays, but specific assays for PTHrP are commercially available. Assays that measure the C-terminal fragment of PTHrP may show an increase when used in pregnant patients or patients with renal failure. Median survival from the onset of hypercalcemia with HHM is only 3 months. Squamous cell tumors, renal cell carcinomas, and most breast neoplasms produce PTHrP. The diagnoses of primary hyperparathyroidism and malignancy are not mutually exclusive. An increased incidence of primary hyperparathyroidism appears in patients with malignancy.

      Multiple myeloma is associated with hypercalcemia and localized osteolytic lesions in the skeleton. Approximately 30% of myeloma patients experience hypercalcemia at some time during the course of their disease. Bone destruction occurs as a consequence of the release of interleukin-6, interleukin-1, and tumor necrosis factor–b by malignant plasma cells. The bony lesions demonstrate a marked increase in osteoclastic reabsorption without manifestations of increased bone formation, in contrast to metastatic lesions of breast and prostate cancer, which generally show some increase in bone formation and radionuclide uptake at sites of increased osteoblastic activity.
   d. **Hyperthyroidism** results in mild hypercalcemia in 10% to 20% of patients as a result of increased bone turnover. Immobilization and Paget's disease also cause hypercalcemia, although this is more likely in children. In adults, hypercalciuria is more common than hypercalcemia.
4. **Rare causes of hypercalcemia** include lithium (mild; interferes with the calcium sensing receptor); thiazides (rare; occult primary hyperparathyroidism should be suspected); pheochromocytoma; primary adrenal insufficiency; and a rare genetic disorder, familial hypocalciuric hypercalcemia (FHH). FHH is an autosomal dominant disorder caused by a defect in the calcium-sensing receptor. It presents with mild hypercalcemia early in life, hypocalciuria, and a normal or slightly increased PTH level in the absence of signs or symptoms of hypercalcemia. As a result of the defect, the calcium-sensing receptor is less sensitive to plasma calcium concentration, and a higher than normal calcium concentration is required to suppress PTH. The physician should be aware of FHH, because this condition is often mis–diagnosed as primary hyperparathyroidism, and patients may be inappropriately subjected to neck exploration. FHH may account for a small percentage of patients who undergo surgery for primary hyperparathyroidism in whom no adenoma is found.

B. **Signs and symptoms** of hypercalcemia are related to the severity and rapidity of the rise in serum ionized calcium concentration. Mild hypercalcemia is generally asymptomatic and often incidentally discovered on routine blood chemistries, as is the case in many patients with primary hyperparathyroidism. In contrast, severe hypercalcemia is often associated with neurologic and gastrointestinal symptoms. The patient may present with a wide range of central nervous system symptoms, from mild mental status changes to stupor and coma. Gastrointestinal symptoms include constipation, anorexia, nausea, and vomiting. Abdominal pain may result from hypercalcemia-induced peptic ulcer disease or pancreatitis. As is discussed in Chapter 2, Hypernatremia section (**I.C.2.a**), hypercalcemia results in polyuria and secondary polydipsia that leads to ECF volume depletion, a reduction in the glomerular filtration rate (GFR), and an elevation in the blood urea nitrogen (BUN) and creatinine. Hypercalcemia also potentiates the cardiac effects of digitalis toxicity.

C. **Diagnosis.** The most common causes of hypercalcemia are primary hyperparathyroidism and malignancy. These two disorders make up more than 90% of all cases. Initial evaluation includes a history and physical examination. Use of calcium supplements, antacids, vitamin preparations, and over-the-counter medications should be determined. A chest x-ray should be obtained to rule out pulmonary malignancies and granulomatous disorders.
   1. **Initial laboratory examination** includes measurement of electrolytes, BUN, creatinine, and phosphorus; serum protein electrophoresis; and a 24-hour urine for calcium and creatinine. The presence of a high serum chloride concentration and a low serum bicarbonate concentration in a ratio greater than 33 to 1 is suggestive of primary hyperparathyroidism resulting from the effect of PTH in decreasing proximal tubular bicarbonate reabsorption. A low serum chloride concentration, a high serum bicarbonate concentration, and elevated BUN and creatinine levels are characteristic of milk-alkali syndrome. A monoclonal spike on either serum protein electrophoresis or urine protein electrophoresis is suggestive of multiple myeloma or light chain disease. A low plasma phosphate concentration is found in primary hyperparathyroidism and HHM. The 24-hour urinary calcium level is low in hypercalcemia caused by the milk-alkali syndrome, use of thiazide diuretics, or FHH.

      As a general rule, primary hyperparathyroidism is the etiology in outpatients who are asymptomatic with a serum calcium concentration lower than or at 11 mg per dL, whereas malignancy is often the cause in symptomatic patients with an abrupt onset of disease and serum calcium concentration higher than or at 14 mg per dL.
   2. An **intact PTH level** is obtained after the initial evaluation is completed. The most common cause of an elevated PTH level is primary hyperparathyroidism, although an elevated PTH level may also be seen with lithium use and FHH. Occasionally, the PTH level will be inappropriately within the normal range based on the increase in the serum calcium in primary hyperparathyroidism. In all other conditions, PTH will be suppressed by the hypercalcemia. If no obvious malignancy is present and the PTH level is not increased, then the possibility of vitamin D intoxication or granulomatous disease should be evaluated further using calcidiol and calcitriol levels. An increased calcidiol level is seen with ingestion of either vitamin D or calcidiol. An elevated calcitriol

level is observed with calcitriol ingestion, granulomatous disease, lymphoma, and primary hyperparathyroidism. As a final step, if the calcitriol level is increased without apparent cause, occult granulomatous disease can be looked for with a hydrocortisone suppression test. After the administration of 40 mg of hydrocortisone every 8 hours for 10 days, the hypercalcemia will resolve if it is the result of granulomatous disease.

D. **Treatment** of hypercalcemia varies depending on the severity of the serum calcium elevation. It is directed at increasing urinary calcium excretion, inhibiting bone reabsorption, and decreasing intestinal calcium absorption.
   1. **Urinary calcium excretion is increased** by expanding the plasma volume and, subsequently, adding loop diuretics. Calcium reabsorption in the proximal tubule is passive and parallels sodium reabsorption. Therefore, volume contraction increases proximal sodium reabsorption and helps maintain the hypercalcemia. Patients with hypercalcemia are often volume contracted. Hypercalcemia acts directly in the thick ascending limb of Henle to decrease sodium reabsorption and also antagonizes the effects of antidiuretic hormone. In the setting of renal insufficiency, higher doses of loop diuretics may be required. In the presence of little or no renal function and severe hypercalcemia, hemodialysis is indicated. If the hypercalcemia is moderate, volume expansion and loop diuretics may be the only therapy required.
   2. **An agent that inhibits bone reabsorption** is often required when hypercalcemia is moderate or severe. In the acute setting, calcitonin is often helpful because of its rapid onset of action (2 to 4 hours). Calcitonin inhibits osteoclastic bone reabsorption and increases renal calcium excretion. However, it reduces serum calcium concentration by only 1 to 2 mg per dL, and tachyphylaxis often develops with repeated use. For these reasons, calcitonin should not be used as the sole agent to inhibit bone reabsorption.
      a. **Bisphosphonates** have become the agents of choice for the management of hypercalcemia due to bone reabsorption. They are analogues of inorganic pyrophosphate that are selectively concentrated in bone, where they interfere with osteoclast attachment and function. Bisphosphonates have a slow onset (2 to 3 days) and a long duration of action (several weeks). Etidronate was the first bisphosphonate approved for the treatment of hypercalcemia. The serum calcium concentration begins to fall on day 2 with etidronate and reaches a nadir on day 7. The hypocalcemic effect may be prolonged for several weeks. If the serum calcium falls rapidly within the first 48 hours, the drug should be discontinued to avoid hypocalcemia. It can be given intravenously at a dosage of 7.5 mg per kg given over 4 hours for 3 consecutive days. However, a single intravenous dose of 30 mg per kg given as an infusion over 24 hours in 1 L of normal saline may be more effective.
      b. **Pamidronate** is more potent than etidronate and is the most widely used bisphosphonate in the treatment of hypercalcemia. The drug is given at a dose of either 60 or 90 mg intravenously over 4 hours. If the serum calcium concentration is less than 13.5 mg per dL, 60 mg is given. If the serum calcium concentration is higher than 13.5 mg per dL, 90 mg is administered. The serum calcium gradually falls over the ensuing 2 to 4 days. A single dose is usually effective for 1 to 2 weeks. Serum calcium concentration normalizes in most patients after 7 days. The dose of both etidronate and pamidronate must be adjusted for renal insufficiency.
      c. **Plicamycin (mithramycin)** can also be used except in patients with severe hepatic, renal, and marrow disorders. Its effect begins in 12 hours and peaks at 48 hours. The dose can be repeated at 3- to 7-day intervals. However, its side-effect profile (nausea, hepatotoxicity, proteinuria, and thrombocytopenia) has led to decreased enthusiasm for its use.
      d. **Gallium nitrate** also inhibits bone reabsorption by unknown mechanisms and is an additional agent that can be used to treat the hypercalcemia of malignancy. It is administered as a continuous infusion at a dose of 100 to 200 mg per m^2 for 5 consecutive days. Gallium nitrate should not be administered to patients with serum creatinine concentrations above 2.5 mg per dL and is probably best reserved for patients who have not responded to more conventional agents. A summary of treatment options is shown in Table 5-2.

Drug	Dosage
Normal saline	2–4 L/d initially
Furosemide	20–160 mg i.v. q6h after volume expansion
Salmon calcitonin	4 IU/kg s.c. q12h
Etidronate disodium	7.5 mg/kg i.v. over 4 hr q.d. for 3–7 d 30 mg/kg i.v. over 24 hr as a single dose
Pamidronate disodium	60–90 mg i.v. over 4 hr
Plicamycin	25 μg/kg i.v. over 4 hr q.d. for 3–4 d
Corticosteroids	200–300 mg hydrocortisone i.v. q.d. for 3–5 d
Gallium nitrate	100–200 mg/m^2 for 5 d

Table 5-2. Treatment of hypercalcemia

   3. **Measures to decrease intestinal absorption** of calcium are often used in outpatients with mild disease. Corticosteroids may be helpful in vitamin D intoxication, granulomatous disease, and certain neoplasms (lymphoma, myeloma). Alternatives to corticosteroids include ketoconazole and hydroxychloroquine. Oral phosphate can be used, providing the patient does not have an elevated serum phosphate level or renal failure. However, oral phosphate often causes diarrhea and only lowers the serum calcium by about 1 mg per dL.
   4. Whether to **surgically remove** a solitary parathyroid adenoma remains a difficult management issue. The following criteria for surgical intervention were suggested at a 1991 National Institutes of Health consensus conference focused on this problem: a total serum calcium concentration that is more than 1 mg per dL above the upper limit of the normal range; evidence of overt bone disease; cortical bone mineral density that is more than 2 SD below the adjusted mean for age, sex, and race; reduction in renal function by more than 30%; a history of nephrolithiasis or nephrocalcinosis; urinary calcium excretion greater than 400 mg per day; and an episode of acute symptomatic hypercalcemia. It is estimated that approximately 50% of patients meet these criteria.

III. Hypocalcemia

A. **Etiology.** True hypocalcemia is the result of decreased calcium absorption from the gastrointestinal tract or decreased calcium reabsorption from bone. Given that 98% of total body calcium is contained within the skeleton, sustained hypocalcemia cannot occur without an abnormality of either PTH or calcitriol action in bone.

Total plasma calcium is composed of three components: ionized calcium (50%), complexed calcium (10%), and protein-bound calcium (40%). True hypocalcemia is present only when the ionized calcium concentration is reduced. The reference range for serum ionized calcium is 4.2 to 5.0 mg per dL (1.05 to 1.25 mmol per L). Therefore, whenever a low total serum calcium concentration is observed, this value must be compared with the serum albumin concentration. For every decrease of 1 g per dL in serum albumin concentration from its normal value of 4 g per dL, a decrement of 0.8 mg per dL in total serum calcium concentration can be expected. Thus, for each fall of 1 g per dL in serum albumin concentration, 0.8 mg per dL must be added to the total serum calcium concentration. The binding of calcium to albumin is affected by ECF pH. Acidemia increases and alkalemia decreases the ionized calcium concentration. Ionized calcium concentration increases approximately 0.2 mg per dL for each 0.1 decrease in pH. These correction factors are only general guidelines and should not be used as a substitute for the direct measurement of ionized serum calcium concentration if clinical suspicion warrants.

True hypocalcemia is caused by decreased PTH secretion, end-organ resistance to PTH, or disorders of vitamin D metabolism. Rarely, hypocalcemia occurs acutely as a result of either the extravascular deposition of calcium or the intravascular binding of calcium. The most common etiologies of true hypocalcemia are shown in Table 5-3.

Hypoparathyroidism
Idiopathic—HAM syndrome
Familial
Postsurgery—hungry bone syndrome
Infiltrative disorders
Pseudohypoparathyroidism 1A, 1B, 2
Hypomagnesemia
Defects in vitamin D metabolism
Nutritional
Malabsorption
Drugs
Liver disease
Renal disease
Vitamin D–dependent rickets
Miscellaneous
Tumor lysis syndrome
Osteoblastic metastases
Acute pancreatitis
Toxic shock syndrome
Sepsis

HAM, hypoparathyroidism, adrenal insufficiency and mucocutaneous candidiasis.

Table 5-3. Etiologies of hypocalcemia

1. **Hypoparathyroidism** can be associated with a wide variety of acquired and inherited diseases that result from either impaired synthesis and release of PTH or from peripheral tissue resistance to PTH. The most common cause of idiopathic hypoparathyroidism is polyglandular autoimmune syndrome type I, characterized by chronic mucocutaneous candidiasis and primary adrenal insufficiency. Occasionally, pernicious anemia, diabetes mellitus, vitiligo, and autoimmune thyroid disease are also associated. The candidiasis often presents first in early childhood and is followed several years later by hypoparathyroidism. Adrenal insufficiency appears in adolescence. The combination of *h*ypoparathyroidism, *a*drenal insufficiency, and *m*ucocutaneous candidiasis is referred to as the *HAM syndrome*.

   Familial hypocalcemia results from activating mutations in the calcium-sensing receptor that create a receptor that is more sensitive to the ionized calcium concentration. Parathyroid and radical neck surgery can result in loss of glandular tissue. Surgical removal of parathyroid tissue in secondary or tertiary hyperparathyroidism is often complicated by severe hypocalcemia due to the remineralization of bone, the so-called hungry bone syndrome. Hypocalcemia also occurs after thyroid surgery (5% of cases); in approximately 0.5% of these patients, the hypocalcemia is permanent. Risk factors for the development of permanent hypocalcemia include removal of three or more parathyroid glands; postoperative PTH level less than or at 12 pg per mL; serum total calcium concentration less than or at 8 mg per dL after 1 week of oral calcium supplementation; and a serum phosphate level of higher than or at 4 mg per dL after 1 week of calcium supplementation. Transient hypoparathyroidism may occur after the removal of a parathyroid adenoma. Infiltrative disorders such as hemochromatosis, Wilson's disease, and infection with human immunodeficiency virus can also decrease PTH secretion.

   Severe hypomagnesemia is the most common cause of hypoparathyroidism. Magnesium deficiency results in end-organ resistance to PTH and a decrease in PTH secretion. Patients with hypocalcemia as a result of hypomagnesemia do not respond to calcium or vitamin D replacement until the magnesium deficit has been replaced.

   A variety of other **rare genetic disorders** cause end-organ resistance to PTH, including pseudohypoparathyroidism types I and II. Patients with pseudohypoparathyroidism are classified on the basis of the response of nephrogenous cyclic adenosine monophosphate to PTH administration. A decreased response is indicative of type I, and a normal response is indicative of type II.
2. **Defects in vitamin D metabolism** also result in hypocalcemia. These defects are a result of decreased intake of vitamin D, malabsorption, drugs, liver disease, renal disease, and vitamin D–dependent rickets. Nutritional vitamin D deficiency is rare in the United States, as a result of the supplementation of milk and other food products. However, it can occur in poorly nourished patients with little sunlight exposure. Because vitamin D is fat-soluble, vitamin D deficiency can be seen in gastrointestinal malabsorption from any cause. Anticonvulsants can result in vitamin D deficiency through unclear mechanisms; this generally happens in patients with additional predisposing factors, such as poor nutrition and decreased sunlight exposure. Phenobarbital enhances the hepatic metabolism of both vitamin D and calcidiol. Vitamin D deficiency can result from hepatocellular disease if the disease is severe enough to impair the hydroxylation of vitamin D to calcidiol. Chronic renal disease impairs the hydroxylation of calcidiol to calcitriol. Vitamin D–dependent rickets is a result of either the impaired hydroxylation of calcidiol to calcitriol (type I) or end-organ resistance to calcitriol (type II). Type I patients respond to physiologic doses of calcitriol. Patients with type II disease have dramatically increased concentrations of calcitriol, respond poorly to calcitriol therapy, and have mutations in the vitamin D receptor.
3. **Other rare causes** of hypocalcemia include the tumor lysis syndrome, osteoblastic metastases, acute pancreatitis, toxic shock syndrome, and sepsis.

B. As is the case for hypercalcemia, the **signs and symptoms** of hypocalcemia depend not only on the degree of hypocalcemia, but also on the rate of decline of the serum calcium concentration. The threshold at which symptoms develop depends on the serum pH and on whether concomitant hypomagnesemia, hypokalemia, or hyponatremia are present. Symptoms of neuromuscular excitability predominate. The patient may complain of circumoral and distal extremity paresthesias or of carpopedal spasm. Central nervous system manifestations include mental status changes, irritability, and seizures. On physical examination, hypotension, bradycardia, laryngeal spasm, and bronchospasm may be present. The presence of Chvostek's and Trousseau's signs should be checked. (Chvostek's sign is a facial twitch elicited by tapping on the facial nerve just below the zygomatic arch with the mouth slightly open. A positive sign is occasionally observed in normal patients. Trousseau's sign is the development of wrist flexion, metacarpophalangeal joint flexion, hyperextended fingers, and thumb flexion after a sphygmomanometer cuff has been inflated about the arm to 20 mmHg above systolic pressure for a duration of 3 minutes.)

C. **Diagnosis.** The differential diagnosis of true hypocalcemia is often straightforward, and a diagnostic algorithm is shown in Figure 5-3. The most common causes are magnesium deficiency, renal failure, and complications of parathyroid surgery.

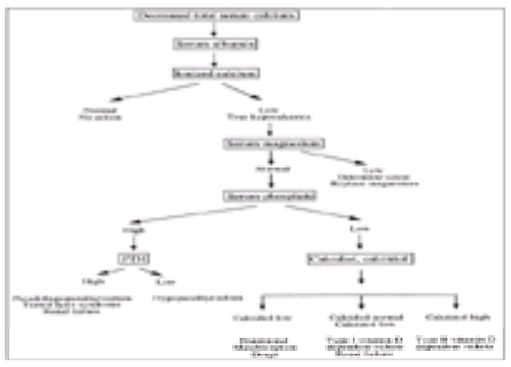

Figure 5-3. Evaluation of hypocalcemia. (PTH, parathyroid hormone.)

1. The first step in the evaluation of the patient with a decreased total serum calcium concentration is to evaluate the serum albumin and, if necessary, measure the ionized serum calcium concentration. If true hypocalcemia is documented, then blood should be obtained for BUN, creatinine, magnesium, and phosphate levels, and a 24-hour urine sample should be collected to test phosphate and creatinine levels.
2. The second step is to **evaluate the serum magnesium concentration**. Hypomagnesemia is the most common cause of hypocalcemia in hospitalized patients. A high index of suspicion should be present in patients with a history of steatorrhea, diarrhea, or chronic alcoholism. These patients generally have severe hypomagnesemia, and the hypocalcemia does not correct until the magnesium losses have been replaced.
3. Next, **serum and urinary phosphate concentrations are evaluated**. Hyperphosphatemia in the absence of renal failure suggests a diagnosis of either hypoparathyroidism or pseudohypoparathyroidism. Measuring the PTH concentration can differentiate these disorders. In primary hypoparathyroidism, PTH is low; in pseudohypoparathyroidism, PTH is increased.

   A decrease in serum phosphate indicates a defect in vitamin D metabolism. The hypocalcemia causes secondary hyperparathyroidism that, in turn, reduces proximal tubular reabsorption of phosphate and results in phosphate wasting. Therefore, the fractional excretion (FE) of phosphate is expected to be high (more than 5%). (In hypophosphatemia, the kidney has an extraordinary ability to conserve phosphate, and, in a normal individual, the FE of phosphate is below 1%.) If phosphaturia is noted, then calcidiol and calcitriol levels should be obtained. Calcidiol levels are reduced with malabsorption, liver disease, and phenobarbital. Calcitriol levels are reduced in renal failure and increased in type II vitamin D–dependent rickets.

D. The **management** of hypocalcemia depends on both its severity and cause.
   1. In an **emergency situation in which hypocalcemia is suspected and seizures, tetany, hypotension, or cardiac arrhythmias are present**, intravenous calcium should be administered (100 to 300 mg over 10 to 15 minutes) before the results of the serum calcium concentration return from the clinical laboratory. Patients with symptomatic hypocalcemia or a total serum calcium concentration corrected for albumin of less than or at 7.5 mg per dL should be initially managed with parenteral calcium. Chronic, mild hypocalcemia, as is seen in the outpatient setting, can be treated with oral calcium supplements, to which a vitamin D preparation may be added.
   2. **Acute symptomatic hypocalcemia** is treated with intravenous calcium. In the absence of seizures, tetany, or cardiac arrhythmias, an infusion of 15 mg per kg of elemental calcium given over 4 to 6 hours raises the total serum calcium by 2 to 3 mg per dL. Calcium gluconate (10%) is supplied in 10-mL ampules and contains 94 mg of elemental calcium. The first ampule can be administered over several minutes followed by a constant infusion begun at a rate of 0.5 to 1.0 mg per kg per hour, with adjustment in the rate based on serial serum calcium determinations. Calcium gluceptate (10%) provides 90 mg of elemental calcium in a 5-mL ampule. Calcium chloride has higher bioavailability, and 272 mg of elemental calcium is contained in each 10-mL ampule. Treatment of hypocalcemia is ineffective in the presence of hypomagnesemia. In the setting of metabolic acidosis, hypocalcemia should be corrected before the acidosis is.
   3. Patients with **hypoparathyroidism** are treated with calcium and vitamin D supplements. The serum calcium level should be maintained at the lower limit of normal. Oral elemental calcium, 1 to 3 g per day, is usually sufficient. A variety of oral calcium preparations are available, some of which are shown in Table 5-4. Calcium is best absorbed when taken between meals, and a variety of preparations are available. Calcium citrate is more soluble than calcium

carbonate, especially in those patients who require H_2 blockers or proton pump inhibitors. In the presence of severe hyperphosphatemia, calcium supplementation should be delayed, if possible, until the serum phosphate concentration has been reduced below 6 mg per dL with phosphate binders.

Preparation	Formulation	Elemental calcium per tablet
Calcium carbonate	Tums—500 mg	200 mg
	Rolaids—550 mg	220 mg
	Os-cal—1,250 mg	500 mg
Calcium citrate	Citracal—950 mg	200 mg
Calcium lactate	650 mg	85 mg
Calcium gluconate	1,000 mg	90 mg

Table 5-4. Oral calcium preparations

Calcitriol is the most potent of the vitamin D preparations and has the fastest onset and the shortest duration of action, but it is also the most expensive. A dose of 0.5 to 1.0 µg per day is usually required. As one moves back up the metabolic pathway to calcidiol, cholecalciferol, and ergocalciferol, cost decreases and duration of action increases. These agents, however, may be less efficacious in the presence of renal or hepatic disease.

Patients with hypoparathyroidism have decreased distal tubular calcium reabsorption as a result of a lack of PTH. Therefore, the increase in the filtered load of calcium that results from calcium and vitamin D–replacement therapy can lead to hypercalciuria, nephrolithiasis, and nephrocalcinosis. If urinary calcium excretion exceeds 350 mg per day despite serum calcium concentration in the low normal range, sodium intake should be restricted; if this is not effective, a thiazide diuretic should be added.

Disorders of Serum Phosphorus

I. Overview. Of total plasma phosphate, approximately two-thirds is organic phosphate (phospholipids), and one-third is inorganic. Clinical chemistry laboratories assay the inorganic fraction. The reference range is 2.8 to 4.5 mg per dL (0.89 to 1.44 mmol per L). Approximately 85% of the inorganic phosphate is free and circulates as either $HPO_4(-2)$ or $H_2PO_4(-1)$ (the ratio of these two ions is dependent upon the ECF pH). Of the remainder, 10% is protein-bound, and 15% is complexed with either calcium or magnesium.

As is the case for calcium, the majority of total body phosphate is contained within the skeleton (80%). Of the remainder, about 10% is contained in skeletal muscle and viscera. Only a small fraction of the phosphorus pool is inorganic and available for the synthesis of adenosine triphosphate. The average Western diet contains 800 to 1400 mg of phosphorus per day, of which approximately 80% is absorbed in the small intestine. The majority is absorbed passively, but an active component exists that is regulated by calcitriol. PTH and calcitriol, through their effects in bone, intestine, and kidney, regulate extracellular phosphate concentration. However, the major regulator of plasma phosphate concentration is renal phosphate excretion. In kidney, phosphate is reabsorbed primarily in the proximal tubule (80%), where it is cotransported across the luminal membrane with sodium. The sodium-phosphate cotransporter is upregulated in response to phosphate depletion, and, under these circumstances, the kidney is capable of reducing the FE of phosphate to very low levels.

II. Phosphate regulation. PTH acts directly in bone to increase phosphate entry into the ECF and indirectly in intestine by stimulating the production of calcitriol. The majority of dietary phosphate is reabsorbed in the small intestine, but, a component of unregulated secretion is present in the colon (100 to 200 mg per day). PTH reduces proximal tubular reabsorption of phosphate in the kidney. The net effect is to increase plasma calcium concentration while keeping plasma phosphate concentration constant. The major roles of calcitriol are to enhance the availability of calcium and phosphate for new bone formation and to defend the ECF from hypocalcemia and hypophosphatemia. PTH and hypophosphatemia are the main stimulators of calcitriol production in proximal tubule. However, as discussed above, the kidney is the primary regulator of plasma phosphate concentration. Hypophosphatemia causes the insertion of sodium-phosphate cotransporters into the luminal membrane of the proximal tubule, whereas PTH results in their removal. The ability of PTH to remove sodium-phosphate cotransporters from the apical membrane is blunted in chronic phosphate depletion.

III. Hyperphosphatemia

A. **Etiology.** Hyperphosphatemia can result from renal failure, an acute phosphate load from either exogenous or endogenous sources, or increased proximal tubular reabsorption of phosphate. Etiologies of hyperphosphatemia are shown in Table 5-5.

Decreased renal excretion
Acute renal failure
Chronic renal failure
Acute phosphate load
Tumor lysis syndrome
Rhabdomyolysis
Bowel infarction
Severe hemolysis
Vitamin D intoxication
Increased renal phosphate reabsorption
Hypoparathyroidism
Acromegaly
Thyrotoxicosis
Drugs—bisphosphonates
Tumoral calcinosis
Pseudohyperphosphatemia

Table 5-5. Etiologies of hyperphosphatemia

1. **Renal failure** is the underlying cause in 90% or more of cases. As the GFR begins to decline, the FE of phosphate begins to increase. However, once GFR falls below 30 mL per minute, phosphate reabsorption is maximally suppressed and the FE cannot increase further. As a result, renal excretion can no longer keep pace with dietary intake, and the plasma phosphate rises. A new steady state is eventually established, albeit at a higher plasma phosphate concentration.
2. A **sudden, massive phosphate load** may result in an increase in plasma phosphate concentration. This phosphate may be released from either the intracellular space, as is the case in the tumor lysis syndrome or rhabdomyolysis, or it can be ingested and absorbed, as in vitamin D intoxication. Tumor lysis syndrome most commonly is seen with the treatment of rapidly growing malignancies such as leukemias and lymphomas. It can occur after the treatment of solid tumors such as small cell carcinoma, breast cancer, and neuroblastoma. Risk factors for tumor lysis syndrome in patients with solid tumors include pretreatment renal insufficiency, an increased lactate dehydrogenase, and hyperuricemia. Increased lactate dehydrogenase and hyperuricemia are indicators of a large tumor volume.
3. **Primary increases in the tubular reabsorption of phosphate** are much less common. They can occur in hypoparathyroidism; in acromegaly, as a result of direct stimulation of insulin-like growth factor on phosphate transport; with bisphosphonates, via a direct effect on renal phosphate reabsorption; and in tumoral calcinosis. Tumoral calcinosis is caused by an abnormality in the proximal tubule that leads to an increase in phosphate transport.

B. Many of the **signs and symptoms** of an acute rise in serum phosphate are the result of concomitant hypocalcemia due to the deposition of calcium in soft tissues and a resultant fall in ECF ionized calcium. Hyperphosphatemia can also cause hypocalcemia by decreasing the activity of 1-a hydroxylase and calcitriol formation.

C. **Diagnosis.** Clinically unexplained, persistent hyperphosphatemia should raise the suspicion of pseudohyperphosphatemia, the most common cause of which is paraproteinemia. No consistent relationship of immunoglobulin type or subclass has been identified. This is a method-dependent artifact, and paraprotein

interference may be a general problem inspectrophotometric assays. If paraproteinemia is indeed present, the cause is generally acute or chronic renal failure.

D. The **treatment** of hyperphosphatemia is aimed at reducing the intestinal absorption of phosphate. This is accomplished through the use of oral phosphate-binding agents such as calcium carbonate and aluminum hydroxide. Calcium carbonate is the agent of choice and should be administered with meals. Aluminum hydroxide may be used in the short term, but chronic use in patients with renal failure should be avoided because of the potential for aluminum toxicity. In patients with coexistent hypocalcemia, lowering the serum phosphate below 6 mg per dL, if possible, before treating the hypocalcemia is preferable, to avoid the potential complication of metastatic calcification from calcium phoshate coprecipitation.

IV. Hypophosphatemia

A. **Etiology.** Hypophosphatemia may result from the redistribution of extracellular phosphate into the intracellular space, a decrease in intestinal absorption of phosphate, or a decrease in renal reabsorption of phosphate. The differential diagnosis of hypophosphatemia is presented in Table 5-6.

Decreased dietary intake
Alcoholism
Phosphate-binding agents
Shift of phosphate into the intracellular fluid
Respiratory alkalosis
Refeeding
Diabetic ketoacidosis
Hungry bone syndrome
Increased renal excretion
Hyperparathyroidism
Vitamin D deficiency
X-linked hypophosphatemic rickets
Fanconi's syndrome
Drugs—acetazolamide
Osmotic diuresis
Oncogenic osteomalacia

Table 5-6. Etiologies of hypophosphatemia

1. The most common causes of a **shift of phosphate from the ECF to the intracellular fluid** in hospitalized patients are respiratory alkalosis and the refeeding syndrome. Respiratory alkalosis causes a rise in intracellular pH that in turn stimulates phosphofructokinase, the rate-limiting step in glycolysis. This can result in severe hypophosphatemia with serum phosphate concentrations lower than 0.5 to 1.0 mg per dL. Intracellular shifts can also be seen with the treatment of diabetic ketoacidosis and in the hungry bone syndrome that occurs after parathyroidectomy for secondary hyperparathyroidism. In the hungry bone syndrome, the serum calcium and phosphate concentration fall dramatically in the postoperative period, although clinically, hypocalcemia is more of a management issue than hypophosphatemia.
2. **Decreased dietary intake** is an unusual cause of hypophosphatemia, because oral intake almost always exceeds gastrointestinal losses, and the kidney is capable of reclaiming nearly all of the filtered load of phosphate. In general, decreased intake is combined with increased gastrointestinal losses (e.g., diarrhea) or the use of phosphate binders.
3. **Increased urinary excretion of phosphate** occurs in primary hyperparathyroidism, secondary hyperparathyroidism due to defects in vitamin D metabolism, Fanconi's syndrome, osmotic diuresis, acetazolamide, and oncogenic osteomalacia. Oncogenic osteomalacia is a rare disorder associated with mesenchymal tumors that is characterized by hypophosphatemia, phosphaturia, decreased calcitriol concentration, normal calcidiol concentration, and clinical and histological evidence of osteomalacia. There may be a considerable delay between the presentation of the syndrome and the discovery of the tumor. The tumor produces a humoral factor that interferes with proximal tubular reabsorption of phosphate, as well as the production of calcitriol. The syndrome resolves on removal of the tumor.

B. **Signs and symptoms.** Hypophosphatemia may result in a variety of clinical sequelae. Correction of moderate hypophosphatemia has been shown to improve diaphragmatic function in patients with acute respiratory failure. In patients with severe hypophosphatemia, failure to wean from mechanical ventilation until repletion of phosphate was demonstrated. *In vitro* hypophosphatemia causes a leftward shift in the oxygen dissociation curve. Hypophosphatemia is also thought to produce reversible myocardial dysfunction and an impaired response to pressors. Neuromuscular symptoms include paresthesias, tremor, muscle weakness, and altered mental status; severe hypophosphatemia increases red cell fragility, which can lead to hemolysis and decreases chemotaxis, phagocytosis, and bacterial killing by white cells, with an increased susceptibility to infection the possible result.

C. **Diagnosis.** Either the FE of phosphate or the 24-hour urinary phosphate can be used to distinguish among the pathophysiologic mechanisms of hypophosphatemia. If the kidney is responding appropriately to decreased intestinal absorption or redistribution of phosphate into cells, FE of phosphate is below 5% and the 24-hour urine phosphate concentration is less than 100 mg per day. When the kidney is the cause of the hypophosphatemia, the FE of phosphate is greater than 5% and the 24-hour urine contains more than 100 mg of phosphate. In this case, a urinalysis for glycosuria, a PTH level to rule out hyperparathyroidism, and calcidiol and calcitriol level checks are indicated.

D. **Treatment** is indicated for severe hypophosphatemia (less than or at 1 mg per dL) or symptoms. It is complicated by the fact that phosphate is largely an intracellular ion, and the serum phosphate concentration is not a reliable indicator of total body phosphate stores. Hypophosphatemia is often associated with potassium and magnesium depletion as well. Phosphate repletion should be undertaken with extreme caution in the rare patient with renal insufficiency; the safest mode of therapy is oral, and hypophosphatemia can usually be corrected with 1,000 mg of phosphorus per day. Several forms of oral phosphate replacement therapy are listed in Table 5-7. Diarrhea is the most common complication.

Preparation	Dosage	Contents
K-phos-neutral	2 tablets, b.i.d. or t.i.d.	250 mg phosphate, 12 mEq sodium, 2 mEq potassium per tablet
Fleets Phospho-Soda	5 mL b.i.d.	149 mg phosphate, 6 mEq sodium per mL
Neutra-Phos-K	1–2 capsules, b.i.d. or t.i.d.	250 mg phosphate, 14 mEq potassium per capsule
K-phos	2 tablets, t.i.d. or q.i.d.	114 mg phosphate, 3.68 mEq potassium per tablet

Table 5-7. Oral phosphate preparations

Intravenous replacement carries the risk of hypocalcemia and hyperphosphatemia and is only warranted in patients with severe symptomatic phosphate depletion. Sodium phosphate should be used unless the serum potassium is less than 4 mEq per L. Plasma phosphate, calcium, magnesium, potassium, and urine output should be carefully monitored during intravenous replacement. Once the serum phosphate concentration has increased to more than 1 mg per dL, the patient should be switched to an oral preparation. Administration of doses larger than 0.32 mmol per kg over a 12-hour period is rarely warranted.

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Chapter 6 The Patient with Renal Stones

Robert F. Reilly

Initial presentation
Types of stones
Evaluation of the patient
Treatment

Nephrolithiasis is a common disorder in the United States, with an annual incidence of 7 to 21 per 10,000. Kidney stones account for approximately 1 in every 100 hospital admissions, with males affected three to four times more frequently than females. It is estimated that, by the age of 70 years, as many as 20% of all white males and 7% of all white females will form a stone. Blacks and Asians are affected far less often. The peak incidence occurs between the ages of 20 and 30 years.

Kidney stones are a major cause of morbidity due to associated renal colic, urinary tract obstruction, urinary tract infection (UTI), and renal parenchymal damage. In the United States, calcium-containing stones make up approximately 90% of all stones; they contain primarily calcium oxalate, either alone or in combination with calcium phosphate. The remaining 10% are composed of uric acid, struvite-carbonate, and cystine.

A kidney stone can form only when urine is supersaturated with respect to a stone-forming salt. Interestingly, urine in many normal people is often supersaturated with respect to calcium oxalate, and yet stone formation does not occur. At least two other factors play a role in the pathogenesis of stone formation: heterogeneous nucleation and the presence in the urine of inhibitors of crystallization. Crystallization of a salt requires much less energy when a surface on which it can precipitate (heterogeneous nucleation) is present, as opposed to crystallization that occurs in the absence of such a surface (homogeneous nucleation). In addition, normal urine contains a variety of inorganic and organic substances that act as inhibitors of crystallization. The most clinically important of these are citrate, magnesium, and pyrophosphate.

I. Initial presentation

. A kidney stone most commonly presents with flank pain that is severe, sudden in onset, and often associated with nausea and vomiting. The radiation of the pain may provide some clue as to where in the urinary tract the stone is lodged. Stones in the ureteropelvic junction may cause pain that radiates to the groin, whereas stones lodged in the narrowest portion of the ureter, where it enters the bladder, may be associated with signs of bladder irritation (dysuria, frequency, and urgency). Struvite-carbonate stones are, on occasion, incidentally discovered on abdominal radiograph. A careful abdominal examination and , in women, a pelvic examination, is important to rule out other potential causes of abdominal pain.

A. **Laboratory evaluation** should include a complete blood cell count, serum chemistries, and urinalysis. The white blood cell count may be mildly elevated but is generally less than 15,000 per mm^3. A white blood cell count greater than 15,000 per mm^3 is suggestive of another intraabdominal cause for the pain or an associated infection behind an obstructing calculus. An elevation of the blood urea nitrogen and creatinine indicates prerenal azotemia, parenchymal renal disease, or obstruction of a solitary functioning kidney. A urinalysis should be performed routinely in any patient with abdominal pain. Microscopical hematuria is observed in approximately 90% of patients with nephrolithiasis.
B. **Establishing a definitive diagnosis** is the focus of the next stage of the evaluation, once the diagnosis is suspected based on the history, physical examination, and preliminary laboratory studies.
    1. A **flat radiographic plate of the abdomen** is often obtained and is capable of identifying radiopaque stones (calcium oxalate, calcium phosphate, struvite-carbonate, and cystine) that are greater than or equal to 2 mm in size. It will miss radiolucent stones, the most common of which are uric acid stones, and stones that overlie the bony pelvis. For these reasons, a flat plate of the abdomen is most valuable in ruling out other intraabdominal processes.
    2. An **ultrasound examination of the genitourinary tract** can often identify stones in the renal pelvis; however, the majority of stones are lodged in the ureter, and the ultrasound examination often misses these.
    3. The **intravenous pyelogram** (IVP) was formerly considered the gold standard for the diagnosis of nephrolithiasis and is still of considerable value in the acute setting. Although the stone itself may not be visualized on an IVP, the site of the obstruction is regularly identified. Structural or anatomic abnormalities that may be present in the urinary tract, and renal or ureteral complications can be recognized. Disadvantages of the IVP include the need for intravenous contrast and the prolonged waiting times often required to visualize the collecting system on the side of the obstruction.
    4. **Spiral computed tomography** (CT), when available, is the test of choice in the patient with suspected nephrolithiasis. Advantages of spiral CT include higher sensitivity, faster scan times, and the lack of a need for contrast.

II. Types of stones

A. **Calcium-containing stones** make up 90% of all stones and are generally composed of a mixture of calcium oxalate and calcium phosphate. In mixed stones, calcium oxalate usually exceeds calcium phosphate, and pure calcium oxalate stones are more common than pure calcium phosphate stones. Calcium phosphate tends to precipitate in alkaline urine, as occurs with renal tubular acidosis (RTA), whereas the precipitation of calcium oxalate does not vary greatly with pH. Because urine is acidic in most patients, calcium oxalate stones are more common. The major risk factors for the formation of calcium-containing stones include hypercalciuria, hypocitraturia, low urine volume, hyperoxaluria, medullary sponge kidney, and hyperuricosuria. These risk factors can occur either alone or in combination. Their relative frequency is shown in Table 6-1.

Risk factor	Alone	Combined
Hypercalciuria	60%	80%
Low urine volume	10%	50%
Hypocitraturia	10%	50%
Hyperuricosuria	10%	40%
Hyperoxaluria	9%	15%

Table 6-1. Risk factors for calcium-stone disease

1. **Hypercalciuria** is defined as urinary calcium excretion greater than 250 mg per 24 hours in women and greater than 300 mg per 24 hours in men. Hypercalciuria is present in about two-thirds of patients with calcium stones and may result from an increased filtered load, decreased proximal reabsorption, or decreased distal reabsorption of calcium. Proximal reabsorption of calcium parallels sodium reabsorption. Any situation that decreases proximal reabsorption of sodium will also decrease proximal reabsorption of calcium. Distal tubular reabsorption of calcium is stimulated by parathyroid hormone (PTH), thiazides, and amiloride and is inhibited by acidosis and phosphate depletion.

   Causes of hypercalciuria include idiopathic causes, primary hyperparathyroidism, RTA, sarcoidosis, immobilization, Paget's disease, hyperthyroidism, milk-alkali syndrome, and vitamin D intoxication. The idiopathic group makes up 90% of all hypercalciuria. This category of patients is characterized by increased $1,25(OH)_2$ vitamin D_3 levels, suppressed PTH, and reduced bone mineral densities. Three potential pathophysiologic mechanisms for idiopathic hypercalciuria exist: increased intestinal absorption of calcium, decreased renal reabsorption of calcium or phosphorus, and enhanced bone demineralization. On the basis of a fast-and-calcium-load study, some authors advocate subdividing idiopathic hypercalciuria into absorptive hypercalciuria types I, II, and III and renal leak hypercalciuria. The rationale for this approach is that the physiologic mechanism identified will help guide specific therapy. In practice, however, this is often unnecessary. As is shown in Table 6-3, the majority of studies showing that a given pharmacologic intervention reduces the

risk of stone disease have not subdivided patients in this fashion.

Author	Treatment	Dose	Condition	No. of patients; length of follow-up	Risk reduction
Borghi	Water	—	First stone	199; 5 yr	35%
Laerum	Hydrochlorothiazide	25 mg b.i.d	Noncategorized, recurrent	50; 3 yr	54%
Ettinger	Chlorthalidone	25–50 mg	Noncategorized, recurrent	54; 3 yr	69%
Ettinger	Allopurinol	100 mg t.i.d	Hyperuricosuria, recurrent	60; 3 yr	65%
Borrelo	Potassium citrate	30–60 mEq	Hypocitraturia, recurrent	57; 3 yr	65%
Ettinger	Potassium-magnesium citrate	42/21/63 mEq	Noncategorized, recurrent	64; 3 yr	81%
Ettinger	Potassium phosphate	1.4 g	Noncategorized, recurrent	71; 3 yr	None
Ettinger	Magnesium hydroxide	650–1,300 mg	Noncategorized, recurrent	52; 3 yr	None

Table 6-3. Randomized trials in idiopathic calcium oxalate nephrolithiasis

In primary hyperparathyroidism, the filtered load of calcium is increased as a result of calcium release from bone and increased intestinal absorption mediated by $1,25(OH)_2$ vitamin D_3. An increase in the filtered calcium load overcomes the distal actions of PTH to increase tubular calcium reabsorption. In RTA, the decreased systemic pH results in increased calcium release from bone. In addition, acidosis directly inhibits distal reabsorption. Macrophages in sarcoidosis produce $1,25(OH)_2$ vitamin D_3 that leads to increased intestinal absorption. Immobilization, Paget's disease, and hyperthyroidism cause hypercalciuria by releasing calcium from bone and thereby increasing the filtered calcium load.

2. **Hypocitraturia.** Citrate combines in the tubular lumen with calcium to form a nondissociable but soluble complex. As a result, less free calcium is available to combine with oxalate. Citrate also prevents nucleation and aggregation of calcium oxalate. Chronic metabolic acidosis from any cause enhances proximal tubular citrate reabsorption and decreases citrate concentration in the urine; this is the mechanism whereby chronic diarrhea, RTA, and increased dietary protein loads result in hypocitraturia. Another important cause of hypocitraturia is hypokalemia, which increases the amount of the sodium-citrate cotransporter present in the brush-border membrane of the proximal tubule.
3. **Hyperuricosuria.** Uric acid and monosodium urate can act to decrease the solubility of calcium oxalate and calcium phosphate in urine by several mechanisms. They can act as a nidus on which calcium salts can precipitate. Uric acid also binds naturally occurring macromolecular inhibitors and attenuates their activity. Finally, the addition of increasing concentrations of sodium urate to normal human urine can induce the precipitation of calcium oxalate via a poorly understood physiologic phenomenon known as *salting out*.
4. Etiologies of **hyperoxaluria** include enteric hyperoxaluria from inflammatory bowel disease, small bowel resection, or jejuno-ileal bypass; dietary excess (e.g., spinach, Swiss chard, rhubarb); and the rare genetic disorder primary hyperoxaluria. Urinary oxalate is derived from two major sources: 80% to 90% comes from endogenous production in the liver, and the remainder is obtained from dietary oxalate or ascorbic acid. With enteric hyperoxaluria, intestinal hyperabsorption of oxalate occurs via two mechanisms. First, free fatty acids complex with calcium and limit the amount of free calcium available to complex oxalate, thereby increasing the oxalate pool available for absorption. Second, bile salts and fatty acids increase the permeability of the colon to oxalate. In addition, intestinal fluid losses result in a decreased urine volume, and intestinal bicarbonate and potassium losses result in hypocitraturia.
5. **Medullary sponge kidney** should be suspected in women with calcium stones. Studies have shown that as many as 3% to 12% of patients with calcium nephrolithiasis have this disorder. It has a prevalence of about 1 in 5,000 and affects males and females equally. The anatomic abnormality is an irregular enlargement of the medullary and inner papillary collecting ducts. The diagnosis is usually established in the fourth or fifth decade of the patient's life by an IVP that reveals radial, linear striations in the papillae or cystic collections of contrast media in ectatic collecting ducts. Patients present with stones or recurrent UTI, often associated with a distal RTA. Malformations of the terminal collecting duct may create urinary stasis that promotes crystal precipitation and attachment to the tubular epithelium.
6. In one report, **nanobacteria** were isolated from 30 of 30 calcium stones. Nanobacteria are members of the Proteobacterium family, and they grow in protein- and lipid-free environments. They are capable of nucleating carbonate apatite directly on their surfaces at physiologic pH. This finding awaits confirmation from other laboratories. Perhaps calcium-containing stones, as is the case for struvite-carbonate stones, are related to infection.

B. **Uric acid stones** represent approximately 5% of all cases of kidney stone disease in Western countries. The highest incidence has been reported from Israel and the Middle East, where as many as 75% of all stones consist solely of uric acid. This may be the result of the arid climate and reduced urinary volume. Uric acid is the major metabolic end product of purine metabolism in humans. Unlike most other mammals, humans do not express uricase, which degrades uric acid into the much more soluble allantoin. Uric acid stones are the most common radiolucent stone.
   1. **Clinical findings.** The principal determinant of uric acid crystallization is its relative insolubility at acidic pH. Uric acid is a weak organic acid with two dissociable protons: The first has a pK_a of 5.5, and the second a pK_a of 10. As a result, only the first proton can be dissociated in urine. At a pH of less than 5.5, most of it remains as an undissociated acid, where it is more likely to crystallize. As the pH increases, it dissociates into the more soluble anionic form, sodium urate. Because of the great increase in solubility that can be gained with changes in pH, uric acid stones are the only stone that can be completely dissolved with medical therapy.

      The main determinants of uric acid solubility are pH, concentration, and other cations present in the urine. Higher sodium concentration decreases, whereas increased potassium concentration increases, uric acid solubility. This may explain the complications of calcium stone formation that can occur during sodium alkali therapy but not during treatment with potassium alkali.
   2. **Signs and symptoms.** Patients with uric acid stones exhibit a lower mean urinary pH and ammonium ion excretion rate. As many as 75% of patients demonstrate a mild defect in renal ammoniagenesis in response to an acid load. Urinary buffers other than ammonia are titrated more fully than in unaffected individuals, with a resultant urine pH approximating 4.5.

      Patients with defects in ammoniagenesis, such as the elderly and those with polycystic kidney disease, are at increased risk for uric acid lithiasis. The second most important risk factor is a decreased urine volume. Hyperuricosuria is the least important risk factor and is seen in less than 25% of patients with recurrent uric acid stones.
   3. A **definitive diagnosis** is established by stone analysis. The diagnosis is suggested by the presence of a radiolucent stone, although xanthine and 2,8-dihydroxyadenosine stones can also be radiolucent, or by the presence of uric acid crystals in unusually acidic urine.

C. **Struvite-carbonate stones** are also known as infection stones and are composed of a mixture of magnesium ammonium phosphate (struvite: $MgNH_4PO_4 \bullet 6H_2O$) and carbonate apatite [$Ca_{10}(PO_4)_6CO_3$]. Ten percent to 15% percent of all stones are estimated to be struvite-carbonate stones. However, this is likely an overestimate, given that these figures are based on reports from chemical stone analyses, and a greater proportion of stones chemically analyzed are obtained from surgical specimens. It is likely that struvite-carbonate stones make up no more than 5% of stones. Their presence is also known as *stone cancer* because before more recent therapeutic advances, they were the cause of numerous operations, renal failure, and death. Struvite-carbonate stones are the most common cause of staghorn calculi, although cystine, calcium oxalate, and urate stones may occasionally cause staghorns. Struvite-carbonate becomes supersaturating in the urine only in one circumstance: infection with urea-splitting organisms that secrete urease. The most common urease-producing bacteria include *Proteus*, *Morganella*, *Providencia*, *Pseudomonas*, and *Klebsiella*. *Escherichia coli* and *Citrobacter* do not produce urease.
   1. **Risk factors.** Women with recurrent UTI and patients with spinal cord injury, other forms of neurogenic bladder, or ileal diversions of the ureter are most prone to the formation of struvite-carbonate stones. Male patients with indwelling bladder catheters and complete spinal cord transection are at highest risk.
   2. **Signs and symptoms.** Struvite stones may present in a variety of ways, including fever, hematuria, flank pain, recurrent UTI, and septicemia. They can grow to a very large size and fill the renal pelvis as a staghorn calculus, and they are radiopaque because of the presence of carbonate apatite. Rarely, if ever, do they pass spontaneously, and 25% are discovered incidentally. If untreated, they result in loss of the affected kidney in 50% of cases.
   3. **For struvite-carbonate stones to form**, the urine must be alkaline, with a pH greater than 7, and supersaturated with ammonium hydroxide. Bacterial urease hydrolyzes urea to ammonia and carbon dioxide. The ammonia then hydrolyzes spontaneously to form ammonium hydroxide, and the carbon dioxide hydrates to form carbonic acid and, subsequently, bicarbonate. At high pH, the bicarbonate loses its proton to become carbonate. UTI with a urease-producing organism is the only situation in which urinary pH, ammonium, and carbonate are elevated simultaneously. The bacteria produce supersaturation in their own immediate environment. Crystals form around clusters of bacteria, and bacteria permeate every crevice of a struvite-carbonate stone. The stone itself is an infected foreign body.

D. **Cystine stones.** Cystinuria is the result of an autosomal recessive defect in the proximal tubular and jejunal reabsorption of the dibasic amino acids cysteine, ornithine, lysine, and arginine. Excessive amounts of all these amino acids are excreted in the urine, but clinical disease is due solely to the poor urinary solubility of cystine. Cystine is a dimer of cysteine. Cystine stones make up less than 1% of all calculi in adults but may constitute as many as 5% to 8% of all stones in children. The prevalence of cystinuria is approximately 1 per 15,000 in the United States. Stones consisting entirely of cystine form only in

homozygotes. The normal adult secretes less than 19 mg of cystine per g of creatinine in 24 hours. Cystine stones are radio-opaque because of the presence of the sulfhydryl moiety of cysteine.

The solubility of cystine is approximately 250 mg per L, and increases in urinary pH cause an increase in solubility. The P K_a of cysteine is 6.5; therefore, a gradual increase in solubility occurs as the pH rises from 6.5 to 7.5. Urinary supersaturation occurs at cystine concentrations greater than 250 mg per L. If the cystine concentration can be maintained below 200 mg per L, cystine stones should not occur. Because homozygotes excrete 800 to 1,000 mg of cystine per day, at least 4 L of urine are required at a normal urinary pH to keep the cystine concentration within the soluble range.

Renal stones begin to form in the first to fourth decades. Patients tend to have bilateral obstructive staghorn calculi with associated renal failure. Characteristic hexagonal crystals may be identified, particularly in the first morning urine, which is usually acidic. Heterozygotes can form stones either with no cystine or with cystine as only a minor component, because cystine can act as a nidus for the crystallization of both calcium oxalate and calcium phosphate.

E. **Drug-related stones.** A variety of drugs can precipitate in urine including sulfonamides, triamterene, acyclovir, and the antiretroviral agent indinavir. Microscopical hematuria occurs in up to 20% of patients on indinavir. Nephrolithiasis develops in 3%, and 5% experience either dysuria or flank pain that resolves when the drug is discontinued. Reports show that patients with flank pain may have abnormal CT scans with a decrease in contrast excretion in the medullary rays.

Approximately 1 in every 2,000 stones are ephedrine stones. This can result from either abuse of over-the-counter cold formulations or the ingestion of Ma-huang. Ma-huang is prepared from the dried stems of ephedra and is rich in ephedrine, norephedrine, pseudoephedrine, and norpseudoephedrine. It is contained in a variety of health food store preparations.

III. Evaluation of the patient

A. **Calcium stones.** The first question to be addressed in the patient with calcium stones is whether the calcium stone disease is simple or complicated. Simple disease is defined as a single stone in the absence of an associated systemic disorder. Complicated calcium stone disease is present if the patient has multiple stones, evidence of the formation of new stones, enlargement of old stones, or the passage of gravel. This distinction is made based on the initial evaluation. A history should be taken, looking for a family history of stone disease, skeletal disease, inflammatory bowel disease, and UTI. Environmental risk factors are evaluated, such as fluid intake, urine volume, immobilization, diet, medications, and vitamin ingestion. A physical examination is performed. Initial laboratory evaluation includes blood chemistries, urinalysis, and a flat radiographic plate of the abdomen to assess stone burden. Stone analysis should always be carried out if the patient has saved the stone. Stone analysis is inexpensive, it is the only way to establish the diagnosis of a specific disorder, and it often helps direct therapy.

In the patient with complicated stone disease, two to three measurements of serum calcium should be performed, and, if any of these serum calcium levels is above 10 mg per dL, a PTH level should be obtained. Blood chemistries should also be evaluated. An IVP is indicated to rule out structural abnormalities that predispose to stone formation. A first morning void urine should be examined for cystine crystals. One or more 24-hour urine collections should be obtained on the patient's usual diet for calcium, citrate, uric acid, oxalate, sodium, and creatinine. Further therapeutic intervention depends on the results of these collections. Normal values for 24-hour urine collection are shown in Table 6-2.

Substance	Male (mg/24 hr)	Female (mg/24 hr)
Calcium	<300	<250
Uric acid	<800	<750
Citrate	>300	>400
Oxalate	<40	<40

Table 6-2. Normal values for 24-hour urine collection

B. The etiologies of **uric acid stones** can be subdivided into three pathophysiologic groups based on risk factors. Low urine volume contributes to uric acid stones in gastrointestinal disorders such as Crohn's disease, ulcerative colitis, diarrhea, and ileostomies, as well as with dehydration. Acidic urinary pH plays an important role in primary gout and gastrointestinal disorders. Hyperuricosuric disorders can be further divided into those with hyperuricemia (primary gout, enzyme disorders, myeloproliferative diseases, hemolytic anemia, and uricosuric drugs) and those without hyperuricemia (dietary excess).

Primary gout is an inherited disorder most likely transmitted in an autosomal dominant fashion with variable penetrance. It is associated with hyperuricemia, hyperuricosuria, and a persistently acid urine. Ten percent to 20% of affected patients have uric acid stones, and in 40% of these patients the stones precede the first attack of articular gout. Because the urine is always acidic, the risk of uric acid lithiasis varies directly with the serum and urine uric acid concentration.

Uric acid stones are typically round and smooth and are more likely to pass spontaneously than calcium oxalate stones, which are often jagged. They are also radiolucent, as are xanthine, hypoxanthine, and 2,8-dihydroadenine stones. Xanthine, hypoxanthine, and 2,8-dihydroadenine stones should be suspected if a radiolucent stone fails to dissolve with alkali therapy.

C. **Struvite-carbonate stones.** Seventy-five percent of all staghorn calculi are composed of struvite-carbonate. Struvite-carbonate stones are large and less radiopaque than calcium oxalate. As with any stone, the definitive diagnosis can only be established on stone analysis, but a diagnosis of struvite-carbonite stones should be strongly suspected in any patient with an infected alkaline urine. In the presence of an infected acid urine and a staghorn calculus, one should consider the possibility that the two are unrelated and that the calculus may be either calcium oxalate or uric acid. Stone analysis and culture should be carried out in all patients after either percutaneous nephrolithotomy or extracorporeal shock wave lithotripsy treatment. Some patients, especially ambulatory men, have stones that contain a mixture of struvite-carbonate and calcium oxalate. These patients should always undergo a complete metabolic evaluation because virtually all of them have an underlying metabolic defect, and they are probably at higher risk for stone recurrence, even with complete removal of the stone.

Proteus mirabilis accounts for more than one-half of all urease-positive infections. Stone culture, when possible, is important, because culture of the urine is not always completely representative of the organisms present in the stone. If no organisms are cultured, then the possibility of infection with *Ureaplasma urealyticum*, which is often difficult to culture, should be considered.

D. **Cystine stones.** The presence of characteristic hexagonal cystine crystals in a first morning void urine is diagnostic of cystinuria, although this is a very infrequent finding. The simplest and most rapid screening test for cystinuria is the sodium-nitroprusside test, which has a lower limit of detection of 75 mg per g of creatinine. The nitroprusside complex binds to sulfide groups and may yield a false positive in patients taking sulfur-containing drugs. Phosphotungstic acid has also been used in an alternative screening test. Patients with a positive screening test should undergo 24-hour urine cystine quantitation.

Cystine stones are usually less radiodense on radiography than either calcium or struvite-carbonate stones. They typically have a homogeneous structure without striation.

IV. Treatment

A. Treatment of the patient with **calcium stones** depends on whether the patient has simple or complicated disease. The patient with a single isolated stone and no associated systemic disease can be managed with nonspecific forms of treatment alone, including increased fluid intake and a normal calcium diet. The patient with complicated disease should be managed with both nonspecific and specific forms of therapy. The specific form of treatment varies depending on the assessment of risk factors derived from the 24-hour urine results.
   1. **Nonspecific therapeutic options** include manipulation of fluid intake and diet. Increasing fluid intake is the cheapest way to reduce urinary supersaturation with calcium oxalate. In a prospective randomized trial of 199 first-time stone formers followed for a 5-year period, it was shown that the risk of recurrent

stone formation could be reduced from 27% to 12% by raising the urinary volume to more than 2 L per day with water ingestion.

Before 1993, the majority of patients with calcium stones were advised to follow a diet low in calcium. However, more recent studies in both men and women suggest that a low-calcium diet may actually increase the risk of calcium stone formation. The postulated mechanism is that ingested calcium may aid in complexing dietary oxalate and that a reduction in dietary calcium may result in a reciprocal increase in the intestinal absorption of oxalate. This may result in an increase in urinary supersaturation of calcium oxalate. In these studies, however, the ingestion of a diet high in calcium was also associated with an increased intake of magnesium, potassium, and phosphate that may have acted as a confounding variable in reducing the stone risk. Based on these findings, the safest approach may be to consume a diet that is normal in calcium. The question of whether supplemental calcium increases the risk of nephrolithiasis is a difficult one. One report has suggested that any use of supplemental calcium raises the relative risk of stone disease approximately 20%. The risk did not increase with increasing dose.

2. **Specific forms of treatment** are directed at the results of the 24-hour urine samples. Therapy should be centered on agents that were shown to be effective in randomized, controlled clinical trials, the results of which are shown in Table 6-3. This is important because of the "stone clinic effect." After patients present for evaluation of nephrolithiasis, the subsequent period is often associated with a reduced risk for new stone formation (the stone clinic effect). This is due to at least two factors: (a) regression to the mean and (b) increased adherence to nonspecific forms of treatment. Agents that have been shown to be effective in randomized, placebo-controlled trials are thiazides, allopurinol, potassium citrate, and potassium magnesium citrate.
   a. **Hypercalciuria** should be managed initially with thiazide diuretics. Thiazides act directly to increase distal calcium reabsorption and indirectly to increase calcium reabsorption in the proximal tubule by inducing a state of mild volume contraction. In order for thiazides to remain maximally effective, volume contraction must be maintained and hypokalemia avoided. Thiazides generally produce a reduction in urinary calcium of approximately 50%. If they are ineffective, noncompliance with the low-sodium diet is usually the reason. This can be monitored with a 24-hour urine test for sodium. Amiloride acts independently of thiazides at a more distal site and can be added if required. Two randomized, controlled trials in recurrent stone formers have shown a reduction in the risk for new stone formation with thiazides. Although all of the patients in these trials were calcium stone formers, the minority of them were actually hypercalciuric. This suggests either that thiazides have additional effects beyond reducing urinary calcium or that reduction of urinary calcium, even in the absence of hypercalciuria, may reduce the risk for recurrent stone formation.

      In patients that cannot tolerate thiazides, other potential therapies include sodium cellulose phosphate and orthophosphate. However, these are often poorly tolerated. In addition, randomized, controlled trials of potassium acid phosphate and magnesium hydroxide showed no benefit when compared with placebo. Slow-release neutral phosphate appears to be better tolerated and may become the second-line agent of choice.
   b. **Hypocitraturia** is managed with either potassium citrate or potassium-magnesium citrate. Each of these agents was shown to reduce the relative risk of stone formation in controlled trials. Potassium-magnesium citrate may be especially beneficial in patients receiving thiazides, because it replaces potassium and magnesium losses induced by the diuretic. Patients with struvite-carbonate stones should not be given citrate, because it may increase deposition of magnesium ammonium phosphate and carbonate apatite. Citrate may also increase the intestinal absorption of aluminum in patients with renal failure.
   c. **Hyperuricosuria** is probably best managed with allopurinol. Whether alkalinization is of benefit is unclear, because heterogeneous nucleation and the salting out phenomenon can both be initiated by sodium urate. Citrate therapy might reduce the precipitation of calcium oxalate in this setting, but this remains to be proven.
   d. **Hyperoxaluria** should be managed with a low-oxalate diet. Enteric hyperoxaluria should be initially treated with a low-fat, low-oxalate diet. If this is unsuccessful, calcium carbonate, cholestyramine, or both can be added.

B. Therapy for **uric acid stones** is directed at the three major risk factors for uric acid lithiasis (decreased urine pH, decreased urine volume, hyperuricosuria). First, urine volume should be increased to 3 or more L per day. Second, the urine should be alkalinized to a pH of 6.5 with potassium citrate. The starting dose is 30 mEq b.i.d., to be titrated upward according to urinary pH. More than 80 to 100 mEq is rarely required. Sodium alkali therapy should be avoided, because it may result in hypercalciuria. In one study of 12 patients, alkali therapy resulted in the dissolution of stones within a period of 3 weeks to 5 months. Increases in urinary pH above 6.5 should be avoided. If the first morning void urine is still acidic, acetazolamide (250 mg) can be added before bedtime.

   If hyperuricosuria is present, purine consumption in the diet should be decreased. Allopurinol should only be used in patients whose stones recur despite fluid and alkali administration, or when uric acid excretion is above 1,000 mg per day. When allopurinol is administered for massive uric acid overproduction, adequate hydration must be maintained to avoid the precipitation of xanthine crystals.

C. **Struvite-carbonate stones.** Open surgical removal was formerly the treatment of choice for staghorn struvite calculi. However, the recurrence rate of stones 6 years after surgery is 27%, and UTI persists in 41%. A second pyelolithotomy carries substantial morbidity. More recently, the combination of percutaneous nephrolithotomy and extracorporeal shock wave lithotripsy has decreased morbidity substantially and is now the treatment modality of choice. Total elimination of the stone remains a challenge because of the inability to remove small particles that contain bacteria and can act as nidi for further crystal growth. After complete removal, chronic culture-specific antimicrobial agents are indicated as prophylaxis against recurrent infection. If a struvite-carbonate stone is not removed in its entirety, the patient will continue to have recurrent UTIs and the stone will eventually regrow. Stone growth in the majority of patients with residual fragments progresses despite antibiotic treatment. Stone growth can be slowed by reducing the bacterial population, but the chance of cure with antibiotics alone is remote. Urease inhibitors, such as acetohydroxamic acid, can reduce urinary saturation of struvite-carbonate and prevent stone growth and may, on occasion, cause dissolution of existing stones. However, these agents are associated with a variety of severe complications, including hemolytic anemia, thrombophlebitis, and nonspecific neurologic symptoms (e.g., disorientation, tremor, headache).

D. **Cystine stones.** Water is the hallmark of the treatment of cystinuria. The required dose should be based on the patient's cystine excretion. The goal is to reduce the cystine concentration in the urine to below 250 mg per L. In the usual patient this requires a urine output of at least 4 L per day. Two 8-oz glasses of water should be ingested every 4 hours. When patients void during the night, they should also drink two glasses of water. The urine can be periodically examined for cystine crystals to assess the adequacy of fluid intake.

   Alkalinization of the urine may be of some benefit. The dissociation constant of cystine is 6.5. As a result, a pH of 7.5 is required for 90% of cystine to be in the ionized form. At this pH, the risk of calcium phosphate stones is increased. Therefore, alkalinization should be viewed as an ancillary measure. Potassium citrate is the agent of choice and is preferable to sodium-containing alkali because volume expansion increases cystine excretion.

   If these measures are ineffective, then either D-penicillamine, alpha-mercaptopropionylglycine, or captopril can be tried. These compounds are thiols that bind preferentially to cysteine, forming compounds that are more soluble than cysteine-cysteine dimers (cystine). Alpha-mercaptopropionylglycine causes fewer complications than D-penicillamine. D-Penicillamine may also bind pyridoxine, and thus pyridoxine (50 mg per day) should be administered to prevent deficiency. Zinc supplements can usually prevent the anosmia and loss of taste that often occurs with D-penicillamine. Captopril has fewer side effects than either D-penicillamine or alpha-mercaptopropionylglycine, but it may also be less effective in reducing urinary cystine.

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Chapter 7 The Patient with Urinary Tract Infection

Jay Redington and L. Barth Reller

Definitions
Risk factors and pathogenesis
Clinical setting
Clinical features
Laboratory diagnosis
Treatment of UTI

Urinary tract infections (UTIs) are some of the most common infections experienced by humans, exceeded in frequency among ambulatory patients only by respiratory and gastrointestinal infections. Indeed, bacterial infections of the urinary tract are the most common cause of both community-acquired and nosocomial infections for patients admitted to hospitals in the United States. The prognosis and management of UTIs, however, depend on the site of infection and any predisposing factors.

I. Definitions. Some definitions are necessary, because infection of the urinary tract may result from microbial invasion of any of the tissues extending from the urethral orifice to the renal cortex. Although the infection and resultant symptoms may be localized at one site, the presence of bacteria in the urine (bacteriuria) places the entire urinary system at risk of invasion by bacteria.

A. **Significant bacteriuria** is defined as the presence of 100,000 or more colony-forming units (CFU) of bacteria per mL of urine, although smaller colony counts can be of diagnostic importance.
B. **Anatomic location.** The first useful distinction is between upper (kidney) and lower (bladder, prostate, and urethra) UTIs. Infections confined to the bladder (cystitis), the urethra (urethritis), and the prostate (prostatitis) commonly cause dysuria, frequency, and urgency. Pyelonephritis is nonspecific inflammation of the renal parenchyma; acute bacterial pyelonephritis is a clinical syndrome characterized by chills and fever, flank pain, and constitutional symptoms caused by bacterial invasion of the kidney. Chronic pyelonephritis has a histopathology that is similar to tubulointerstitial nephritis, a renal disease caused by a variety of disorders, such as chronic obstructive uropathy, vesical ureteral reflux (refluxnephropathy), renal medullary disease, drugs and toxins, and possibly (chronic or recurring renal bacteriuria.
C. **Recurrence of UTI** is the result of either relapse or reinfection; making this distinction is clinically important. Reinfection is a recurring infection due to a different microorganism, which is usually drug-susceptible. Most recurring episodes of cystourethritis are due to reinfection. Relapse is a return of infection due to the same microorganism, which often is drug-resistant. Most relapses occur after treatment of acute pyelonephritis or prostatitis. Finally, asymptomatic bacteriuria is an important clue to the presence of parenchymal infection somewhere in the urinary tract; how ever, the importance of the infection and the need for treatment depend :on the age, sex, and underlying condition of the patient.
D. **Complicated and uncomplicated UTIs.** For the clinician, another important distinction is made between uncomplicated and complicated infections. An uncomplicated infection is an episode of cystourethritis following bacterial colonization of the urethral and bladder mucosae. This type of infection is considered *uncomplicated* because sequelae are rare and exclusively due to the morbidity associated with reinfections in a subset of women. A subset of patients with pyelonephritis (acute uncomplicated pyelonephritis), namely, young women, who often respond well to therapy, may also have a low incidence of sequelae. In contrast, complicated infections include those involving parenchyma (pyelonephritis or prostatitis) and frequently occur in the setting of obstructive uropathy or after instrumentation. Episodes may be refractory to therapy, often resulting in relapses and occasionally leading to significant sequelae such as sepsis, metastatic abscesses, and, rarely, acute renal failure.
E. Several authors have proposed a **clinical classification** for the practicing clinician (1).
    1. **Asymptomatic bacteriuria**
    2. **Acute uncomplicated cystitis in women**
    3. **Recurrent infections in women**
    4. **Acute uncomplicated pyelonephritis in women**
    5. **Complicated UTIs in both sexes**
    6. **Catheter-associated UTIs**

II. Risk factors and pathogenesis Early recognition and possible prevention depend on an understanding of the pathogenesis and epidemiology of UTIs. Figure 7-1 shows the major risk periods of life for symptomatic UTIs, and the increasing prevalence of asymptomatic bacteriuria that accompanies aging is apparent. Much has been learned about the risk factors for UTIs. Associations have been established between UTI and age, pregnancy, sexual intercourse, use of a diaphragm and a spermicide, delayed postcoital micturition, menopause, and a history of recent UTI. Factors that do not seem to increase the risk include diet, use of tampons, clothing, and personal hygiene, including methods of wiping after defecation and bathing practices. Studies on pathogenesis have elucidated specific interactions between the host and microbes that are causally related to bacteriuria. Bacteria in the enteric flora periodically gain access to the genitourinary tract. How such bacteria actually migrate from the gastrointestinal tract to the periurethra is unknown; close proximity of the anus in women is a likely factor. Subsequent bacterial colonization of uroepithelial cells is the biological phenomenon that sets the stage for persistent bacteriuria. Colonization of the periurethra often precedes the onset of bladder bacteriuria. P-fimbriated strains of *Escherichia coli* adhere to uroepithelial cells, in which glycolipids function as receptors in women who secrete blood group antigens. Opposing colonization are several host factors, most notably acid pH, normal vaginal flora, and type-specific cervicovaginal antibodies.

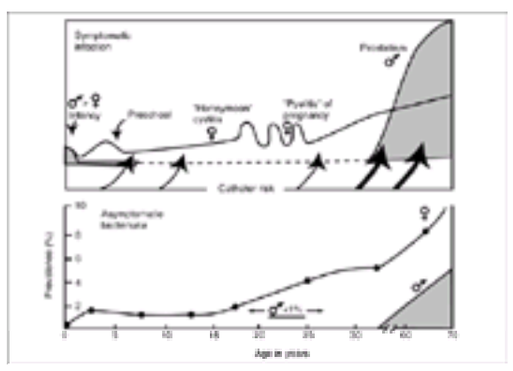

Figure 7-1. Frequency distribution of symptomatic urinary tract infections and prevalence of asymptomatic bacteriuria by age and sex (male, *shaded area* female, *line*). (Modified from Jawetz's original concept. From Kunin CM. *Detection, prevention and management of urinary tract infections*, 4th ed. Philadelphia: Lea & Febiger, 1987. Reprinted with permission.)

After periurethral colonization, uropathogens gain access to the bladder via the urethra, to the kidneys via the ureters, and to the prostate via the ejaculatory ducts. The urethra and ureterovesical junction are mechanical barriers that prevent ascension. Aside from instrumentation and mechanical obstruction, however, factors promoting ascent of bacteria are not as well understood. In the bladder, organisms multiply, colonize the bladder mucosa, and invade the mucosal surface. Although urine adequately supports the growth of most uropathogens, the bladder has several mechanisms that prevent bacteriuria: (a) A mucopolysaccharide (urine slime) layer covers the bladder epithelium and prevents colonization; (b) Tamm-Horsfall protein, which is a component of uromucoid, adheres to P fimbriae and prevents colonization; and (c) urine flow and bladder contraction serve to prevent stasis and colonization. Bladder bacteriuria sets the stage for subsequent migration to the kidneys, where organisms such as P-fimbriated *E. coli* adhere to renal tubular cells. In fact, outside the setting of obstructive nephropathy, this strain of *E. coli* is the most common cause of pyelonephritis. With obstruction, however, bacterial adherence is ostensibly unimportant. Other host factors that prevent a renal infection are a high osmolality, high ammonium concentration, phagocytes, and increased urine flow rate.

III. Clinical setting

A. **Asymptomatic bacteriuria** is especially common in women as evidenced by a minimum prevalence of 2% to 4% in young and 10% in elderly women. The cumulative prevalence of asymptomatic bacteriuria in women increases about 1% per decade throughout life. Of note, this phenomenon has been observed in different ethnic groups and geographic locations. In contrast to women, the occurrence of asymptomatic bacteriuria in men is rare until after the age of 60 years, at which time the prevalence increases per decade and often approaches the rate in elderly women. For example, in noncatheterized, institutionalized elderly men, the prevalence of bacteriuria exceeds 20%. Prostatic hypertrophy and increased likelihood of instrumentation are thought to account for the bacteriuria of older men. Moreover, differences between men and women in the rates of bacteriuria have been attributed to the shorter female urethra and its proximity to the vaginal and rectal mucosae and their abunant microbial flora.
B. **Symptomatic UTIs** occur in all age groups. Among newborns and infants, boys are affected more often than girls. When the urinary tract is the source of neonatal sepsis, serious underlying congenital anomalies are frequently present. During childhood, persistent bacteriuria, with or without repeated symptomatic episodes, occurs in a small group (less than 2%) of school-aged girls. Such girls, and also school-aged boys with bacteriuria, should have a urologic evaluation to detect correctable structural abnormalities when UTIs are documented. Sexually active women have a markedly increased risk of episodes of cystitis. In the absence of prostatitis, bacteriuria and symptomatic UTIs are unusual in men. More recently, uropathogenic strains of *E. coli* have been recognized as causes of cystitis in young men at risk because of homosexuality and anal intercourse, lack of circumcision, or having a partner with vaginal colonization with such P-fimbriated *E. coli*. At any age, both sexes may develop symptomatic infections in the presence of risk factors that alter urinary flow.
    1. **Obstruction to urine flow**
        a. **Congenital anomalies**
        b. **Renal calculi**
        c. **Ureteral occlusion (partial or total)**
    2. **Vesicoureteral reflux**
    3. **Residual urine in bladder**
        a. **Neurogenic bladder**
        b. **Urethral stricture**
        c. **Prostatic hypertrophy**
    4. **Instrumentation of urinary tract**
        a. **Indwelling urinary catheter**
        b. **Catheterization**
        c. **Urethral dilation**
        d. **Cystoscopy**

IV. Clinical features

A. **Acute urethral syndrome.** The cardinal symptoms of frequency and dysuria occur in more than 90% of ambulatory patients with acute genitourinary tract infections. One-third to one-half of all patients with frequency and dysuria, however, do not have significant bacteriuria, although most have pyuria. These patients have acute urethral syndrome, which can mimic both bladder and renal infections. Vaginitis, urethritis, and prostatitis are common causes of the acute urethral syndrome. Although certain signs and symptoms help to differentiate these clinical entities, a classic UTI can be definitively diagnosed only by quantitative cultures of urine.
    1. **Vaginitis.** Approximately 20% of women in the United States have an episode of dysuria each year, and one-half of these seek medical care. The presence of an abnormal vaginal discharge (leukorrhea) and irritation makes vaginitis the likely cause of dysuria, unless a concomitant UTI can be confirmed by culture. *Candida albicans*, the most common specific cause of vaginitis, can be demonstrated readily by culture or by finding yeast cells in a Gram-stained smear of vaginal secretions or in a saline preparation with potassium hydroxide added. Trichomoniasis can be documented with a saline preparation that shows the motile protozoa of *Trichomonas vaginalis*. Nonspecific vaginitis most often is associated with *Gardnerella vaginalis*. A clue to this diagnosis is the presence of many small gram-negative bacilli that adhere to vaginal epithelial cells.
    2. **Urethritis.** Acute urinary frequency, dysuria, and pyuria in the absence of vaginal symptoms favor a diagnosis of urethritis or UTI rather than vaginitis. *Chlamydia trachomatis* is a common cause of the acute urethral syndrome in women, as well as of nonspecific urethritis in men. *Neisseria gonorrhoeae* is also a widespread cause of urethritis and dysuria. The diagnosis and treatment of gonorrhea are now well standardized. Low colony count (100 to 1,000 CFU) infections with coliforms are now a recognized cause of urethritis in sympomatic young women with pyuria. Herpes simplex virus, usually type 2, is another sexually transmitted agent that can cause severe dysuria through ulcerations in close proximity to the urethral orifice. The diagnosis of herpes progenitalis can be confirmed by finding giant multinucleated transformed cells in epidermal scrapings stained with Wright's stain (Tzanck smear), by isolating the virus in tissue culture, or by direct fluorescent antibody test.
    3. **Prostatitis.** Prostatitis is a common affliction in men that causes dysuria and urinary frequency in middle-aged and younger men more frequently than UTIs do. Prostate syndromes have classically been divided into four clinical entities: (a) acute bacterial prostatitis, (b) chronic bacterial prostatitis, (c) nonbacterial prostatitis, and (d) prostatodynia.
        a. **Acute bacterial prostatitis** is easily distinguished from the other prostatitis syndromes by its acute characteristics. The patient often appears acutely ill, with the sudden onset of chills and fever, urinary frequency and urgency, dysuria, perineal and low back pain, and constitutional symptoms. Rectal examination should not be performed because of the risk of precipitating sepsis, but it may disclose an exquisitely tender, hot, and swollen prostate gland. Microscopical examination of the urine usually displays numerous white blood cells. Urine culture is usually positive for enteric gram-negative bacteria (especially E. coli), and gram-positive bacteria (staphylococci and enterococci) are less frequently isolated.
        b. **Chronic bacterial prostatitis.** A hallmark of chronic prostatitis is relapsing UTIs. Urinary frequency, dysuria, nocturia, and low back and perineal pain are the usual symptoms, although patients may have a minimum of symptoms between UTIs. The patient is often afebrile, does not appear acutely ill, and may have an unremarkable prostate examination. This syndrome is distinguished from other forms of chronic prostatitis by displaying an initial negative midstream urine examination and culture, but after prostate massage, the urine displays a positive microscopical examination or white blood cells, and culture grows a uropathogen (see section V). Nonbacterial prostatitis is the most common form of chronic prostatitis. It mimics chronic of nonbacterial prostatitis bacterial prostatitis clinically and displays inflammatory cells on post–prostate massage specimens. However, bacteriologic cultures of urine and prostatic secretions are sterile. The etiology is unknown, but some evidence exists for an infectious etiology involving organisms that are difficult to culture.
        c. **Prostatodynia** has also been referred to as chronic noninflamatory prostatitis. Clinically, it presents with symptoms similar to other forms of chronic prostatitis. It is distinguished by the absence of inflammatory cells or uropathogens from all specimens.
B. **UTIs.** Despite the mimicking syndromes, a presumptive diagnosis of infections of the urinary tract can be established economically by analyzing urine in patients with characteristic, albeit nonspecific, signs and symptoms. Acute uncomplicated UTIs occur mainly in women of childbearing age. The presenting features are only suggestive of the site of infection. Patients with bacterial cystourethritis, as distinct from urethritis caused by a sexually transmitted disease (STD) pathogen, will have had prior episodes and experienced symptoms for less than 1 week, and will experience suprapubic pain.

V. Laboratory diagnosis

A. **Urine specimens for culture**
    1. **Indications.** The diagnosis of UTI, from simple cystitis to complicated pyelonephritis with sepsis, can be established with absolute certainty only by quantitative cultures of urine. The major indications for urine cultures are
        a. **Patients with symptoms or signs of UTIs**
        b. **Follow-up of recently treated UTI**
        c. **Removal of indwelling urinary catheter**
        d. **Screening for asymptomatic bacteriuria during pregnancy**
        e. **Patients with obstructive uropathy and stasis, before instrumentation**
    2. When universally applied, the first two indications may not be the most cost effective approach to diagnosing UTIs in nonpregnant, young-adult women. These individuals present with dysuria, urgency, and pyuria due to an uncomplicated episode of cystourethritis, with organisms usually susceptible to a variety of antimicrobial agents, or due to an STD pathogen such as gonococcus or chlamydia. Moreover, because the beneficial outcome of therapy is to minimize morbidity rather than prevent life-threatening complications, laboratory costs and use of resources can be minimized if pretreatment cultures are not ordered in this clinical setting. Additionally, posttreatment cultures also are unnecessary for patients with uncomplicated infections if symptoms completely resolve.
    3. **Methods.** Urine specimens must be cultured promptly within 2 hours or be preserved by refrigeration or a suitable chemical additive (e.g ., boric acid sodium formate preservative). Acceptable methods of collection are
        a. **Midstream urine voided into a sterile container after careful washing (water or saline) of external genitalia (any soap must be rinsed away).**

b. **Urine obtained by single catheterization or suprapubic needle aspiration of the bladder.**
c. **Sterile needle aspiration of urine from the tube of a closed catheter drainage system (do not disconnect tubing to get specimen).**

Not acceptable, because of constant contamination and the impossibility of quantitative counts, are tips from indwelling urinary catheters and randomly obtained urine without adequate preparation of the patient. The clean-voided, midstream technique of collection is preferred whenever possible to avoid the risk of introducing infection at the time of catheterization, a hazard that is greater in elderly patients confined to bed, in men with condom catheters, and in diabetic patients with dysfunctional bladders. Because contamination is exceedingly rare in circumcised men, a clean-catch, midstream specimen is unnecessary in such patients. Occasionally, suprapubic aspiration of the bladder is necessary to verify infection. This technique has been most helpful in obtaining specimens from possibly septic infants and from adults in whom repeated clean-voided specimens have yielded equivocal colony counts on culture.

The usual microbial pathogens isolated from patients with UTIs are listed in Table 7-1. Results of cultures highly depend, however, on the clinical setting in which bacteriuria occurs. For example, *E. coli* is found in the urine of 80% to 90% of patients with acute uncomplicated cystitis and acute uncomplicated pyelonephritis. Many patients with staghorn calculi of the kidneys harbor urea-splitting *Proteus* organisms in their urine. *Klebsiella, Pseudomonas aeruginosa, and Entero bacter* infections are commonly acquired in the hospital. The presence of *Staphylococcus aureus* in the urine most often is a clue to concomitant staphylococcal bacteremia, unless an underlying risk factor exists. Microorganisms in young men are similar to the organisms that cause uncomplicated infections in women. Enterococci and coagulase-negative staphylococci are more common in elderly men, most likely representing recent instrumentation of catheterization. *C. albicans* is rarely encountered, except in patients with indwelling catheters, nosocomial UTIs, or relapsing infections after multiple courses of antibiotic therapy. Although the likely microorganism and usual susceptibility patterns are sufficient to guide initial empiric therapy of uncomplicated cystitis, adequate treatment of acute bacterial pyelonephritis and complicated UTIs necessitates precise therapy based on isolation of the causative bacterium and standardized antimicrobial susceptibility testing by the disc-diffusion or the broth- or agar-dilution methods.

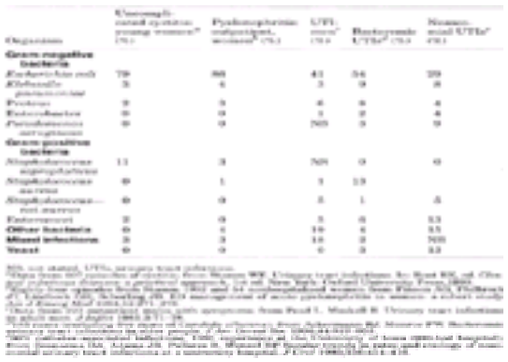

Table 7-1. Microbial pathogens of kidney and bladder

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B. **Interpretation of urine cultures.** Organisms residing in the distal urethra and on pubic hairs contaminate voided, clean-catch specimens. This bacterial contamination must be distinguished from “true infection” or “significant bacteriuria” in urine cultures. The use of quantitative bacteriology makes this distinction. Because quantitation of bacteriuria is so important clinically, methods for culture of urine must enable the number of CFU of a potential pathogen per mL of urine to be assessed. The standard procedure involves use of calibrated bacteriologic loops that deliver a known volume of urine to the surface of agar plates. Proper plating techniques achieve isolated colonies that can be enumerated accurately. A satisfactory alternative for the diagnosis of uncomplicated UTIs is the dipslide method, which is particularly well suited to quantitative urine cultures in smaller clinics. Rapid methods based on filtration and colorimetry, bioluminescence, growth kinetics, and biochemical reactions are being used more widely to screen urine specimens for the presence of bacteria. Their sensitivities are in the range of 10^4 to 10^5 CFU per mL. The simplest is the paper-strip test for detection of leukocyte esterase and nitrite in first morning urine specimens. However, these methods are not a substitute for standard cultures in symptomatic patients.

1. **Colony counts.** A basic guide to the interpretation of quantitative cultures of urine is shown in Figure 7-2. Colony counts greater than 10^5 CFU per mL in properly collected and transported specimens usually indicate infection. Colony counts of 10^3 or fewer CFU per mL from untreated patients are uncommon with true UTIs, except in symptomatic young women with pyuria and urethritis, in whom colony counts of *E. coli* as low as 10^3 may be interpretable if the urine was obtained by single catheterization. Intermediate counts, especially with mixed flora, usually imply poor collection or delayed transport and culture. Brisk diuresis may transiently reduce an otherwise high colony count.

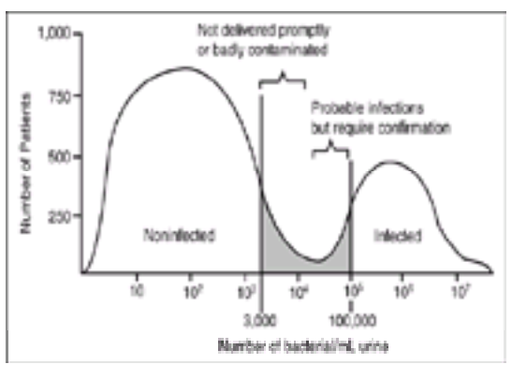

Figure 7-2. Results of quantitative bacterial counts from cultures of urine specimens. (From Brumfitt W, Percival A. Pathogenesis and laboratory diagnosis of nontuberculous urinary tract infection: a review. *J Clin Pathol* 1964;17:482. Reprinted with permission.)

2. **Suprapubic needle aspiration.** Any growth from urine obtained by suprapubic needle aspiration may be important. Use of a 0.01-mL quantitative loop for culturing aspirated urine permits detection of as few as 100 CFU per mL. Two or more colonies (less than or equal to 200 CFU per mL) of the same microorganism ensure the purity of growth from such specimens and permit standardized antimicrobial susceptibility testing. Similar criteria should be used for patients who are receiving antimicrobials at the time of culture. Except in unusual circumstances, the isolation of diphtheroids, alpha-hemolytic streptococci, and lactobacilli indicates contamination of the urine specimen with vaginal or periurethral flora.
3. **Prostatic secretions.** In men, the distinction between a urinary source and prostatic focus of infection must be made. The procedure for obtaining voided urine and expressed prostatic secretions in partitioned segments that enable proper interpretation is diagrammed in Figure 7-3. Leukocytes (greater than 10 to 15 white blood cells per high-power field) and lipid-laden macrophages are seldom observed in expressed prostatic secretion of healthy males and signify prostatic inflammation. Therefore, a prostatic focus of infection should be considered when there is a significant step-up of pyuria or colony counts in the prostate specimens. A UTI with a prostatic origin is indicated by colony counts of 10^5 or more CFU per mL of the same microorganism in all four specimens. Both urologists and primary care physicians are underusing this procedure. In one study, a two-step procedure involving microscopical examination and culture of pre–and post–prostate massage urine specimens compared favorably to this four-step procedure. This simplified approach was able to arrive at a similar diagnosis in 91% of patients. Further trials are needed to valuate this approach, which may improve physician use.

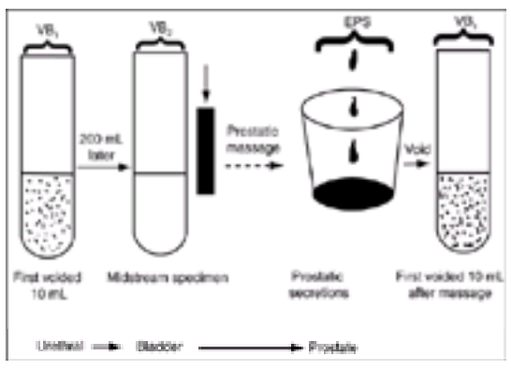

Figure 7-3. Localization of infection with segmented cultures of the lower urinary tract in men. VB_1 is the first 10 mL of voided urine, and VB_2 is the midstream specimen of urine obtained before prostatic massage. Subsequently, the expressed prostatic secretions (EPS) are collected before the final voided urine specimen (VB_3). When the bacterial colony counts in the urethral culture exceed by tenfold or more those of the midstream and prostatic cultures, the urethra is the source of the infection. The diagnosis is bacterial prostatitis if the quantitative counts of the prostatic specimens exceed those of the urethral and midstream samples. (From Meares EM, Stamey TA. Bacteriologic localization patterns in bacterial prostatitis and urethritis. *Invest Urol* 1968;5:492. Reprinted with permission.)

C. **Microscopical examination of urine.** Procedures for the microscopical examination of urine are poorly standardized; nonetheless, visualization of bacteria leukocytes and epithelial cells in urine can provide some useful information and enable the clinician to make a presumptive diagnosis of UTI. The advantages of microscopical analysis are immediate availability and low cost. The disadvantages, depending on the method, are lack of sensitivity, specificity, or both. Only properly collected and processed specimens for quantitative urine cultures can provide definitive diagnosis. The microscopical examination can be done on either unspun urine or the centrifuged sediment. A critical comparison of these two techniques is not available. The presence of squamous epithelial cells and mixed bacterial flora indicates contamination and the need for a repeat specimen.
   1. **Unspun urine.** When fresh, unspun urine from patients with significant bacteriuria (greater than 10^5 CFU per mL) is examined microscopically (×1,000), 90% of specimens show one or more bacteria, and 75% of specimens show one or more white blood cells per oil-immersion field. The best assessment of pyuria is the finding of approximately 10 white blood cells per mm^3 of unspun urine examined in a counting chamber.
   2. **Centrifuged sediment.** After 10 mL of urine is centrifuged in a standard 15-mL conical tube for 5 minutes at 2,500 revolutions per minute in a clinical centrifuge, three or four drops of the sediment are examined under a coverslip at high power (×400) in diminished light. Patients with significant bacteriuria almost always show bacilli in the urinary sediment, whereas only approximately 10% of patients with fewer than 10^5 CFU per mL show bacteria. Approximately 60% to 85% of patients with significant bacteriuria have ten or more white blood cells per high-power field in the sediment of midstream voided urine; however, approximately 25% of patients with negative urine cultures also have pyuria (ten or more white blood cells per high-power field), and only approximately 40% of patients with pyuria have 105 or more bacteria per mL of urine by quantitative culture. The principal pitfall is false-positive pyuria owing to leukocytes from a contaminating vaginal discharge.
   3. **Gram's stain.** A simple Gram-stained smear of unspun urine or spun sediment can enhance the specificity of the test, because morphology and stain characteristics aid in identifying the likely pathogen and in targeting empiric therapy.
   4. **Pyuria.** Although the presence of pyuria in a midstream specimen has low predictive value for significant bacteriuria, pyuria is a sensitive indicator of inflammation. Thus, pyuria may be more accurate than bacteriuria in distinguishing a “true infection” from contamination: 95% of patients with pyuria have a genitourinary tract infection; however, pyuria cannot distinguish a bacterial UTI from acute urethral syndrome. In addition to a UTI, any of the causes of acute urethral syndrome (see section **IV.A**) can result in pyuria. For example, tuberculosis is a cause of pyuria with negative routine urine cultures, although mycobacterial cultures are positive in 90% of instances. Analgesic nephropathy, interstitial nephritis, perinephric abscess, renal cortical abscess, disseminated fungal infection, and appendicitis may also result in pyuria.

D. **Biochemical tests for bacteriuria.** Two metabolic capabilities shared by most bacterial pathogens of the urinary tract are use of glucose and reduction of nitrate to nitrite; these are properties of all Enterobacteriaceae. Because small amounts of glucose and nitrate are normally present in urine, the presence of significant numbers of bacteria in urine results in absence of glucose and presence of nitrite. Dipstick devices are commercially available for both types of testing. Studies with nitrite-indicator strips show that 85% of women and children with culture-confirmed significant bacteriuria show positive results if three consecutive morning urine specimens are tested. A morning urine specimen is preferred for the nitrite test, because most bacteria take 4 to 6 hours to convert nitrate to nitrite. A negative nitrite test may be observed in patients taking diuretics or with organisms that do not produce nitrate reductase (*Staphylococcus* species, *Enterococcus* species, and *Pseudomonas aeruginosa*). The sensitivity of the glucose-use test is about 90% to 95% in patients without diabetes mellitus. Both biochemical tests have fewer than 5% false-positive results. Therefore, these biochemical tests can be used by patients or parents, after proper instruction, to determine when quantitative cultures are needed in the management of recurrent episodes of UTI. Spectrum bias in the use of dipsticks must be avoided. They should only be used for patients with symptoms suggestive of UTI (i.e., high pretest probability of UTI), and not for asymptomatic screening as in pregnancy.

E. **Localization of the site of infection.** The site of infection in the urinary tract has great therapeutic and prognostic importance. Upper UTI (pyelonephritis) indicates a much greater likelihood of underlying uropathy (e.g., congenital anomalies, renal stones, ureteral occlusion, vesicoureteral reflux, neurogenic bladder, or prostatic hypertrophy) or previous instrumenation (see section **III.B**). Relapses with the same, often multiple-antibiotic-resistant bacteria are common with pyelonephritis or chronic bacterial prostatitis. Treatment is long (minimum, 10 to 14 days) and may be arduous. On the other hand, cystitis rarely is complicated and treatment can be short (single-dose or 3-day) and usually is easy. No ready way to distinguish between upper and lower UTIs by simple laboratory tests exists. The difficulty in making this distinction reliably on clinical grounds alone has been discussed (see section **IV.B**). Older, indirect methods (e.g., serum antibodies, urine concentration test, and urinary beta-glucuronidase activity) areneither sensitive nor specific. Direct methods for localization (e.g., ureteral catheterization, renal biopsy, and the bladder washout technique) are hazardous, expensive, or both. Eradication of bacteriuria with single-dose or short-course (3-day) therapy in symptomatic patients with uncomplicated disease is a practical method for presumptive localization of infection to the ladder or urethra.

F. **Radiography and other diagnostic procedures: indications.** The principal role of radiographic and urologic studies for patients with UTIs is to detect vesicoureteral reflux, renal calculi, and potentially correctable lesions that obstruct urine flow and cause stasis.

Uncomplicated reinfections (cystitis and urethritis) in women that respond to short-course antimicrobial therapy are not an indication for radiographic and cystoscopic investigation of the urinary tract. Radiologic and urologic evaluation should be considered in all children with a first episode of UTIs (except for school-aged girls). Special emphasis should be on early detection of urologic abnormalities in all young children and boys with a first infection, as well any child with pyelonephritis or a complicated course. A review of studies evaluating diagnostic imaging in children with UTIs expressed the need for better outcome-based research in this area.

Radiologic and urologic evaluation should be considered in adults with UTIs in the following situations: (a) males with first episode, (b) all patients with a complicated infection or bacteremia, (c) suspected obstruction or renal stones, and (d) hematuria following infection. In the past, all UTIs in males were considered complicated. Some sexually active males are at a higher risk for cystitis (homosexual males, males with a partner who harbors a uropathogen, uncircumcised males). The value of urologic evaluation in this high-risk group, with a single episode of cystitis and an uncomplicated course, is not known.

Some experts recommend evaluation of all patients with pyelonephritis. The radiologic evaluation of a subgroup of patients with pyelonephritis (young and otherwise healthy women who respond well to therapy) may have a low diagnostic yield. In one study, only 1 of 25 young women with uncomplicated pyelonephritis had a surgically correctable etiology, and 2 of 25 had focal abnormalities that resolved on a follow-up ultrasound. This has led others to recommend a diagnostic evaluation in young women with uncomplicated pyelonephritis after the second recurrence, or at any time, if a complicating course is present. The ease in obtaining a noninvasive test (ultrasound) has increased radiologic evaluations for most patients admitted with pyelonephritis.

Ultrasound with a plain film of the abdomen has replaced the intravenous pyelogram as the initial radiologic studies for most adults. For a detailed evaluation of the ureterovesical junction, bladder, and urethra, a voiding cystourethrogram and measurement of the residual urine after voiding may be necessary. If vesicoureteral reflux is present after acute infection has been treated, a urologist should be consulted. Cystoscopy may be warranted. Renal calculi can usually be detected on a plain radiograph of the abdomen. An IVP confirms the presence and the location of calculi, detects radiolucent stones (fewer than 10% of renal calculi), and discloses the degree of obstruction and dilation. Ordinarily, radiographic studies should not be performed within 6 weeks of acute infections.

Gram-negative bacilli have the ability to impede ureteral peristalsis, and transient abnormalities of the IVP are common with acute pyelonephritis. These include

hydroureter, vesicoureteral reflux, diminished pyelogram, loss of renal outline, and renal enlargement. Acute pyelonephritis with an obstructed ureter is a surgical emergency, and a perinephric abscess also requires surgical drainage. These complications, however, are best detected initially by ultrasound and by computed tomography, respectively. To avoid radiocontrast-induced acute renal failure, excretory urography and other radiocontrast studies should be avoided whenever possible in patients with a serum creatinine above 1.5 mg per dL, diabetes mellitus, dehydration, or advanced age.

VI. Treatment of UTI

A. **Principles of underlying therapy and follow-up.** To successfully treat a UTI, the clinician must have knowledge of microbial susceptibility and mechanisms of resistance, pharmacokinetics and pharmacodynamics, and status of host defenses. First, most uropathogens are susceptible to a wide range of antibiotics; however, resistant gram-negative bacteria frequently are seen with indwelling catheters, in immunocompromised patients, and in patients with relapsing bacteriuria. Second, the majority of antibiotics are filtered by the kidney and thus achieve a urinary concentration that is many times higher than the minimum inhibitory concentration. Third, although most antibiotics achieve adequate concentration in renal tissue, only tetracyclines, trimethoprim-sulfamethoxazole, and fluoroquinolones achieve any reasonable concentration in the prostate. Finally, patients with systemic or local abnormalities in host defenses usually develop a renal infection that is refractory to therapy. In this case, antibiotics that achieve adequate serum concentrations and are bactericidal are preferable to bacterial static agents. The basic caveats for effective management of UTIs are outlined here.
   1. **Asymptomatic patients** should have colony counts greater than or equal to 100,000 per mL on at least two occasions before treatment is onsidered.
   2. Unless symptoms are present, **no attempt should be made to eradicate bacteriuria** until catheters, stones, or obstructions are removed.
   3. **Selected patients with chronic bacteriuria** may benefit from supressive therapy.
   4. A patient who develops **bacteriuria as a result of catheterization** should have treatment to reestablish a sterile urine.
   5. **Antimicrobial agents used for treatment** should be the safest and least expensive agents to which the causative microorganisms are susceptible.
   6. **Efficacy of treatment** should be evaluated by urine culture 1 week after completion of therapy, except in nonpregnant adult women with uncomplicated cystitis and uncomplicated pyelonephritis who respond to therapy.

B. **Antimicrobial agents**
   1. **Beta-lactams.** Amoxicillin has replaced oral ampicillin due to improved bioavailability and less frequent dosing. Amoxicillin is effective for uncomplicated cystitis, but short-course therapy (single-dose and 3-day regimens) has generally been less effective than trimethoprim-sulfamethoxazole or fluoroquinolones given for a similar duration. Increasing antimicrobial resistance observed in *E. coli* make amoxicillin and ampicillin less attractive choices for empiric therapy in the patient with a complicated UTI, unless enterococcus is strongly considered to be the etiologic agent. Cefixime and cefpodoxime are oral third-generation cephalosporins with enhanced activity against enteric gram-negative bacteria, longer serum half-life, and less frequent dosing then first-generation cephalosporins.

      Parenteral beta-lactams are generally reserved for more complicated infections. Ceftriaxone is a third-generation cephalosporin with good activity against most community-acquired gram-negative enteric bacteria (lacks actvity *Pseudomonas aeruginosa*). Ceftazidime and cefepime are examples of cephalosporins with good activity against many gram-negative bacteria, including *Pseudomonus aeruginosa*.
   2. **Nitrofurantoin** is active against many uropathogens, including *E. coli, Staphylococcus saprophyticus,* and *Enterococcus faecalis*. Some gram-negative bacteria are resistant to nitrofurantoin (*Klebsiella, Enterobacter,* and *Pseudomonas* species), making it a less than ideal agent for empiric therapy of complicated UTIs. No clinically significant increase in resistance has been observed. The major role of nitrofurantoin in therapy includes treatment of uncomplicated cystitis and as an alternative agent for cystitis caused by *E. faecalis*. The oral adult dose for both crystalline and macrocrystalline preparations is 50 to 100 mg every 6 hours for 7 days. Although a 3-day regimen is successful in many patients with uncomplicated cystitis, one clinical trial found nitrofurantoin to be less effective than a 3-day regimen of trimethoprim-sulfamethoxazole. Patients with renal insufficiency (creatinine clearance less than 60 mL per minute) should not receive this agent. Nitrofurantoin has been used in pregnancy [U.S. Food and Drug Administration (FDA) category B], although it is contraindicated in nursing mothers, pregnant women near term, and newborns (in whom it is associated with hemolytic anemia). Suppressive therapy has been successful in some patients, although concern for less common reactions (e.g., peripheral neuropathy, pneumonitis, and hepatitis) may limit long-term use.
   3. **Trimethoprim-sulfamethoxazole and trimethoprim.** Trimethoprim-Sulfamethoxazole has a wide spectrum of activity against many uropathogens. Limited activity against enterococci and *P. aeruginosa* as well as increased resistance by some enteric gram-negative bacteria (*Klebsiella* species, *Enterobacter* species), makes trimethoprim-sulfamethoxazole a less than ideal agent for treatment of complicated UTIs.

      Trimethoprim-sulfamethoxazole is well tolerated in most patients. Adverse effects due to sulfonamides are well described and include gastrointestinal symptoms, transient elevation in the serum creatinine, and hematologic and dermatologic reactions. Sulfonamides displace warfarin and hypoglycemics from albumin, potentiating these drug effects. Trimethoprim-sulfamethoxazole is highly effective for prophylaxis and therapy of uncomplicated cystitis and for therapy of uncomplicated pyelonephritis. A randomized trial with four different 3-day drug regimens in women with uncomplicated acute cystitis found a 3-day regimen of trimethoprim-sulfamethoxazole was the most cost-effective regimen. Complicated UTIs, especially catheter-associated infections and nosocomial UTIs, should have *in vitro* susceptibility testing performed. Trimethoprim-sulfamethoxazole has been used in pregnancy, but it is not FDA-approved for pregnant women. Other agents, such as amoxicillin, nitrofurantoin, and cephalosporins, are preferred.

      Trimethoprim alone is preferred over trimethoprim-sulfamethoxazole by some experts for prophylaxis and treatment of uncomplicated cystitis, because its efficacy is similar and the side effects fewer (because of the absence of sulfamethoxazole). This agent should not be used alone for the therapy of complicated UTIs.
   4. Multiple **fluoroquinolones** are now available for clinical use (Table 7-2 and Table 7-3). These agents achieve very high concentrations in the urine and renal tissue easily exceeding the minimal inhibitory concentration of most uropathogens. Fluoroquinolones should not be used as first-line agents for the therapy of uncomplicated cystitis because of concern for development of resistance and because of the cost. However, their antimicrobial spectrum and generally low side-effect profile make them excellent choices for empiric therapy of complicated UTIs. Among current agents within this antimicrobial class, no particular drug has demonstrated superior clinical efficacy for the therapy of patients with UTIs. Fluoroquinolones should not be used during pregnancy or in children (until further information is availble). Aluminum- and magnesium-containing antacids and iron-, calcium-, and zinc-containing preparations should not be administered with oral fluoroquinolones due to a significant decrease in absorption. In general, these agents are well tolerated by most patients. The most common adverse effects are gastrointestinal and on the central nervous system, but they infrequently lead to drug discontinuation. Photosensitivity may limit the use of some of these agents (e.g., lomefloxacin, sparfloxacin). Many of these agents are available for both parenteral and oral administration. Conversion from parenteral to oral therapy (step-down therapy) should be considered for patients who are clinically stable and tolerating oral medications. The excellent bioavailability of these drugs, good clinical success with oral therapy, and the high cost of parenteral therapy (intravenous catheter–related complications, cost of intravenous :preparation) are all good reasons for this consideration.

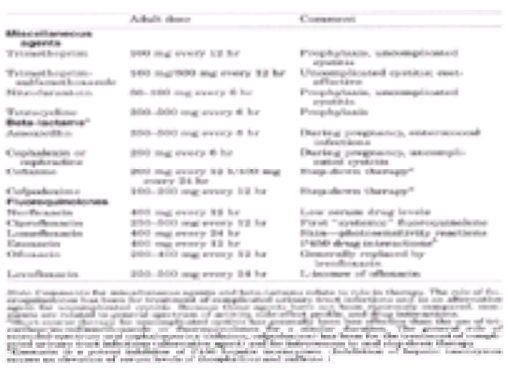

Table 7-2. Oral antimicrobial agents commonly used for treatment of urinary tract infections

	Adult dose	Comment
Beta-lactams		
Ampicillin	1–2 g every 4 hr	*Enterococcus faecalis*; usually combined with gentamicin
Ceftriaxone	1 g every 12–24 hr	Pyelonephritis
Cefuroxime	1–2 g every 8–12 hr	Complicated UTI, including *Pseudomonas aeruginosa*
Cefepime	1–2 g every 12 hr	Complicated UTI, including *Pseudomonas aeruginosa*
Aztreonam	1 g every 8–12 hr	Penicillin-allergic patient
Fluoroquinolones*		
Ciprofloxacin	200–400 mg every 12 hr	
Ofloxacin	200–400 mg every 12 hr	Generally changed to levofloxacin
Levofloxacin	500 mg every 24 h	
Miscellaneous agents		
Trimethoprim-sulfamethoxazole	160 mg/800 mg every 12 hr	Prophylaxis, uncomplicated cystitis
Vancomycin	1 g every 12 hr	Methicillin-resistant *Staphylococcus aureus*; serious enterococcal infection in the penicillin-allergic patient
Gentamicin	4–7 mg/kg every 24 hr 1.5–2.0 mg/kg every 8 hr	Serious gram-negative infection Other dosing schedule, for enterococcus combined with ampicillin

*Because oral fluoroquinolones have excellent bioavailability and cost approximately 20% as much as parenteral fluoroquinolones, convenient from intravenous to oral therapy should be done when that patient is clinically stable.

Table 7-3. Intravenous antimicrobial agents commonly used for treatment of urinary tract infections (UTIs)

C. **Treatment of asymptomatic bacteriuria**

1. **Pregnancy** increases the risk of UTI complications. The rate of prematurity in children born to women who have bacteriuria during pregnancy is increased, and 20% to 40% of these patients develop pyelonephritis. Successful therapy of these patients with bacteriuria decreases the risk of symptomatic infection by 80% to 90%. Therefore, all women should be screened twice during gestation for asymptomatic bacteriuria. All bacteriuria patients should be treated for 7 days, with follow-up cultures to identify relapses. Long-term prophylaxis offers no advantage over close surveillance. In selecting therapy, the risk to the fetus should be considered. Short-acting sulfonamides or amoxicillin for 7 days usually suffices, because almost all of these infections are caused by susceptible *E. coli*. Tetracyclines (FDA category D), trimethoprim (FDA category C), and fluoroquinolones (FDA category C) should be avoided.
2. **Children.** Asymptomatic bacteriuria in preschool- and school-aged girls may signify underlying vesicoureteral reflux. Moreover, vesicoureteral reflux, when combined with recurring bacteriuria, can result in progressive renal scarring. Therefore, in this at-risk populaion, asymptomatic bacteriuria should routinely be detected and treated, with follow-up urologic evaluations after 6 weeks.
3. **General population.** Asymptomatic bacteriuria in men and nonpregnant women, a common condition in the elderly, does not appear to cause renal damage in the absence of obstructive uropathy or vesical ureteral reflux. Prospective randomized studies of therapy for asymptomatic bacteriuria in the elderly have been recently reviewed. Of five clinical trials reviewed, three studies had very small sample sizes, and one non-blinded study displayed a nonstatistical significant decrease in symptomatic infections. The largest randomized trial failed to demonstrate any significant difference in mortality between treated and untreated patients. Therefore, repeated attempts to clear the bacteriuria with antimicrobial agents seem unwarranted; they may only select for more resistant microorganisms and create a need for more toxic and costly antibiotics should the patient subsequently develop symptoms.
4. **Miscellaneous.** Instrumentation of the genitourinary tract should be avoided in patients with asymptomatic bacteriuria or, if necessary, done under the cover of prophylactic antimicrobial therapy. Selected high-risk patients (e.g., with renal transplantation or neutropenia) may benefit from therapy for asymptomatic bacteriuria.

D. **Treatment of uncomplicated cystitis.** Acute cystitis and low-colony-count coliform urethritis are almost exclusively diseases of women, mostly sexually active women between the ages of 15 and 45 years. Although reinfection is common, complications are rare.

1. **Short-course therapy.** Appreciable evidence exists that infections truly confined to the bladder or urethra respond as well to single-dose or short-course (3-day) therapy as to conventional therapy for 10 to 14 days. Indeed, response to single-dose or short-course therapy implies a lower UTI. Reviews of short-course therapy have concluded that 3-day regimens are more effective than single-dose therapy. One randomized trial evaluated four different 3-day drug regimens in women with uncomplicated acute cystitis. A 3-day regimen of trimethoprim-sulfamethoxazole was more effective than a 3-day regimen of nitrofurantoin. Cure rates for cefadroxil (66%) and amoxicillin (67%) were not statistically different from the cure rate for trimethoprim-sulfamethoxazole (82%). The 3-day regimen of trimethoprim-sulfamethoxazole was the most cost-effective regimen. Further clinical trials are needed to evaluate other patients with uncomplicated cystitis and to measure the impact of newer agents (fluoroquinolones) on outcomes and cost effectiveness. Recommended oral 3-day regimens include trimethoprim-sulfamethoxazole, trimethoprim, and a fluoroquinolone. This variety of treatments is an important breakthrough in the management of uncomplicated cystitis and coliform urethritis, because all patients were treated formerly -with the standard 10 to 14 days of therapy.
2. **Seven-day regimen.** A longer course of therapy for cystitis should be considered in patients with complicating factors that lead to a lower success rate and a higher risk of relapse. These complicating factors include a history of prolonged symptoms (more than 7 days), recent UTI, diabetes, age older than 65 years, and use of a diaphragm. Importantly, both elderly and diabetic women frequently have concurrent renal bacteriuria; thus, short-course therapy should not be used.
3. **Symptomatic pyuria without bacteriuria** in an otherwise healthy young person suggests chlamydial or gonococcal urethritis. The importance of documenting these infections as well as screening for other STDs (e.g., human immunodeficiency virus infection, syphilis), and the necessity of counseling about STD risk reduction cannot be understated. Recent guidelines suggest that either a single dose of azithromycin or a 7-day course of doxycycline is effective for chlamydial urethritis. Therapy for gonococcal urethritis includes a single dose of ceftriaxone or cefixime, or a fluoroquinolone combined with therapy for chlamydial infection.

E. **Management of recurrent cystitis (reinfections).** Some women, especially those whose periurethral and vaginal epithelial cells avidly support attachment of coliform bacteria, suffer from recurrent episodes of cystitis in the absence of recognized structural abnormalities of the urinary tract. A recent prospective study of UTIs in young women identified recent use of a diaphragm and spermicide, recent sexual intercourse, and a history of recurrent infection as risk factors for infection.

1. **Antimicrobial strategies.** Strategies for managing the disease of women with frequent episodes of cystitis include (a) postcoital prophylaxis, (b) continuous low-dose prophylaxis, and (c) patient self-administered therapy. Postcoital prophylaxis is most helpful for patients who associate recurrent UTIs with sexual intercourse. In these women, a single dose of an antimicrobial after sexual intercourse or thrice weekly at bedtime has been shown to significantly reduce the frequency of episodes of cystitis from an average of three per patient-year to 0.1 per patient-year. Women with frequent recurrent infections (more than three UTIs per year) are offered these prophylactic regimens. Women with fewer than three UTIs per year can be offered self-administered treatment. Multiple antimicrobial agents have demonstrated efficacy in prophylaxis and self-administered therapy. Some of these regimens include nitrofurantoin, 50 or 100 mg; trimethoprim, 100 mg; trimethoprim-sulfamethoxazole, 40 mg per 200 mg; and cephalexin, 250 mg. Fluoroquinolones and cephalosporins are also effective but are more expensive. Although antimicrobial prophylaxis is effective and usually safely tolerated for months to years, single-dose therapy for acute cystitis makes prophylaxis more expensive and possibly more hazardous for most patients because of alterations in fecal and vaginal bacterial flora. Indeed, self-administration of a single-dose regimen at the onset of symptoms has proved to be as cost-effective as prophylaxis.
2. **Non-antimicrobial prophylaxis issues.** Encouraging women to practice regular and complete emptying of the bladder may help prevent recurrent cystitis. Postcoital emptying of the bladder has also been widely recommended, although one prospective study failed to demonstrate any relationship with recurrent infections (3). Moreover, several theoretical preventive measures relate to use of an alternative contraceptive method: to use a properly fitted diaphragm, to void frequently when wearing a diaphragm, and to limit diaphragm use to the recommended 6 to 8 hours after intercourse. In postmenopausal women, intravaginal administration of estriol can reduce recurrent UTIs by modifying the milieu for vaginal flora. Cranberry juice (300 mL per day) was effective in decreasing asymptomatic bacteriuria with pyuria in postmenopausal women. The small difference in symptomatic UTIs was not statistically significant.

F. **Treatment of acute bacterial pyelonephritis.** The occurrence of flank pain, chills and fever, and nausea and vomiting with or without dysuria suggests acute bacterial pyelonephritis. In this clinical setting, blood cultures and quantitative cultures of urine should be obtained. Whether ambulatory patients should be admitted to the hospital for treatment depends in part on a subjective assessment of toxicity, likely compliance with therapy, and the home situation. When the assessment is doubtful, the patient should be treated in the hospital, at least until a clear response to therapy has occurred. This policy also applies to patients with known underlying uropathies, because complications are more common in these patients.

1. **Outpatient therapy.** Recommendations for therapy of uncomplicated pyelonephritis are outlined in Table 7-4. A fluoroquinolone or trimethoprim-sulfamethoxazole is the drug of choice for initial therapy of pyelonephritis in outpatients. Local susceptibility patterns will influence the choice for initial therapy. After culture results and susceptibility tests are available, a full 10- to 14-day course of antimicrobial therapy may be completed with the least expensive drug to which the patient's microorganism is susceptible.

Table 7-4. Recommendations for therapy for urinary tract infections

2. **Inpatient therapy.** Patients who require admission to the hospital should be treated initially with a third-generation cephalosporin or a fluoroquinolone (intramuscular or intravenous) gentamicin or tobramycin (1.5 to 2.0 mg per kg every 8 hours or 4.0 to 7.0 mg per kg every 24 hours, with appropriate alteration of the dose interval if the serum creatinine exceeds 1 mg per dL) if the urine shows gram-negative bacilli on microscopical examination. If gram-positive cocci are seen in the urine, intravenous ampicillin (l g every 4 hours) should be given in addition to the aminoglycoside, to cover the possibility of enterococcal infection while the results of urine and blood cultures and antimicrobial susceptibility tests are pending. If no complications ensue and the patient becomes afebrile, the remaining days of a 10- to 14-day course can be completed with oral therapy. However, persistent fever, persistent bacteriuria in 48 to 72 hours, or continual signs of toxicity beyond 3 days of therapy suggest the need for an evaluation to exclude obstruction, metastatic focus, or formation of a perinephric abscess. The urinary tract is a common source of sepsis and bacteremic shock in patients with underlying uropathies. As with other patients in septic shock, intravenous fluids must be given to maintain adequate arterial perfusion, which usually results in a urinary output in excess of 50 mL per hour. Failure to respond to seemingly appropriate therapy suggests the possibility of undrained pus. Examination by ultrasound or computed tomography may disclose an obstructed ureter or perinephric abscess, both of which require surgical drainage.

G. **Management of recurrent renal infections (relapses).** Chronic bacterial pyelonephritis is one of the most refractory problems in clinical medicine; relapse rates are as high as 90%. The entity is a heterogeneous one with multiple underlying factors.
   1. **Risk factors.** To improve the success rate, it is of utmost importance that any correctable lesion be repaired, that obstructions to urine flow be relieved, and that foreign bodies (e.g., indwelling urinary catheters or renal staghorn calculi) be removed if possible. If the risk factors cannot be corrected, long-term eradication of bacteriuria is almost impossible. To attempt eradication in such instances leads only to emergence of more resistant strains of bacteria or fungi; consequently, the physician must be resigned to treatment of symptomatic episodes of infection and to suppression of bacteriuria in selected patients.
   2. **Acute symptomatic infection.** The treatment of acute symptoms and signs of UTI in a patient with chronic renal bacteriuria is the same as for patients with acute bacterial pyelonephritis. Urine cultures to detect a possible change in antimicrobial susceptibility of the infecting microorganism are important. Toxic patients should also have blood cultures.
   3. **Prolonged treatment.** Some patients with relapsing bacteriuria after 2 weeks of therapy respond to 6 weeks of antimicrobial therapy. This is especially true of patients with no underlying structural abnormalities and of men with normal prostatic examinations. Patients who fail the longer therapy, who have repeated episodes of symptomatic infection, or who have progressive renal disease despite corrective measures are candidates for suppressive chemotherapy.
   4. **Suppressive therapy.** Patients selected for suppressive therapy should have 2 to 3 days of specific high-dose antimicrobial therapy to which their infecting bacteria are susceptible to reduce the colony counts in their urine. The preferred agent for long-term suppression is methenamine mandelate, 1 g four times daily in adults. To be most effective, the pH of the urine should be maintained below 5.5; this can be accomplished with ascorbic acid, 500 mg two to four times daily. Alternatively, the dosage of methenamine mandelate alone can be increased to 8 g or even 12 g per day. The dosage should be adjusted to the minimum amount required to keep the urine free of bacteria. To avoid metabolic acidosis, the dosage of methenamine mandelate must be reduced in patients with renal insufficiency, in whom 2 g per day may suffice; methenamine mandelate should not be used at all unless the creatinine clearance exceeds 10 mL per minute. Alternative therapy is trimethoprim-sulfamethoxazole (two tablets twice daily) or nitrofurantoin (50 to 100 mg once or twice daily).
   5. **Prognosis.** Although they are a common cause of appreciable morbidity, UTIs do not play a major role in the pathogenesis of end-stage renal disease. Patients who come to renal dialysis or transplantation because of chronic bacterial pyelonephritis almost always have an underlying structural defect. Most often, the lesion is chronic atrophic pyelonephritis associated with vesicoureteral reflux that started in infancy. The role of surgical correction of vesicoureteral reflux is not clear despite years of debate; what is certain, however, is the importance of meticulous control of infection in children to prevent progressive renal scarring and renal failure by early adulthood.

H. **Treatment of prostatitis**
   1. **Acute bacterial prostatitis** is commonly accompanied by acute cystitis, which enables recovery of its causative pathogen by culture of voided urine. Massage of an acutely inflamed prostate gland often results in bacteremia; therefore, this procedure should be avoided unless the patient is already receiving effective antibiotic therapy. The drug of choice is the combination of trimethoprim-sulfamethoxazole (cotrimoxazole) or a fluoroquinolone; treatment, however, must be based ultimately on an accurate microbiological diagnosis. Treatment should be given for 30 days to prevent chronic bacterial prostatitis. After acute symptoms subside, a suitable oral antibiotic can be given in full dose for at least 30 days. Urethral catheterization should be avoided. If acute urinary retention develops, drainage should be by suprapubic needle aspiration or, if prolonged bladder drainage is required, by a suprapubic cystostomy tube, placed while the patient is under local anesthesia.
   2. **Chronic bacterial prostatitis.** The hallmark of chronic bacterial prostatitis is relapsing UTI. It is most refractory to treatment. Although erythromycin with alkalinization of the urine has been effective against susceptible gram-positive pathogens, most instances of chronic bacterial prostatitis are caused by gram-negative enteric bacilli. Cotrimoxazole or a fluoroquinolone is the drug of choice. Approximately 75% of patients improve, and 33% are cured with 12 weeks of cotrimoxazole therapy (two tablets twice daily). For patients who cannot tolerate cotrimoxazole or a fluoroquinolone, nitrofurantoin, 50 or 100 mg once or twice daily, can be used for long-term (6–12 months) supressive therapy.
   3. The therapy for **nonbacterial chronic prostatitis** is difficult because an exact etiology has not been identified. Due to a concern for *C. trachomatis, Ureaplasma urealyticum*, and other fastidious and difficult to culture organisms, many experts recommend a 6-week trial of a tetracycline or erythromycin. Symptomatic therapy with nonsteroidal antiinflammatory drugs and alpha-receptor blockers has also been used.

I. **Recommendations for the care of urinary catheters.** Urinary catheters are valuable devices for enabling drainage of the bladder, but their use is associated with an appreciable risk of infection in the urinary tract. For a single (in-and-out) catheterization, the risk is small (12%), though this prevalence is much higher in diabetic and elderly women. However, bacteriuria occurs in virtually all patients with indwelling urinary catheters within 3 to 4 days unless placement is done under sterile conditions and a sterile, closed drainage system is maintained (Fig. 7-4). The use of a neomycin-polymyxin irrigant does not prevent catheter-associated infections. Urinary catheters are the single most common cause of nosocomial infections and are responsible for more than 5,000 deaths from gram-negative sepsis each year in the United States. Explicit recommendations for the prevention of catheter-associated UTIs, formulated by the Centers for Disease Control and Prevention, are given here.

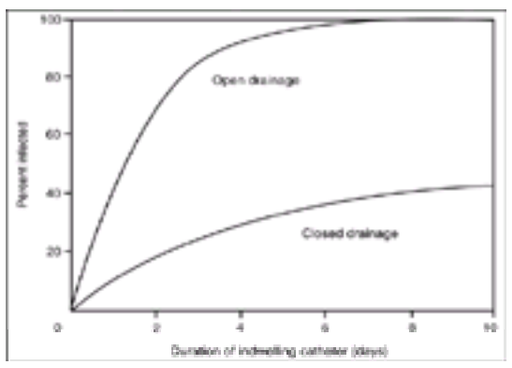

Figure 7-4. Prevalence of bacteriuria in catheterized patients according to duration of catheterization and type of drainage system. (From Fass RJ, Klainer AS, Perkins RL. Urinary tract infection: practical aspects of diagnosis and treatment. *JAMA* 1973;225:1509. Reprinted with permission.)

1. **Indwelling urinary catheters should be used only when absolutely necessary.** They should never be used solely for nurse or physician convenience,

and they should be removed as soon as possible.

2. **Catheters should be inserted only by adequately trained personnel.** If practical, a team of individuals should be given responsibility for catheter insertion and maintenance.
3. **Urinary catheters should be aseptically inserted using proper sterile technique and the following sterile equipment:** gloves, a fenestrated drape, sterile sponges and an iodophor solution for periurethral cleansing, a lubricant jelly, and an appropriately sized urinary catheter. After insertion, catheters should be properly secured to prevent movement and urethral traction.
4. **Once- or twice-daily perineal care for catheterized patients** should include cleansing of the metal-catheter junction with an antiseptic soap; subsequently, an antimicrobial ointment may be applied.
5. **A sterile closed drainage system should always be used.** The urinary catheter and the proximal portion of the drainage tube should not be disconnected (thus opening the closed system) unless it is required for irrigation of an obstructed catheter. Sterile technique must be observed whenever the collecting system is opened and catheter irrigation is done. A large-volume sterile syringe and sterile irrigant fluid should be used and then discarded. If frequent irrigations are necessary to ensure catheter patency, a triple-lumen catheter permitting continuous irrigation within a closed system is referable.
6. **Small volumes of urine for culture** can be aspirated from the distal end of the catheter with a sterile syringe and 21-gauge needle. The catheter must first be prepared with tincture of iodine or alcohol. Urine for chemical analyses can be obtained from the drainage bag in sterile manner.
7. **Nonobstructed gravity flow must be maintained at all times.** This requires emptying the collecting bag regularly, replacing poorly functioning or obstructed catheters, and ensuring that collection bags always remain below the level of the bladder.
8. **All closed collecting systems contaminated by inappropriate technique, accidental disconnection, leaks, or other means should be immediately replaced.**
9. **Routine catheter change is not necessary** in patients with urinary catheterization of less than 2 weeks' duration, except when obstruction, contamination, or other malfunction occurs. In patients with chronic indwelling catheters, replacement is necessary when concretions can be palpated in the catheter or when malfunction or obstruction occurs.
10. **Catheterized patients should be separated from each other whenever possible** and should not share the same room or adjacent beds if other arrangements are available. Separation of bacteriuric and nonbacteriuric patients is particularly important.

These guidelines should be adhered to meticulously, and the use of indwelling urinary catheters should be kept to a responsible minimum.

J. **Catheter-associated infections.** Catheter-associated bacteriuria should only be treated in the symptomatic patient. When the decision to treat a patient with a catheter-associated infection is made, removal of the catheter is an important aspect of therapy. If an infected catheter remains in place, relapsing infection is very common. The interaction between the organisms and catheter (foreign body) cause the organism to form a biofilm or area in which antibiotics are unable to completely eradicate these organisms. Recommendations for empiric therapy are similar to recommendations for complicated UTIs (see Table 7-4). The choice of empiric therapy is based on an initial Gram's stain of the urine, local susceptibility patterns, host factors, and the patient's recent antibiotic use. Final choice of an antibiotic and duration of therapy should be based on identification and susceptibility of the etiologic agent and the host's response to therapy. Patients who respond rapidly to therapy may be treated for 7 days, although making firm conclusions about duration of therapy is very difficult.

Patients with candiduria may fall into several different clinical categories. Otherwise healthy patients with asymptomatic candiduria often require only a urinary catheter change and may not require antifungal therapy. On the other end of the spectrum is the immunocompromised host, in whom candiduria may represent disseminated infection. The patient with disseminated candidiasis requires systemic therapy with either fluconazole or amphotericin B or liposomal preparation of amphotericin. General recommendations for treating patients with candiduria and without evidence of disseminated infection include removal of the urinary catheter and discontinuation of antibiotics. Antifungal options include either fluconazole (200 mg the first day, then 100 mg for 4 days), continuous bladder irrigation with amphotericin B (50 mg per 1,000 mL of sterile water via a three-way catheter for 5 days), or low dose intravenous therapy with amphotericin (0.3 mg per kg in a single dose). Occasionally, longer systemic therapy with oral 5-fluorocytosine, intravenous amphotericin B, or both is required.

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Chapter 8 The Patient with Hematuria, Proteinuria, or Both, and Abnormal Findings on Urinary Microscopy

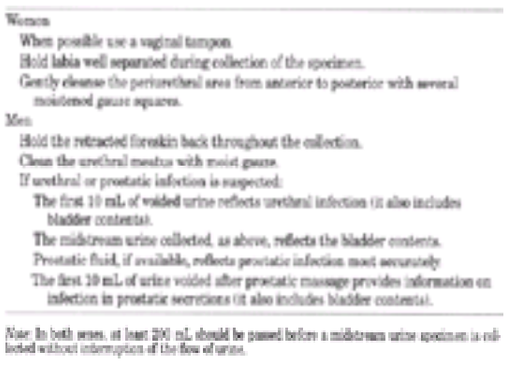
Sharon G. Adler and Kenneth Fairley

Urine analysis
Hematuria
Proteinuria

I. Urine analysis. A urine sample is usually easy to obtain, and it can be studied by very simple techniques on the ward or in the physician's office. Examination of the urine is one of the most rewarding steps in clinical medicine. Not only does it uncover renal parenchymal and urinary tract disease that eludes detection by other methods of investigation, but it frequently points to a specific diagnosis. Almost every patient with renal disease shows abnormal findings on urine microscopy, an increase in urine protein, or both. Urine microscopy reveals abnormalities in many patients with renal disease who have no significant proteinuria. Many renal diseases that require treatment are first suspected on the basis of urinary findings—in particular, infections, glomerulonephritis, and interstitial nephritis.

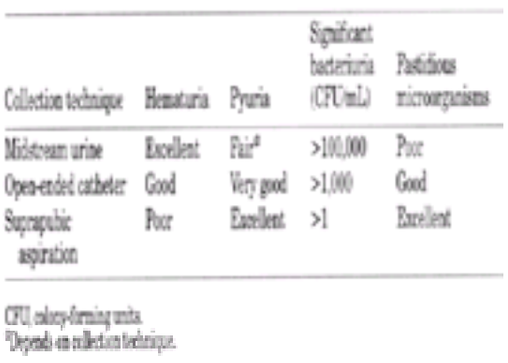
A. **Method of collection of urine specimens.** The method of collecting a Gurine sample is of critical importance when the specimen is to be examined microscopically. For dipstick testing, the sample should be examined promptly for accurate results. Urine pH may change with time after collection, and contaminating bacteria multiply and convert nitrate to nitrite, causing a false-positive test for bacteriuria. At low specific gravity (less than 1.010), cells lyse and casts form less readily. Casts also dissolve in alkaline urine.

1. **Midstream urine collection.** In collecting urine for microscopical examination, avoiding contamination with bacteria, squamous cells, and leukocytes is important. Contamination is very common in women, in whom contaminating cells and bacteria arise in the vagina and vulval area. The important points in collecting a good midstream urine sample are shown in Table 8-1. Although bacteria are often detected on microscopy, infection is best proved by culture, which also allows the antibiotic sensitivity of infecting organisms to be determined. Special media are required for culture of some organisms, such as the tubercle bacillus, *Mycoplasmas* anaerobic organisms, and yeasts. Culture results are reported as colony-forming units (CFU) per mL of urine; the significance of a count depends on the method of collection (Table 8-2).



Women
When possible use a vaginal tampon.
Hold labia well separated during collection of the specimen.
Gently cleanse the periurethral area from anterior to posterior with several moistened gauze squares.
Men
Hold the retracted foreskin back throughout the collection.
Clean the urethral meatus with moist gauze.
If urethral or prostatic infection is suspected:
The first 10 mL of voided urine reflects urethral infection (it also includes bladder contents).
The midstream urine collected, as above, reflects the bladder contents.
Prostatic fluid, if available, reflects prostatic infection most accurately.
The first 10 mL of urine voided after prostatic massage provides information on infection in prostatic secretions (it also includes bladder contents).
Note: In both sexes, at least 200 mL should be passed before a midstream urine specimen is collected without interruption of the flow of urine.

Table 8-1. Guidelines for collecting midstream urine sample



Collection technique	Hematuria	Pyuria	Significant bacteriuria (CFU/mL)	Pathogenic microorganisms
Midstream urine	Excellent	Fair[a]	>100,000	Poor
Open-ended catheter	Good	Very good	>1,000	Good
Suprapubic aspiration	Poor	Excellent	>1	Excellent

CFU, colony-forming units.
[a]Depends on collection technique.

Table 8-2. Influence of collection technique on accuracy of detection of urine abnormalities

2. A catheter specimen in women is best collected as a **midcatheter specimen** using a short open-ended catheter. At least 200 mL must pass through the catheter to flush out contaminating urethral contents before the specimen is collected. Conventional “side hole” catheters push urethral contents into the bladder before urine can run out, and critical bacterial counts are 30-fold higher using a conventional catheter than those obtained on urine collected with an open-ended catheter.
3. **Suprapubic aspiration.** A fine lumbar puncture needle with stylet in place is passed through sterilized suprapubic skin directly into a full bladder. Uncontaminated urine can then be aspirated.

B. **Dipstick testing.** Dipstick testing of urine provides a rapid determination of urine pH, specific gravity, and the presence of protein, blood, glucose, and bile. Dipsticks are less sensitive in detecting pyuria and bacteriuria.

The method of screening for proteinuria is the examination of a randomly excreted urine sample by dipstick. Tetrabromophenol is buffered to a pH of 3, and this results in a yellow-to-blue color change with increasing protein concentration. False-positive dipstick results for proteinuria are seen when urine pH is greater than or equal to 8 and when the patient is excreting metabolites of penicillins, aspirin, or oral hypoglycemic agents in the urine. Standard dipsticks for protein fail to detect very small quantities of abnormal albuminuria and are relatively insensitive to even large amounts of nonalbumin protein. To alleviate the first of these shortcomings, dipsticks capable of detecting small amounts of albumin (microalbuminuria) are currently available and are useful, when used properly, as a screening test to identify patients with insulin-dependent diabetes mellitus and incipient nephropathy. To alleviate the latter problem, dipsticks that are more sensitive to nonalbumin proteins are under development. Currently, a 24-hour urine collection is required to detect such proteins.

Urine color varies with its concentration and with the presence of drugs such as phenazopyridine (Pyridium), phenindione, and multivitamin tablets, and of blood, bile, porphyrin, melanin, and homogentisic acid. Some of these color changes may be mistaken for hematuria. Dipstick examination of the urine accurately determines the presence of hemoglobin, which depends on the oxidation of orthotolidine by cumene hydroperoxide. Although the microscopical examination of urine for erythrocytes provides far more information about the underlying renal lesion, a dipstick is quick and simple and provides quantitative information. The Ames N Multistix and Boehringer nephron tests provide sensitive and specific methods of detecting microscopical hematuria. Ascorbic acid, a strong reducing agent, prevents the chemical reaction in dipsticks that detects hemoglobin and is the cause of many false-negative tests. In the case of a low-specific-gravity urine (below 1.010), lysis of erythrocytes leads to false-negative microscopy, but the dipsticks provide a positive test.

C. **Microscopical analysis.** In the United States, urine is characteristically examined using a standard light microscope to make a semiquantitative estimate of the frequency of the formed elements in the urine by counting their number per high-power field. More quantitative measures can be obtained by examining the urine on a coverslipped counting chamber rather than on a plain glass slide. The counting-chamber method is more accurate, largely because it eliminates the error introduced by the variability of the depth of the layer of urine on the slide, which occurs as a function of viscosity. The accuracy of the microscopical examination can also be enhanced by using phase-contrast microscopy, which allows for more sensitivity in the observation of morphologic detail.

1. **Hematuria.** A large amount of blood present in the urine is obvious to the naked eye. The red blood cell count in such cases is always well above 10^6 cells per mL. The morphology and quantitation of the urinary erythrocytes are two of the most important investigations in clinical nephrology. They not only provide information about the underlying cause, but also assist in determining the nature of investigations required. Since the recognition that glomerular bleeding can be determined by the appearance of erythrocytes on phase-contrast microscopy, prompt assessment of the number and morphology of urinary

erythrocytes in the urine has assumed new significance. In the case of crescentic glomerulonephritis, which can be suspected when red blood cell casts and large numbers of dysmorphic erythrocytes are seen on urine microscopy, the physician is alerted to the urgent need for biopsy confirmation and appropriate treatment.

A high count of glomerular erythrocytes (more than 10^6 red blood cells per mL) has both prognostic and therapeutic implications, because it suggests the presence of crescents on renal biopsy. If 4+ dipstick testing for heme is present, immediate urine microscopy is indicated to determine the nature and hence the source of erythrocytes, and, if possible, the count per mL. The source of erythrocytes can be determined by measuring their size and by examining their morphology. After centrifuging the urine specimen, if a red pellet results, adequate numbers of erythrocytes are present to measure their volume in an automated counter of the type customarily used for complete blood cell counts (CBCs). If the urinary erythrocyte mean corpuscular volume is less than 72 fL, a glomerular bleeding source is likely.

The best method for assessing erythrocyte morphology is phase-contrast microscopy. If bright-field illumination is used, many erythrocytes will not be correctly identified. In particular, those that have lost their hemoglobin staining are not seen, a common occurrence in an acid urine. Small and distorted erythrocytes characteristic of glomerular bleeding may also be missed. Characteristic dysmorphic erythrocytes, which indicate that hematuria is arising in glomeruli, are illustrated in Figure 8-1. They vary considerably in size, shape, and hemoglobin content, and many bizarre forms are present. Normal urine contains up to 8,000 glomerular erythrocytes per mL in a centrifuged specimen and 13,000 per mL in uncentrifuged urine. Erythrocytes that are arising from a nonglomerular source are uniform in size and shape but may show some “ghost cells,” cells that are losing their hemoglobin (Fig. 8-2). The latter change occurs particularly in an acid urine.

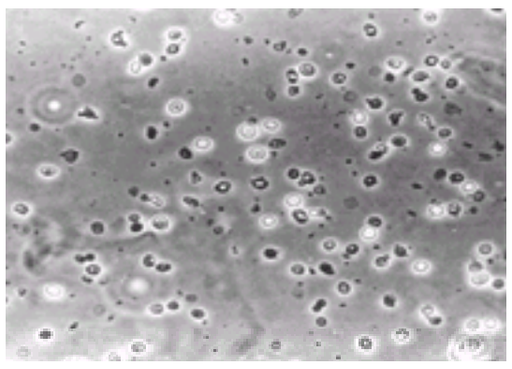


Figure 8-1. Erythrocytes, showing the wide variation in size, shape, and hemoglobin content, in the urine of a patient with glomerulonephritis (phase-contrast microscopy). (From Fairley KF. Urinalysis. In: Schrier RW, Gottschalk CW, eds. *Diseases of the kidney*, 4th ed. Boston: Little, Brown, 1988. Reprinted with permission.)

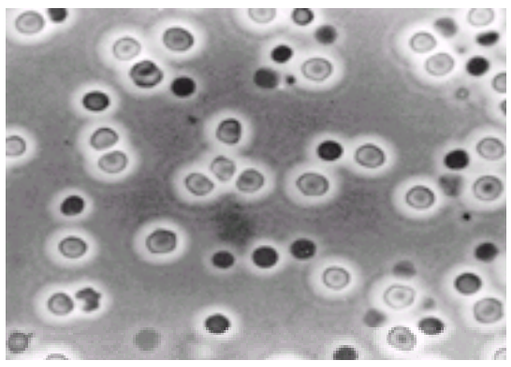


Figure 8-2. Nonglomerular bleeding, showing two populations of cells (phase-contrast microscopy). (From Fairley KF. Urinalysis. In: Schrier RW, Gottschalk CW, eds. *Diseases of the kidney*, 4th ed. Boston: Little, Brown, 1988. Reprinted with permission.)

2. **Urinary casts.** Casts are formed from Tamm-Horsfall glycoprotein, which is synthesized and secreted in the ascending limb of the loop of Henle and distal convoluted tubules.
   a. **Physiologic casts.** Hyaline casts are transparent and cylindrical and are seen in the urine of normal subjects. Their presence does not indicate renal disease. Granular casts are semitransparent cylinders with refractile granules of uncertain origin. These, too, are present in individuals without renal disease. The number of hyaline and granular casts in urine may be increased by fever,exercise, and volume depletion.
   b. **Pathologic casts.** Casts may contain cellular material (erythrocytes, leukocytes, tubular cells, bacteria, or fungi), fibrin, lipids, bile, and crystals.

      The most important cellular cast is that composed of erythrocytes (Fig. 8-3). This indicates glomerular bleeding, as do erythrophagocytic cells. Large nmbers of erythrocyte casts also increase the likelihood of crescents in glomeruli. Casts composed of polymorphonuclear leukocytes usually indicate renal parenchymal infection. They may also be seen in acute interstitial nephritis and occasionally in glomerular lesions where numerous polymorphonuclear leukocytes are in glomeruli. Casts may also contain all varieties of mononuclear leukocytes and may include tubular epithelial cells from all segments of the nephron. In nephrotic syndrome, all casts usually contain fat particles and some contain oval fat bodies. If the fat bodies consist of cholesterol esters, they can be easily identified by their “Maltese cross” birefringence (Fig. 8-4 and Fig. 8-5).

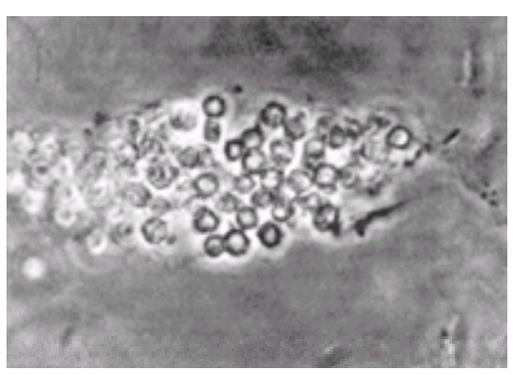


Figure 8-3. An erythrocyte cast in an acid urine, composed of red cells from which much of the hemoglobin has disappeared. (From Fairley KF. Urinalysis. In: Schrier RW, Gottschalk CW, eds. *Diseases of the kidney*, 4th ed. Boston: Little, Brown, 1988. Reprinted with permission.)

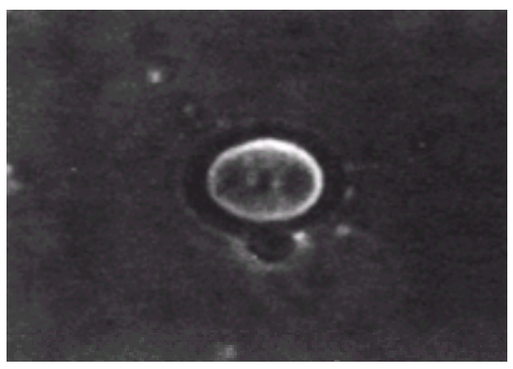


Figure 8-4. A cholesterol ester spherulite approximately the same size as an erythrocyte. (From Fairley KF. Urinalysis. In: Schrier RW, Gottschalk CW, eds. *Diseases of the kidney*, 4th ed. Boston: Little, Brown, 1988. Reprinted with permission.)

Figure 8-5. The particle in Figure 8-4, when viewed with polarized light, shows the classic “Maltese cross.” (From Fairley KF. Urinalysis. In: Schrier RW, Gottschalk CW, eds. *Diseases of the kidney*, 4th ed. Boston: Little, Brown, 1988. Reprinted with permission.)

Crystals in casts are commonly present in patients who are taking triamterene. The crystals disappear when the urine is alkalinized or the drug is discontinued. Crystals may also occasionally be present in casts in patients with hypercalcemia or hyperuricosuria, or as an isolated finding.

Broad waxy casts signify chronic renal disease. They typically have a very sharp border and are easily seen with bright-field illumination. They do not dissolve in alkaline urine.

3. **Leukocytes and nucleated cells in the urine.** Normal midstream urine contains up to 2,000 nucleated cells per mL, and most of these are leukocytes. Normal bladder urine obtained by needle aspiration contains very low counts of leukocytes (mean, 283 per mL, with only 2 of 25 urines containing more than 1,000 per mL). In one author's (KF) laboratory, the mean count in a midstream specimen in the same subjects performed at the same time was 2,018 leukocytes per mL, even when meticulous care was taken to avoid contamination. The additional cells in the midstream sample presumably arise in the urethra.

   An increase in the leukocyte count in the urine most commonly implies infection. Infected urines show an increase in leukocytes in more than 90% of cases. When pyuria is present without bacteriuria, three-fourths of patients show an underlying urinary tract abnormality.

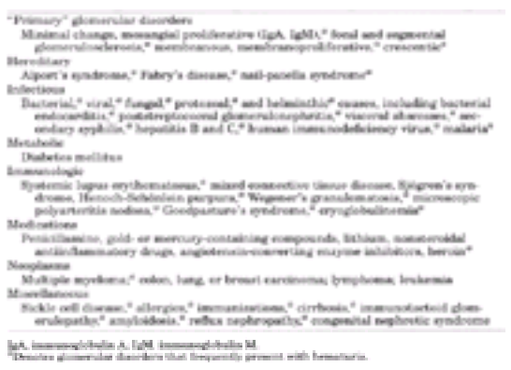
   Sterile pyuria may be seen in tuberculosis, renal papillary necrosis, acute interstitial nephritis, urate nephropathy, glomerulonephritis,and polycystic disease of the kidney. It may also be present in patients with calculi and in a variety of other urinary tract abnormalities. Before a diagnosis of sterile pyuria is made, fastidious organisms such as ureaplasmas, anaerobic bacteria such as *Gardnerella vaginalis*, and chlamydia should be sought in an appropriate specimen using special cultural techniques.

   When it is difficult to distinguish leukocytes from renal tubular epithelial cells, a drop of acetic acid makes it easier to recognize the lobed nuclei of polymorphonuclear leukocytes. Staining the cells also distinguishes them.
4. **Renal tubular cells.** Large numbers of renal tubular cells are found in the urine in acute tubular necrosis and acute interstitial nephritis. Acute interstitial nephritis can be distinguished by a much higher count of leukocytes (more than 15,000 per mL) and a higher total nucleated cell count (more than 75,000 per mL) than are seen in acute tubular necrosis. Eosinophils are present in the urine in most cases of interstitial nephritis in counts above 5,000 per mL and are rare in acute tubular necrosis. Eosinophils in the urine are best seen with Hansel's stain, which, unlike Wright¢s stain, is not pH dependent.

   Nucleated cells are also present in the urine in glomerulonephritis,particularly crescentic glomerulonephritis, in which total cell counts, leukocytes, and renal tubular cells are present in higher numbers than in noncrescentic glomerulonephritis. Glomerular epithelial cells identified by monoclonal antibody staining are also present in a much higher percentage of urines from patients with crescentic glomerulonephritis than from those with noncrescentic glomerulonephritis.
5. **Crystals.** Although crystals of calcium oxalate and uric acid may be seen in normal urine samples, large, bizarre crystals of any type, including calcium oxalate and uric acid, usually indicate increased urinary excretion and may indicate calculous disease. Cystine crystals are always abnormal and indicate cystinuria.

II. Hematuria

A. **Localization and differential diagnosis.** An abnormal quantity of erythrocytes in the urine can either be due to a glomerular disorder or to nonglomerular bleeding. Glomerular bleeding should be suspected if any of the following are present: dysmorphic urinary erythrocytes, erythrocytes with mean corpuscular volume less than 72 fL, red blood cell casts, and concomitant proteinuria, especially higher than 1 g per day. In Table 8-3, an asterisk denotes those glomerular disorders that frequently manifest hematuria. Nonglomerular hematuria is characterized by the presence of isomorphic urinary erythrocytes with a mean corpuscular volume of more than 72 fL in the absence of red blood cell casts or significant proteinuria. The further localization of nonglomerular bleeding can be suggested by the three-glass test. In this procedure, patients with macroscopic hematuria urinate 10- to 15-mL aliquots of urine each into three containers. A urethral site of bleeding is suggested if the hematuria predominates in the first 10 mL, whereas a bladder origin is implied if the majority of blood is in the final aliquot. Upper-tract bleeding is characterized by hematuria in all three collection vessels. The differential diagnosis of nonglomerular proteinuria is outlined in Table 8-4. Many of these disorders are either characterized by or occasionally present with hematuria.



“Primary” glomerular disorders
Minimal change, mesangial proliferative (IgA, IgM),* focal and segmental glomerulosclerosis,* membranous, membranoproliferative,* crescentic*
Hereditary
Alport's syndrome,* Fabry's disease,* nail-patella syndrome*
Infectious
Bacterial,* viral,* fungal,* protozoal,* and helminthic* causes, including bacterial endocarditis,* poststreptococcal glomerulonephritis,* visceral abscesses,* secondary syphilis,* hepatitis B and C,* human immunodeficiency virus,* malaria*
Metabolic
Diabetes mellitus
Immunologic
Systemic lupus erythematosus,* mixed connective tissue disease, Sjögren's syndrome, Henoch-Schönlein purpura,* Wegener's granulomatosis,* microscopic polyarteritis nodosa,* Goodpasture's syndrome,* cryoglobulinemia*
Medications
Penicillamine, gold- or mercury-containing compounds, lithium, nonsteroidal antiinflammatory drugs, angiotensin-converting enzyme inhibitors, heroin*
Neoplasms
Multiple myeloma,* colon, lung, or breast carcinoma; lymphoma; leukemia
Miscellaneous
Sickle cell disease,* allergies,* immunizations,* cirrhosis,* immunotactoid glomerulopathy,* amyloidosis,* reflux nephropathy,* congenital nephrotic syndrome

IgA, immunoglobulin A; IgM, immunoglobulin M.
*Denotes glomerular disorders that frequently present with hematuria.

Table 8-3. Causes of glomerular proteinuria

Hereditary
Polycystic kidney disease, medullary cystic disease
Infectious
Pyelonephritis, tuberculosis
Metabolic
Diabetes mellitus, hyperuricemia, uricosuria, hyperoxaluria, hypercalciuria, hypokalemia, oxalosis, cystinosis
Immunologic
Sjögren's syndrome, renal transplant rejection, drug hypersensitivity, sarcoidosis
Toxic
Analgesic abuse, radiation nephritis, lithium, heavy metals (lead, cadmium, mercury), Balkan nephritis, cyclosporine, cisplatinum, aminoglycosides
Anatomic
Obstruction, ureterovesical reflux, medullary sponge kidney
Miscellaneous
Multiple myeloma, amyloidosis, sickle cell disease, medullary sponge kidney

Table 8-4. Causes of tubular proteinuria

B. **Clinical evaluation and treatment.** Patients with hematuria may present with quantities of blood visible to the naked eye (macroscopic or gross hematuria) or visible only by microscopical examination (microscopic hematuria). The initial evaluation of the patient with gross or microscopic hematuria should include those steps outlined above to distinguish glomerular from nonglomerular causes. If a glomerular cause is suspected, patients should be further evaluated as described in section **III.C**.

For patients who have been determined to have nonglomerular hematuria, the differential diagnosis outlined in Table 8-4 may be narrowed by obtaining a relevant history and physical examination. The history and review of systems should include questions regarding passage in the urine of stones, tissue, or blood clots; frequent urinary tract infections; episodic gross hematuria; fever; weight loss; medication or drug use, particularly oral contraceptives or analgesics; dysuria; tuberculosis; diabetes mellitus; trauma; coagulation disorders; and family history of renal disease. Pertinent aspects of the physical examination should include auscultation for renal bruits, palpation of the prostate for nodules or prostatitis, and palpation of the abdomen for enlarged kidneys indicative of polycystic kidney disease.

Table 8-5 outlines a suggested diagnostic approach to the patient with nonglomerular hematuria. Initial laboratory studies should include a CBC, prothrombin time, and partial thromboplastin time to rule out coagulopathy and hemoglobinopathy. A serum chemistry panel is useful to determine level of renal function and to rule out the presence of hypercalcemia, hyperuricemia, and hyperglycemia. Urine should be cultured for bacterial and mycobacterial infection and, if clinically suspected, mycoplasma or other more fastidious organisms. Once a urinary tract infection has been excluded, an examination of the urinary tract anatomy should be undertaken to define the bleeding site. In the presence of normal or near-normal glomerular filtration rate (GFR), intravenous urography is the most useful diagnostic radiologic procedure available for defining renal anatomy. It should disclose the presence of renal cysts (hereditary and acquired); calculi; papillary necrosis; medullary sponge kidney; renal, pelvic, and ureteral tumors; and ureteral strictures. In the event of a nondiagnostic intravenous urographic study, cystoscopy can be performed to more definitively examine the bladder for the presence of tumors or infectious (inflammatory/interstitial) cystitis and the urethra for the presence of urethritis, strictures, or both. A nondiagnostic cystoscopic examination can be followed, if clinically indicated, by arteriography to pursue the possibility that hematuria is secondary to ureteral varices or aneurysms, arteriovenous malformations, or the loin-pain hematuria syndrome.

Urinary findings		
No erythrocyte casts		
Urinary RBC of normal morphology		
Proteinuria < 1 g/d (< 70 mg/m^2)		
Urinary RBC > 72 fL		
↓		
Urine culture and sensitivity, acid-fast bacteria × 3	Diagnostic →	Urinary tract infection
Prostatic examination		Tuberculosis
Cytology		Tumors
↓		
Nondiagnostic		
↓		
Intravenous urography (or ultrasound)	Diagnostic →	Cystic disorders Intrarenal tumors Calculi Papillary necrosis Trauma/fracture Medullary sponge kidney Horseshoe kidney
↓		
Nondiagnostic		
↓		
Cystoscopy/retrograde	Diagnostic →	Urethral lesions Cystitis Collecting system/bladder tumors
↓		
Nondiagnostic		
↓		
Angiography	Diagnostic →	Ureteral varices Aneurysm Arteriovenous malformations

RBC, red blood cells.

Table 8-5. A diagnostic approach in the patient with nonglomerular hematuria

The treatment of hematuric states is entirely dependent on the underlying cause for erythrocyturia. The reader is therefore referred to textbooks of internal medicine, nephrology, and urology for detailed coverage of these topics. In this section, however, urinary tract infections are discussed briefly, as they are commonly encountered by the general practitioner as well as by the specialist.

The most common presentation with urinary tract infection is dysuria and frequency in a woman of childbearing years. The urine may show macroscopic or heavy nonglomerular microscopical hematuria, as well as pyuria and bacteriuria. Treatment with a single dose of an appropriate antibiotic (e.g., 2 g of amoxicillin or ampicillin) cures the infection in 80% of cases. Antibiotic resistance may be responsible for some treatment failure (e.g., ampicillin-resistant *Escherichia coli*). However, unresponsiveness to treatment may be an indication for further investigation, because a high percentage of those who do not respond to a single dose show abnormalities on further investigation by imaging techniques, such as intravenous urography. Failure to respond to treatment may also suggest an upper rather than lower urinary tract infection.

Urinary tract infection in a child or a man should always be investigated, because of the high incidence of underlying abnormalities. Infection in the presence of an underlying urinary tract abnormality usually requires longer courses of treatment. Eradicating the infection without removing the abnormality may be impossible in some cases, notably with infected stones or staghorn calculi.

III. Proteinuria

A. **Biochemical evaluation.** Although not specific for glomerular disease, an abnormal amount of protein excreted in the urine is a cardinal manifestation of disease in virtually all patients with glomerulonephritis. Fever, exercise, hyperglycemia, and severe hypertension can transiently increase proteinuria.

To precisely quantitate and qualitatively analyze the amount and composition of urinary proteins, an examination of a 24-hour collection of urine is usually required. The collection method involves emptying the bladder and discarding the first urine on the morning of collection, and scrupulously collecting all subsequent urine for the next 24 hours. The final urine at the end of the 24-hour period is also kept as part of the collection. If the urine is refrigerated during the 24-hour period, no preservative is required. If refrigeration is unavailable, a preservative such as acetic acid (or a cup of vinegar) can be added to the collection vessel.

Quantification of the 24-hour urine creatinine should be performed to ensure that a complete collection was submitted. In females under steady-state conditions of renal function, the 24-hour urinary excretion of creatinine should equal approximately 15 to 20 mg per kg of ideal body weight; in males, the excretion should

be 18 to 25 mg per kg. Accurate quantitative methods of protein excretion by precipitation include the sulfosalicylic acid precipitation test, the micro-Kjeldahl method, Esbach's picric acid–citric acid reagent, and the biuret method. Results are expressed either as grams excreted in 24 hours or as a ratio of protein to creatinine excretion.

In following a patient with heavy proteinuria (e.g., assessing responsiveness to therapy), a urinary protein-creatinine concentration ratio on the first voided morning urine sample is useful as a substitute for repeated full 24-hour urine collections. The normal 24-hour urine protein excretion in the adult ranges from 30 to 130 mg. Children and adolescents may excrete as much as twice this amount. Normal spot urinary protein-creatinine ratios on random samples generally fall below 0.2. Values higher than 3 suggest the presence of nephrotic range proteinuria.

Qualitative assessments of urinary protein composition are often a valuable addition to the quantitative examination. Urine protein electrophoresis (UPEP) separates urinary proteins on the basis of molecular weights into five peaks: albumin and a_1, a_2, b and g globulins. Normally, urinary proteins are composed of filtered proteins from plasma (50%) and proteins that are secreted into the urine from urinary tract cells (50%). Of the filtered proteins, albumin is the most abundant, representing approximately 15% of the total urinary protein. This is followed by immunoglobulins (5%), light chains (5%), b_2 microglobulin (<0.2%), and other plasma proteins (25%). Of the secreted proteins, Tamm-Horsfall protein enters the urine after synthesis in the tubular cells of the ascending limb of the loop of Henle. It is the single most abundant protein in normal urine, accounting for 50% of the total urinary protein.

UPEP and immunoelectrophoresis (IEP) can be helpful in identifying the nature of proteins present in the urine. Examining the urine for Bence Jones proteinuria by seeking urinary precipitates at 45° to 55°C that redissolve at higher temperature is a less sensitive method than are UPEP and IEP for identifying overflow proteinuria.

B. **Pathophysiologic classification of proteinuria.** Given the diverse sources of urinary proteins and the implication of source for the site of pathology, proteinuria is classified into three major categories reflecting pathogenesis.

1. **Overflow proteinuria** is due to the filtration by the normal glomerulus of an abnormally large amount of small-molecular-weight protein present in serum whose filtration exceeds the capacity of normal tubules for reabsorption. This occurs in monoclonal gammopathies (such as multiple myeloma), in intravascular hemolysis (hemoglobinuria), and in rhabdomyolysis (myoglobinuria). Overflow proteinuria can be identified by an abnormal peak or “spike” on the UPEP. For example, a “spike” occurring in the g region (or, less commonly, in the a_2 or b region) suggests the presence of a monoclonal gammopathy. Further identification of the protein can be accomplished by performing IEP.
2. **Tubular proteinuria** is found in both acute and chronic injuries involving the renal tubulointerstitial region. Usually quantitatively less than 2 g per day, tubular proteinuria is derived from three sources. First, injured tubules fail to completely reabsorb small-molecular-weight proteins filtered by the glomerulus, such as b_2 microglobulin and amylase. Second, injured tubules secrete brush border components and cellular enzymes, such as n-acetylglucosamine and lysozyme, into the urine. Finally, with tubulointerstitial injury, Tamm-Horsfall protein may be secreted into the urine in greater amounts by the tubular cells of the ascending limb of the loop of Henle and the distal nephron. UPEP and IEP may also aid in distinguishing glomerular from tubular proteinuria. The overwhelming predominance of albumin rather than globulins on a UPEP suggests the presence of glomerular proteinuria. A quantitative comparison of the urinary albumin and b_2 microglobulin levels performed by IEP or other immunologic techniques (including immunoprecipitation, immunodiffusion, or radioimmunoassay) may also be helpful in this regard. A urinary albumin to b_2 microglobulin ratio of 10 to 1 suggests the presence of tubular proteinuria, whereas in glomerular proteinuria, this ratio usually exceeds 1,000 to 1. In normal urine, the albumin to b_2 microglobulin ratio ranges from 50 to 1 to 200 to 1.
3. **Glomerular proteinuria** occurs when injury to the glomerulus results in an ultrafiltrate characterized by a fractional increase in the clearance of serum proteins. In some forms of glomerulonephritis, this is due to changes in the size-selective properties of the glomerular basement membrane that allow the passage of larger-molecular-weight proteins or even of cells (e.g., in crescentic glomerulonephritis). In other forms, this is due to changes in the charge-selective properties of the glomerular basement membrane that enhance the ultrafiltration of negatively charged albumin (e.g., minimal change nephropathy). Some glomerular disorders are characterized by changes in both size and charge selectivity (e.g., diabetic nephropathy). Mesangial injury may also induce proteinuria, perhaps by interfering with normal mesangial clearance functions.

   Glomerular proteinuria is composed predominantly of albumin and, when quantitatively large (i.e., more than 3.0 to 3.5 g per day, or more than 2 g per day per m^2), is said to be in the nephrotic range. The nephrotic syndrome consists of a pentad of nephrotic-range proteinuria, hypoalbuminemia, hyperlipidemia, lipiduria, and edema. With the exception of minimal-change glomerulopathy, the occurrence of heavy proteinuria in glomerular disorders is associated with higher risk for progressive renal insufficiency.
4. **Other types of proteinuria.** Two forms of proteinuria do not fit easily into the classification described above. Benign orthostatic proteinuria is typically found in tall adolescents and occurs in the lordotic position. Protein is found in the urine collected on retiring and in the morning after the patient has been ambulant, but not in the over night specimen collected immediately on rising. There should be no abnormality in the urine sediment, and proteinuria should not exceed 1 g per day. In one-half of these patients, proteinuria disappears within 10 years; however, in a small proportion, overt renal dis ease develops in later life. Finally, functional, transient proteinuria may be associated with such diverse causes as cardiac failure, fever, or heavy exercise. It disappears within hours after cessation of exercise and with resolution of the disease process. Proteinuria after marathon running may be as heavy as 5 g per L of urine.

C. **Clinical evaluation and treatment.** The most important first step in the development of an appropriate differential diagnosis and subsequent treatment plan for patients with proteinuria is classification of the urinary protein.

1. **Classification of proteinuria**
   a. **Overflow proteinuria.** A disparity characterized by a small amount of proteinuria demonstrated by dipstick and a disproportionately larger amount measured on a 24-hour collected specimen suggests the presence of overflow. This is most often due to excretion of monoclonal light chains, which can be confirmed by IEP. Identification of a monoclonal immunoglobulin in the urine should stimulate diagnostic testing for multiple myeloma, amyloidosis, or a lymphoproliferative disorder. Hemoglobinuria and myoglobinuria can also cause overflow proteinuria. However, these are readily identifiable, because in these conditions the dipstick for blood is strongly positive, whereas the microscopical examination of urine demonstrates few or no red blood cells. This finding should stimulate an evaluation for hemolysis and for rhabdomyolysis.
   b. **Tubular proteinuria.** A wide range of conditions can cause tubulointerstitial injury (see Table 8-4). Investigation of tubular proteinuria should begin with a detailed history regarding other affected family members (to rule out polycystic kidney disease); prescribed or over-the-counter medication use (analgesic nephropathy); frequent urinary tract infections (reflux); flank pain; passage of renal stones; skin rash, arthralgias, arthritis (drug hypersensitivity, collagen-vascular disease); dry mouth or eyes (Sjögren's syndrome); occupational or recreational exposure to potential toxins; and manifestations of systemic disease. Physical findings confirmatory of disorders in the differential diagnosis listed in Table 8-4 should be sought. These might include palpably enlarged kidneys (polycystic kidney disease), band keratopathy (hypercalcemia, hyperparathyroidism), skin rash (systemic lupus, drug hypersensitivity), arthritis (gout, lupus), or oral mucosal lead line (lead toxicity). Laboratory tests including CBC with examination of the peripheral smear; measurements of serum creatinine, urea nitrogen, glucose, calcium, phosphorus, uric acid, and potassium; and urine culture are adjunctive information to the history, physical examination, urinalysis, and quantitative urine studies in focusing the differential diagnosis. Positive or negative results in these areas may suggest the need for further tests, which may include renal ultrasound (polycystic kidney disease, renal stones, obstruction); urine, serum, or hemoglobin electrophoresis (monoclonal gammopathy, sickle cell disease or trait); urine culture and sensitivity (pyelonephritis, renal tuberculosis); serum angiotensin-converting enzyme level (sarcoidosis); intravenous urography (medullary sponge kidney); or serum lead levels (lead toxicity). Although some tubulointerstitial disorders have characteristic histomorphologic features (medullary cystic disease, amyloidosis, myeloma kidney, hypokalemia), the microscopical appearance of most tubulointerstitial disorders lacks uniquely distinguishing characteristics. Renal biopsy is therefore used infrequently in the diagnosis of patients with tubulointerstitial disease. Therapy for the tubulointerstitial disorders is dependent on the underlying cause.
   c. **Glomerular proteinuria.** When proteinuria is characterized by a disproportionate amount of albumin, a glomerular origin is implied. Mild transient proteinuria, especially associated with acute and reversible disease, is usually of little long-term significance. However, heavy and sustained proteinuria suggests a more serious disorder. Because the differential diagnosis is large, and many of the implicated disorders are uncommon, consultation with a nephrologist is recommended during the initial evaluation and treatment.

      Patients with constant heavy proteinuria require close diagnostic scrutiny. Glomerular proteinuria in this group is often categorized either as nonnephrotic (less than 3.5 g per day per 1.73 m^2 body surface area) or nephrotic (more than 3.5 g per day per 1.73 m^2 body surface area). This somewhat arbitrary division of patients into those with lesser and greater amounts of urinary protein is justified by two major observations. First, patients with nonnephrotic proteinuria tend to have a better prognosis with regard to renal function than do patients with heavier proteinuria. As a result, an aggressive diagnostic or therapeutic approach may not be immediately indicated. Thus, after a search for underlying causes discernible by history, physical examination, and serologic assessment (see section **III.C.2**), judicious follow-up to observe the course of the renal function and degree of proteinuria may be indicated in individual patients before a consideration of renal biopsy and the use of potentially risky immunosuppressive therapeutic regimens. Second, the morbidity and prognosis of patients with heavier proteinuria is conferred not only by the patient's renal functional outcome, but also by the pathophysiologic consequences of heavy proteinuria (e.g., the nephrotic syndrome).

The nephrotic syndrome is defined by the presence of more than 3.5 g of proteinuria per 1.73 m ^{2}of body surface area per day, hypoalbuminemia, hyperlipidemia, lipiduria, and edema. Heavy proteinuria induces enhanced tubular reabsorption and catabolism of proteins leaked into the glomerular ultrafiltrate, contributing to hypoproteinemia. Sodium and water retention with resultant edema occur secondary to hypoproteinemia in some patients and as a direct result of glomerular injury in others. Hypoproteinemia and an associated decrement in plasma oncotic pressure may stimulate apolipoprotein synthesis in the liver, causing hyperlipidemia and lipiduria. It is postulated that in nephrotic disorders that persist for many years (e.g., membranous nephropathy), hyperlipidemia may contribute to accelerated atherosclerosis. Heavy proteinuria also predisposes to hypercoagulability; variable losses of antithrombin III, protein S, and protein C have been described in some but not all nephrotic patients. Other urinary losses may variably induce subtle abnormalities of function in some patients with nephrotic syndrome, including losses of immunoglobulin and complement (predisposition to infection), thyroid-binding globulin (low total thyroxine, normal thyroid-stimulating hormone), and vitamin D (hypovitaminosis, hypocalcemia, and secondary hyperparathyroidism). Individuals with heavy proteinuria express the complications of nephrotic syndrome variably, reflecting differences in urinary protein losses, dietary intake, and genetic predisposition.

2. **The differential diagnosis of heavy proteinuria.** Once proteinuria is determined to result from glomerular injury, an underlying disorder should be sought. The very large differential diagnosis outlined in Table 8-3 can be narrowed substantially by obtaining a detailed history, physical examination, and appropriate serologic testing. The history should cover the following important details: the presence of diabetes; deafness; similarly affected family members (suggestive of Alport's nephropathy or other familial nephritis); ethnicity [immunoglobulin A (IgA) nephropathy is frequent in Asians and infrequent in blacks]; presence of fever; travel; medication use; transfusions, drug abuse, sexual orientation and partners (human immunodeficiency virus, hepatitis, syphilis); arthritis, arthralgias, malar or skin rash, oral ulcers, alopecia (systemic lupus erythematosus and other immune or hypersensitivity disorders); hemoptysis (Goodpasture's disease, Wegener's granulomatosis); sinusitis, sterile otitis (Wegener's granulomatosis); paresthesias, focal neurologic deficits (Fabry's disease); weight loss, cough, breast mass (malignancy and secondary membranous nephropathy); allergies; childhood/adolescent urinary tract infections (focal sclerosis secondary to reflux nephropathy); and episodes of gross or persistent microhematuria (IgA nephropathy, thin basement membrane disease).

   The physical examination should be directed at establishing whether systemic disease is present and whether the nephrotic syndrome or its complications are present. All adult patients with abnormal proteinuria should also have, at a minimum, a chest x-ray; CBC; serum and urine protein electrophoresis; serum chemistry panel, including tests of renal and hepatic function; and measurement of serum albumin, total protein, total and high-density lipoprotein cholesterol, triglycerides, glucose, and calcium levels. For patients older than the age of 40 to 50, stool guaiac examination in men and women and mammography in women should also be performed. Additional serologic testing may be warranted, depending on the presence or absence of hematuria and the results of the aforementioned studies. Such additional tests include, but are not limited to, antinuclear antibody (lupus); antineutrophil cytoplasmic antibody (Wegener's granulomatosis and other vasculitic syndromes); C3, C4 (may be low in endocarditis, poststreptococcal glomerulonephritis, lupus, membranoproliferative glomerulonephritis, cryoglobulinemia); antihyaluronidase, anti-DNase B, antistreptolysin O (poststreptococcal glomerulonephritis); anti–glomerular basement membrane antibody (Goodpasture's disease); rheumatoid factor (endocarditis, cryoglobulinemia, rheumatoid arthritis); serum cryoglobulins; angiotensin-converting enzyme (sarcoidosis); glycosylated hemoglobin; serologic testing for syphilis; hepatitis B antigens and antibody; recombinant immunoblot testing for hepatitis C; and enzyme-linked immunoabsorbent assay/Western blot for human immunodeficiency virus. In the spirit of cost-consciousness, these tests should not be routinely ordered in all patients with glomerular proteinuria. Rather, a thoughtful synthesis of the history and physical examination should guide the selection of appropriate tests among those listed (and potentially others not mentioned).

   A renal biopsy should be considered if no underlying disorder emerges as a cause for glomerular proteinuria after a thorough evaluation. In addition, renal biopsy is indicated when a secondary cause has been identified and a histologic examination of the renal tissue would help guide therapy.

3. **Therapy.** The treatment of glomerular disorders falls into three categories: treatment of the underlying systemic disease, general management of the nephrotic syndrome, and therapies for specific glomerular diseases.
   a. **Treatment of underlying systemic disease.** Due to the large number of entities that potentially cause glomerulonephritis, the reader is referred to a textbook of internal medicine or nephrology for their treatment. However, special mention should be made of diabetes mellitus and systemic lupus erythematosus. Data suggest that tight glycemic control and angiotensin converting enzyme inhibitors (ACEi) are useful in preventing or forestalling the development of overt diabetic nephropathy in patients with insulin-dependent diabetes mellitus (type 1) and microalbuminuria. ACEi have also been shown to have a favorable impact on serum creatinine levels, progression to end-stage renal disease, and overall mortality in patients with type 1 diabetes and overt diabetic nephropathy. For the treatment of diffuse proliferative lupus nephritis, most data suggest that the use of cytotoxic agents (oral or intravenous cyclophosphamide) with steroids is superior to therapy with steroids alone.
   b. **General management of the nephrotic syndrome.** The treatment of edema due to the nephrotic syndrome begins with sodium restriction and diuretics. Care should be taken to avoid inducing a state of marked prerenal azotemia.

      Many strategies have been advocated to decrease heavy proteinuria. Nonsteroidal antiinflammatory drugs (NSAIDs) reportedly produce a decrease in proteinuria in some patients, along with a smaller decrement in GFR. Despite their utility in a few patients, however, the overall impact of NSAIDs in substantially diminishing proteinuria for the majority of patients with nephrosis is disappointingly small. ACEi are also useful to decrease proteinuria, and their efficacy has been tested both in patients with diabetic nephropathy and in patients with the idiopathic nephrotic syndrome. The minimum dose required for maximal decrement of proteinuria is unknown, which is an issue of some concern when applying this treatment to nephrotic patients who may not be hypertensive, many of whom have diminished intravascular volume from salt restriction and diuretics. Many months may elapse between ACEi initiation and a decrement in proteinuria, a phenomenon that suggests more than hemodynamic change as its mechanism of action. Proteinuria may also be reduced by lowering patients' mean arterial pressure to levels lower than 92 mm Hg, independent of the class of antihypertensive agents used to achieve this target. Finally, dietary protein restriction in the range of 0.6 to 0.8 g per kg per day has been suggested, both to slow the rate of loss of renal function and as a further means of diminishing proteinuria. Long-term studies regarding nutritional safety are still necessary before this strategy should be advocated in patients with heavy proteinuria (i.e., more than 10 g per day).

      The hyperlipidemia of the nephrotic syndrome may contribute to accelerated atherosclerosis. Use of the HMG-CoA (3-hydroxy-3-methylglutaryl-coenzyme A) reductase inhibitors or agents such as gemfibrozil often lowers serum low-density lipoprotein cholesterol and triglyceride levels substantially in patients with nephrosis. For the patient with venous or, less commonly, arterial thrombosis or pulmonary emboli, long-term anticoagulation for the duration of the nephrotic syndrome is recommended.
   c. **Therapies for specific glomerular diseases.** The so-called primary glomerular disorders fall into essentially seven histologic categories: minimal change glomerulopathy, IgM mesangial proliferative glomerulonephritis, focal and segmental glomerulosclerosis, IgA nephropathy, membranous nephropathy, membranoproliferative glomerulonephritis (MPGN), and crescentic glomerulonephritis. From a therapeutic standpoint, the first three are often considered as a group, and the latter four are considered separately. Because these disorders are relatively uncommon and therapies often involve the use of potentially toxic drugs, referral to a nephrologist is advised.
      1. **Minimal change glomerulopathy—IgM mesangial proliferation glomerulonephritis—focal and segmental glomerulosclerosis.** If the nephrotic syndrome is present, conservative general care as described in section **III.C.3.b** may be appropriate as an adjunct to specific therapy. These glomerular disorders are variably responsive to high-dose prednisone (1 mg per kg, maximum, 80 mg). More than 90% of children with minimal change glomerulopathy have a complete remission of proteinuria within 2 months of starting steroid therapy. In adults, this figure is approximately 80% to 90%. Response rates for the latter two disorders are not as high (approximately 40% to 50% and 20% to 30%, respectively). Extending the duration of high-dose prednisone to 4 months may accrue as many as 10% to 15% additional complete remissions. Prednisone should then be slowly tapered over approximately 4 months. Relapse, steroid dependence, or both can be treated with the addition of cytotoxic agents (e.g., cyclophosphamide or chlorambucil), cyclosporine A, or possibly mycophenolate mofetil, depending on the severity of the nephrotic syndrome and the level of renal function. Treatment of prednisone resistant patients is controversial.
      2. **IgA nephropathy (Berger's disease).** This is the most common form of primary glomerular disease in the world. It is particularly prevalent in Asia and Australia, and rare in African-Americans. Originally thought to be benign, it is now apparent that the condition progresses to end-stage renal disease in 20% to 40% of patients affected. Occasionally, reversible acute renal failure has been noted, particularly in association with gross hematuria. It may, rarely, be complicated by the presence of crescents. Clinically, it may be confused with the benign familial disorder thin basement membrane disease because the presenting manifestation of each is predominantly glomerular hematuria. These two entities may be distinguished by a family history of hematuria (occasional in IgA nephropathy, frequent in thin basement membrane disease), the presence of abnormal proteinuria (frequent in IgA nephropathy, rare in thin basement membrane disease), and renal biopsy (no glomerular immunoglobulins present in thin basement membrane disease, mesangial IgA in Berger's disease). No therapeutic regimen has been shown to clearly affect outcome in IgA nephropathy. However, warfarin and dipyridamole with or without cyclophosphamide have been suggested as worthy of further investigation. A national collaborative trial comparing the efficacy of omega-3 fatty acids, ACEi, and longterm steroids on clinical outcome in IgA nephropathy is under way.
      3. **Membranous nephropathy.** Two-thirds of patients with this disorder either have a spontaneous remission or have stable or very slowly progressive renal insufficiency. Thus, the majority do well with conservative therapy directed at minimizing complications from the nephrotic syndrome. For patients at high risk for progression (e.g., those with heavy proteinuria, more than 10 g per day; hypertension; diminished GFR; male gender; or tubulointerstitial fibrosis on renal biopsy), specific therapy may be indicated. In this setting, steroids with a cytotoxic agent (either chlorambucil or

cyclophosphamide) appear to be preferable to steroids alone in inducing a timely complete or partial remission.

4. **MPGN.** Some investigators controversially suggest that children with MPGN type I (mesangial and subendothelial deposits) benefit from steroid therapy. Initial enthusiasm for the use of aspirin and dipyridamole has waned. No therapy is effective for type II (dense-deposit disease). Evidence suggests that hepatitis C infection induces an MPGN type I pattern and clinical glomerulonephritis. Definitive therapy for these patients is uncertain, but interferon-a and ribavirin may be indicated and steroids and cytotoxics relatively contraindicated.
5. **Crescentic glomerulonephritis.** When glomerulonephritis is accompanied by crescents, a nephrologic emergency is present, due to the propensity for rapid progression to end-stage renal disease. Early diagnosis and implementation of therapy are essential to preserve renal function. After excluding poststrep tococcal glomerulonephritis, three forms of crescentic glomerulonephritis are recognized. The reader is referred to a textbook of nephrology for the treatment of type I (antiglomerular basement membrane nephritis, or Goodpasture's syndrome) and type III (pauci-immune glomerulonephritis, Wegener's granulomatosis). Type II (immune complex–mediated glomerulonephritis) is treated initially with intravenous methylprednisolone sodium succinate (Solu-Medrol), followed by high-dose oral prednisone. Because of the relative rarity of the syndrome, no randomized controlled trials have proved that additional benefits accrue from the use of cytotoxic agents. However, largely due to the clear-cut benefits of cyclophosphamide in types I and III and plasmapheresis in type I, some investigators have recommended their use in type II.

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Chapter 9 The Patient with Acute Renal Failure

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Making the diagnosis
Etiology
Differential diagnosis
Management

I. Making the diagnosis

A. **Acute renal failure (ARF)** is characterized by a decrease in glomerular filtration rate (GFR) occurring over a period of hours to days, resulting in the failure of the kidney to excrete nitrogenous waste products and maintain fluid and electrolyte homeostasis. Clinically, it can be diagnosed by one of the following:
   1. **An increase in blood urea nitrogen (BUN) only** (prerenal ARF).
   2. **An increase in BUN and serum creatinine.** Normal BUN is 8 to 18 mg per dL, and normal serum creatinine is 0.6 to 1.2 mg per dL. Serum creatinine should be interpreted in relationship to the muscle mass of the patient. For example, a serum creatinine of 1.2 mg per dL in a 40-kg patient with cancer and wasted muscles may represent a severely impaired GFR. On the other hand, a serum creatinine of 1.2 mg per dL in a 100-kg weightlifter with large muscle mass may represent a normal GFR. The GFR may also be estimated by one of the following methods:
      a. Cockcroft-Gault formula (accurate only if renal function is in a steady state):

$$\text{In a male, the GFR} = \frac{[140 - \text{age (yr)}] \times \text{lean body weight (kg)}}{\text{serum creatinine (mg/dL)} \times 72}$$

      In a female, the GFR is 0.85 of the value for a male.
      b. Creatinine clearance (C_{Cr}) gives a better estimate of GFR:

$$C_{Cr} = \frac{\text{urine creatinine (mg/dL)} \times \text{urine volume (mL/24 hr)}}{\text{Serum creatinine (mg/dL)} \times 1{,}440 \text{ min}}$$

      Normal ranges for C_{Cr} are 97 to 137 mL per minute per 1.73 m^2 for males and 88 to 128 mL per min per 1.73 m^2 for females.
   3. **Oliguria.** Oliguria is defined as a urine output of less than 400 mL per day; 400 mL is the minimum amount of urine that a person in a normal metabolic state must excrete to get rid of the daily solute production. For example, a person with a daily solute production of 500 mOsm that concentrates urine to a maximum of 1,200 mOsm per L would need to pass 400 mL of urine per day to excrete the daily solute production.

B. **Chronic renal failure** is the likely cause of increased BUN and serum creatinine in patients who are not acutely ill. Increased BUN and serum creatinine in an acutely ill patient with oliguria is likely to be caused by ARF. Features suggesting chronic renal failure are
   1. **Symptoms lasting longer than 3 months** (e.g., malaise, nocturia).
   2. **Increased BUN or serum creatinine documented months earlier.** A previous systemic disease (e.g., diabetes mellitus, hypertension, systemic lupus erythematosus) or a history of kidney disease (e.g., kidney infection, abnormal urinalysis on a previous physical examination, nephrolithiasis) suggests that the azotemia may be chronic.
   3. **Normocytic normochromic anemia.** Patients with ARF and a microangiopathic hemolytic anemia (e.g., hemolytic uremic syndrome) may have a normocytic anemia.
   4. **Small kidneys (less than 10 cm) on renal ultrasound.** Some patients with chronic renal failure, such as diabetic nephropathy, amyloidosis, or autosomal dominant polycystic kidney disease, or malignant hypertension may have normal-sized kidneys.

II. Etiology. The causes of ARF are classified as prerenal, intrinsic renal, and postrenal.

A. **Prerenal azotemia.** Prerenal azotemia may be defined as an acute rise in BUN, serum creatinine, or both due to renal hypoperfusion associated with a bland urine sediment (absence of cells and casts) and the return of renal function to normal within 24 to 72 hours of correction of the hypoperfused state. Acute azotemia can be classified as prerenal in the majority of patients. Prerenal azotemia represents a decrease in GFR resulting from a decrease in renal perfusion pressure, intense renal vasoconstriction, or both.

   Prerenal azotemia often precedes and predisposes to the development of intrinsic ARF and as such is a risk factor for the more serious forms of ARF. Because the causative factors for prerenal azotemia and intrinsic ARF overlap, distinguishing between these two disease states may become possible only by the outcome of therapy (e.g., if volume repletion improves cardiac function and rapidly reverses the azotemia, then prerenal azotemia was present).

B. **Underlying causes** of prerenal azotemia
   1. Intravascular volume depletion, secondary to
      a. Hemorrhage
      b. Renal fluid losses (e.g., excessive diuresis, osmotic diuresis, salt-wasting nephritis, diabetes insipidus)
      c. Gastrointestinal losses (e.g., vomiting, diarrhea, bleeding, tube drainage)
      d. Skin loss of sweat
      e. Third-space losses
         1. Burns
         2. Traumatized tissue
         3. Peritonitis
         4. Pancreatitis
   2. Reduced cardiac output, secondary to
      a. Congestive heart failure
      b. Cardiogenic shock (e.g., acute myocardial infarction)
      c. Pericardial effusion with tamponade
      d. Massive pulmonary embolism
   3. Peripheral vasodilation, secondary to
      a. Gram-negative sepsis
      b. Antihypertensive medications
      c. Anaphylaxis
   4. Increased renal vascular resistance from
      a. Surgery
      b. Anesthesia
      c. Hepatorenal syndrome
      d. Prostaglandin inhibitors [aspirin, nonsteroidal antiinflammatory drugs (NSAIDs)]
      e. Vasoconstricting drugs (cyclosporine, tacrolimus, radiocontrast)
   5. Decreased intraglomerular pressure
   6. Angiotensin-converting enzyme (ACE) inhibitors

C. **Postrenal azotemia.** The common denominator of acute azotemia in this setting is obstruction to the flow of urine. Obstruction of urine flow in both ureters, the bladder, or the urethra may cause postrenal ARF.
   1. The **common causes of postrenal ARF** include
      a. Bilateral ureteral obstruction or unilateral obstruction in a solitary kidney
         1. Intraureteral
            a. Stones

b. Blood clots
c. Pyogenic debris or sloughed papillae
d. Edema following retrograde pyelography

2. Extraureteral
a. Prostatic, bladder, or cervical cancer
b. Retroperitoneal fibrosis
c. Accidental ureteral ligation or trauma during pelvic surgery

b. Bladder neck obstruction
1. Prostatic hypertrophy
2. Prostatic and bladder carcinoma
3. Autonomic neuropathy or ganglionic blocking agents

c. Urethral obstruction
1. Urethral valves
2. Urethral stricture

2. **Risk factors and indications.** Patients most at risk for acute postrenal azotemia are elderly men, in whom prostatic hypertrophy or prostatic cancer may lead to complete or partial obstruction to urine flow. Young boys with congenital urethral valves may also have acute obstruction. In women, complete urinary tract obstruction is relatively uncommon in the absence of pelvic surgery, pelvic malignancy, or previous pelvic irradiation.

D. **Intrarenal or intrinsic ARF.** In contrast to prerenal azotemia and postrenal failure, the disorders listed here represent problems within the kidney itself. These problems may be renal vascular (large or small vessel), glomerular, interstitial, or tubular. The diseases may be primary renal or part of a systemic disease. The course of ARF in these situations cannot be changed by manipulating factors outside the kidney (e.g., performing volume repletion, improving cardiac function, correcting hypotension, removing obstruction).

1. Vascular—large vessels: Renal artery stenosis, thrombosis, or embolism
a. Operative arterial cross-clamping
b. Bilateral renal vein thrombosis

2. Vascular—small vessels
a. Vasculitis
b. Atheroembolic disease
c. Thrombotic microangiopathies
1. Hemolytic-uremic syndrome
2. Thrombotic thrombocytopenic purpura
3. Scleroderma renal crisis
4. Malignant hypertension

d. Thrombotic microangiopathies of pregnancy
1. *Hemolysis*, *e*levated *l*iver enzymes, and *l*ow *p*latelets (HELLP) syndrome
2. Postpartum ARF

3. **Glomerular.** When ARF develops in the setting of glomerulonephritis, a rapidly progressive glomerulonephritis (RPGN) should be excluded. Extracapillary proliferation in the glomerulus forms crescents that can rapidly destroy the glomeruli. An RPGN may be primary renal or part of a systemic vasculitis or other systemic disease. Causes of RPGN can be classified according to immunofluorescence staining on renal biopsy.
a. Diseases with linear immune complex deposition
1. **Goodpasture's syndrome** (pulmonary hemorrhage, RPGN, and circulating anti–glomerular basement membrane antibodies)
2. Renal-limited Goodpasture's syndrome

b. Diseases with granular immune complex deposition
1. Acute postinfectious glomerulonephritis
2. Lupus nephritis
3. Infective endocarditis
4. Immunoglobulin A (IgA) glomerulonephritis
5. Henoch-Schönlein purpura
6. Membranoproliferative glomerulonephritis

c. Diseases with no immune deposits (pauciimmune)
1. Wegener's granulomatosis
2. Polyarteritis nodosa
3. Idiopathic crescentic glomerulonephritis

4. **Interstitium.** In contrast to the proximal tubular necrosis seen commonly with ARF, the primary histologic lesion of acute interstitial nephritis is marked edema of the interstitial space and a focal or diffuse infiltration of the renal interstitium with lymphocytes, macrophages, plasma cells, eosinophils, and polymorphonuclear leukocytes. The two most common causes of acute interstitial nephritis (also called *acute tubulointerstitial nephritis*) are bacterial pyelonephritis and drug-induced acute allergic interstitial nephritis (AIN). Loss of renal function from drug hypersensitivity tends to be less abrupt and less severe than with classic ARF; nevertheless, dialysis therapy may be required. Recovery of renal function after withdrawal of the drug may be slow and incomplete. Hansel's stain of the urine may reveal eosinophils (see section **III.B**). Drugs commonly associated with acute interstitial nephritis are
a. Antibiotics, such as beta-lactam antibiotics (penicillins, cephalosporins), rifampicin, sulfonamides, erythromycin, and ciprofloxacin. Although any member of the penicillin group of drugs may cause interstitial nephritis, methicillin is the agent most often implicated.
b. Diuretics (e.g., furosemide, thiazides, chlorthalidone)
c. NSAIDs
d. Anticonvulsant drugs (e.g., phenytoin, carbamazepine)
e. Others (e.g., allopurinol)

5. **Tubular.** Acute tubular necrosis (ATN) is an abrupt decrease in GFR due to proximal tubular dysfunction caused by ischemia (50% of cases) and nephrotoxins (35% of cases). Although this type of renal injury has long been designated *acute tubular necrosis*, in many cases little true necrosis of tubular cells is present. Rather, the tubules demonstrate morphologic changes of sublethal injury (e.g., swelling, vacuolization, loss of brush border, apical blebbing, and loss of basolateral infoldings). Loss of viable tubular epithelial cells into the urine also occurs. The clinical consequences of this tubular dysfunction may be the abrupt recovery of renal function that is often seen in patients with ARF. With ischemic disorders, reduced blood flow to the kidneys results from either a decreased total blood volume or a redistribution of blood away from the kidney. ATN is seen most commonly after shock. In hospitalized patients, nephrotoxins have become a major cause of ATN, particularly those of the aminoglycoside class.

Causes of ATN include

a. Renal ischemia
1. Shock
2. Complications of surgery
3. Hemorrhage
4. Trauma
5. Gram-negative bacteremia
6. Pancreatitis
7. Postpartum hemorrhage

b. Nephrotoxic drugs
1. Antibiotics [e.g., aminoglycosides (especially in combination with vancomycin), amphotericin, pentamidine, foscarnet, acyclovir]
2. Antineoplastics (e.g., cisplatin)
3. Iodine-containing x-ray contrast
4. Organic solvents (e.g., carbon tetrachloride)
5. Ethylene glycol (antifreeze)
6. Anesthetics (enflurane)

c. Endogenous toxins
1. Myoglobin due to rhabdomyolysis
2. Hemoglobin (e.g., incompatible blood transfusion, acute falciparum malaria)

3. Uric acid (e.g., acute uric acid nephropathy)

III. Differential diagnosis A stepwise approach to the patient with ARF, outlined below in section **III.A**, section **III.B**, section **III.C**, section **III.D** and section **III.E**, is crucial. A comprehensive history and thorough physical examination suggest the diagnosis in the majority of patients. Urinalysis should always be performed to confirm the clinical diagnosis. Urinalysis can also make the diagnosis for the few patients in whom the diagnosis is unclear. In difficult cases, urine chemistry is performed.

A. **History and physical examination**
   1. **Evaluation of the acutely azotemic patient.** Whether the patient is seen for the first time in the office, in the emergency room, in the hospital, or in the intensive care unit (ICU), careful tabulation and recording of data are the first steps in diagnosis and treatment. Vital signs, daily weights, records of intake and output, past and current laboratory data, and the fluid and medication list should be recorded on a flow sheet and included in the patient's chart. When the patient has been hospitalized for several days or weeks with a complicated course before developing ARF, a carefully prepared flow sheet may often be the only way to comprehend the problem and guide the way to proper therapy.

      In evaluating a hospitalized patient with acute azotemia, it is helpful to determine whether the ARF developed outside the hospital, inside the hospital but not in the ICU, or inside the hospital and in the ICU.

      a. Common causes of **ARF developing outside the hospital** are
         1. **Chronic systemic illness.** Azotemia first discovered in the office or emergency room may be chronic or acute in origin. Features that suggest the renal failure is chronic are discussed in section **I.B**.
         2. Alternatively, an **acute systemic illness** (e.g., viral influenza, gastroenteritis) may lead to ARF through a variety of mechanisms (e.g., volume depletion, rhabdomyolysis with myoglobinuria). Acute poststreptococcal glomerulonephritis is usually preceded by streptococcal pharyngitis or pyoderma. Pyoderma may occur in children and adults of any age and is characterized by vesicular lesions, usually on the extremities, that become pustular and then crust.
         3. **Trauma** as the cause of acute azotemia is usually apparent at the time of admission to the hospital, but the unconscious or comatose patient may harbor internal injuries, extensive muscle damage, or acute urinary retention that is not discovered on the initial examination.
         4. **Obstructive uropathy.** Male patients with acute azotemia should be screened carefully for symptoms of prostatism. Female patients should be questioned about vaginal bleeding, previous pelvic surgery, and irradiation.
         5. **AIN.** Aspirin, NSAIDs, antibiotics, and diuretics are the main causes of AIN. These drugs are often prescribed outside the hospital. Steroids and tetracycline compounds cause an elevation of BUN, presumably through enhanced protein breakdown and urea production, but GFR is usually not affected, and thus this is not truly a renal disorder. Demecycline, however, may be nephrotoxic in the patient with liver disease.
         6. **Accidental or intentional intoxication** with heavy metal compounds, solvents, ethylene glycol, salicylates, or sedatives, especially in a patient presenting with disordered mentation, may explain an otherwise unexpected episode of ARF.
      b. **ARF developing inside the hospital but not in the ICU.** When azotemia develops in the hospital setting, the list of possible causes narrows. Most of these patients have either ATN (38%) or prerenal azotemia (28%). Acute or chronic renal failure, obstructive uropathy, acute glomerulonephritis, and AIN are also seen. Predisposing factors to ARF in this setting include
         1. **Fluid and electrolyte depletion,** which usually results from a failure to appreciate and replace fluid losses (e.g., excessive diuresis, nasogastric suction, surgical drains, diarrhea) in a patient who is too ill to control his or her own solute and water intake.
         2. Both **surgery and anesthesia** cause a vasoconstriction of the renal arteries and release of antidiuretic hormone; these effects may persist 12 to 24 hours into the postoperative period. As a result, reduced volumes of concentrated urine in the early postoperative period tend to be the rule rather than the exception. If postoperative infection or unexpectedly large wound or drain losses occur, negative fluid balance may supervene, leading to prerenal azotemia.
         3. **Nephrotoxic drugs and diagnostic agents** represent a major and serious cause of acute azotemia.
      c. **ARF developing in the ICU.** The majority of patients who develop ARF in the ICU have ATN (76%), and most of the rest have prerenal azotemia (18%). The mortality rate of these patients is over 70%, which is much higher than the mortality of ARF developing in other areas of the hospital. In a large study of more than 748 episodes of ARF in a hospital setting, the mortality rate was 72% in the ICU group and 32% in the non-ICU group. Seventy-one percent of the ICU patients required dialysis, but only 18% of the non-ICU patients did. In fact, patients with respiratory failure requiring mechanical ventilation who subsequently develop ARF in the ICU requiring dialysis have a very high mortality of more than 90%. However, the severity and mortality of isolated ARF is similar in ICU and non-ICU patients. In the ICU, ARF is often part of the multiorgan dysfunction syndrome.
   2. **Clinical features** of the common causes of ARF
      a. **Prerenal azotemia.** The following history is suggestive of prerenal azotemia: thirst; decreased fluid intake; increased fluid losses from fever, nausea, vomiting, or diarrhea; third-space losses in burns and pancreatitis; compromised cardiac function in patients with congestive heart failure; recent myocardial infarction; liver cirrhosis and failure (hepatorenal syndrome); cyclosporine, NSAID, or ACE inhibitor use. Because prerenal azotemia is a common cause of ARF, the adequacy of extracellular fluid (ECF) volume must be carefully determined. Assessment of volume status at the bedside is important.
         1. Physical findings that suggest a **reduction in ECF volume** include
            a. Absence of axillary sweat
            b. A recent reduction in body weight
            c. **Fall in systolic blood pressure** of more than 10 mm Hg or a rise in pulse rate of more than 10 beats per minute when assuming the upright posture
            d. **"Tenting" of upper thorax skin** when pinched between the fingers
            e. Jugular venous pressure not visible
         2. Prerenal azotemia may also develop in states in which **ECF is expanded** (e.g., cardiac failure, cirrhosis, nephrotic syndrome). Although the ECF may be expanded as judged by bedside criteria (e.g., elevated jugular venous pressure, pulmonary rales, ventricular gallop rhythm, ascites, peripheral edema), the effective arterial blood volume, or that portion of the blood within the arterial circulation, may be decreased in an absolute or relative sense (arterial vasodilation), leading to prerenal azotemia.
      b. **Hepatorenal syndrome** should be considered in patients with decompensated cirrhosis with ascites who present with ARF. This condition is typical of prerenal azotemia; the urine sediment is bland, and the kidney functions normally if transplanted into a person with a normal liver. Hepatorenal syndrome is a diagnosis of exclusion, as other causes of ARF, such as ATN, hypovolemia, acute interstitial nephritis, acute glomerulonephritis, and urinary obstruction need to be excluded. It has a 95% mortality, but it can be reversed by liver transplantation.
         1. **Criteria for the diagnosis of hepatorenal syndrome** include
            a. Decompensated cirrhosis with ascites
            b. Liver encephalopathy
            c. Hypotension
            d. Hyponatremia
            e. Oliguria
            f. **Bland urine sediment** (absence of cells and casts)
            g. Urine sodium less than 10 mEq per L
            h. Unresponsive to fluid challenge (1.5 L of isotonic saline) and diuretic withdrawal
         2. ARF in patients with liver disease may also occur in **other clinical settings.**
            a. Jaundice and ARF (e.g., hemolytic-uremic syndrome, leptospirosis, mismatched blood transfusion, falciparum malaria)
            b. Simultaneous ARF and acute liver failure (e.g., acetaminophen overdose, bacteremia, carbon tetrachloride)
            c. Glomerulonephritis and liver cirrhosis (e.g., cryoglobulinemia, IgA nephropathy , membranous glomerulonephritis associated with hepatitis B and C)
      c. **Vasomotor ARF due to NSAIDs.** A history of NSAID use in all patients with ARF should be aggressively sought. Under euvolemic conditions, administration of NSAIDs does not cause an increase in serum creatinine. In the presence of clinical conditions with increased vasoconstrictor activity (e.g., congestive heart failure, cirrhosis, nephrotic syndrome, hypertension, sepsis, volume depletion, anesthesia, diabetes mellitus), NSAIDs can cause ARF. Patients with chronic renal insufficiency are also at risk of acute vasomotor decline in renal function with NSAIDs. Typical clinical features include the presence of risk factors, modest salt and water retention, decreased urinary output, a benign urine sediment, low (less than 1%) fractional excretion of sodium (FE_{Na}; see section **III.C**), and prompt improvement in renal function on discontinuation of NSAIDs. NSAIDs may also cause AIN and ARF (see section **III.A.2.j**).
      d. **Cyclosporine and tacrolimus** may cause a dose-dependent, hemodynamically mediated ARF in solid-organ and bone marrow transplant patients. A large increase in renal vascular resistance occurs. The loss of renal function is reversible when the dosage of the drug is reduced. The urine sediment is

bland, and ATN is not typically present.

e. **ACE inhibitors** are widely used for the treatment of hypertension, congestive heart failure, and diabetic nephropathy. ARF may occur in conditions where angiotensin plays a crucial role in GFR, such as volume depletion, bilateral renal artery stenosis, autosomal dominant polycystic kidney disease, cardiac failure, cirrhosis, and diabetic nephropathy. Diuretic-induced sodium depletion and underlying chronic renal insufficiency are major predisposing factors. Renal insufficiency is usually asymptomatic, nonoliguric, and associated with hyperkalemia. ARF is reversible in most cases after discontinuation of the ACE inhibitor. It can usually be managed in the outpatient setting by discontinuation of the ACE inhibitor and discontinuation of the diuretic. An asymptomatic increase in BUN and creatinine in a patient on ACE inhibitors should raise the possibility of renal artery stenosis.

f. **Radiographic contrast nephropathy.** Radiocontrast agents cause ARF by causing renal vasoconstriction. These agents are nephrotoxic in kidneys that are compromised in some other way (e.g., from old age; preexisting renal disease, especially diabetes mellitus; multiple myeloma; volume depletion; and recent exposure to other agents, such as ACE inhibitors and NSAIDs). Renal failure occurs 1 to 2 days after exposure. The renal failure is characterized by a prerenal picture with oliguria, high urine specific gravity, bland urine sediment, and low FE_{Na}. Newer, nonionic agents may be less nephrotoxic in high risk patients. The effects of radiocontrast agents can be minimized by hydration with saline before and after the contrast load; diuretics should be avoided if possible. The hemodynamic effect of radiocontrast may to be mediated by calcium, because calcium channel blockers protect against the ARF. Recovery tends to begin within 2 to 3 days. However, patients with advanced renal failure, particularly diabetic patients with nephropathy, may never recover function after x-ray contrast-induced ARF and may require chronic hemodialysis therapy.

g. **Atheroembolic disease.** A history of ARF occurring after cardiovascular surgery, angiography-induced aortic intimal trauma, or intravenous administration of streptokinase for myocardial infarction should raise a suspicion of atheroembolic disease as the cause of ARF. Occasionally, the disease occurs spontaneously. It is characterized by the detachment of atheromatous plaques from the intimal surface of large vessels, which travel distally and occlude small arteries or large arterioles of the kidney. Showers of cholesterol crystals or microemboli from the surface of ulcerated plaques may also occur, traveling distally to occlude small arterioles. Small emboli to the gut and pancreas may cause abdominal pain. Clinical examination may reveal peripheral vascular insufficiency, blue-toe syndrome, or livido reticularis. Laboratory investigation may reveal an increased erythrocyte sedimentation rate, eosinophilia, and hypocomplementemia. The presentation and clinical findings can be confused with those of polyarteritis nodosa, allergic vasculitis, subacute bacterial endocarditis, or left atrial myxoma. Histologic examination of the skin, muscle, or kidney reveals intravascular cholesterol crystals. The usual course is progressive renal insufficiency. However, milder forms of renal failure with some recovery of function have been described. No treatment is known. Prevention of the disease involves avoiding unnecessary invasive procedures (e.g., renal arteriogram in patients with clinical evidence of widespread atherosclerosis).

h. **Thrombotic microangiopathies** are characterized by a microangiopathic hemolytic anemia, thrombocytopenia, and variable renal and neurologic manifestations. This condition should be suspected in patients with ARF, thrombocytopenia, and neurologic signs such as confusion and seizures. Peripheral blood smear always shows increased red blood cell fragmentation. The clinical features of renal failure, hypertension, hematuria, and proteinuria often overlap with other renal syndromes characterized by ARF. All of these disorders most likely begin with endothelial injury followed by secondary platelet thrombi formation in renal arterioles; renal cortical necrosis may result from the arterial lesions. When acute azotemia develops in association with these disorders, it often represents only one of many serious complications of an underlying disease. Moreover, the primary site of injury is the glomerulus or the vascular supply of the glomerulus, with the proximal tubule and the interstitial areas relatively uninvolved. Recovery of renal function after hemolytic-uremic syndrome in children is expected.
   1. Thrombotic microangiopathy and ARF can be caused by
      a. Hemolytic-uremic syndrome
      b. Thrombotic thrombocytopenic purpura
      c. Scleroderma renal crisis
      d. Malignant hypertension
   2. In pregnancy, thrombotic microangiopathy and ARF are caused by
      a. **HELLP syndrome** (usually resolves after delivery of the baby)
      b. **Postpartum ARF.** This syndrome is a rare but ominous condition from which the patient does not usually recover, resulting in the need for chronic hemodialysis.

i. **Glomerular disease.** Patients with known glomerulonephritis may develop ARF; alternatively, glomerulonephritis may present as ARF. The presence of hematuria and red blood cell casts, proteinuria, nephritic syndrome, or nephrotic syndrome should alert the clinician to the presence of glomerulonephritis. Clinical symptoms and signs that suggest that the glomerulonephritis is part of a systemic disease include palpable purpura skin rash, arthralgias or arthritis, fever, cardiac murmurs, sinusitis, hemoptysis, abdominal pain, and acute neuropathy. Hemoptysis is an ominous symptom in an ARF patient and may indicate a life-threatening vasculitis, such as Goodpasture's syndrome or Wegener's granulomatosis. Rapidly progressive (crescentic) glomerulonephritis should be suspected in a patient with glomerulonephritis who has a doubling of serum creatinine within a 3-month period. Rapidly progressive (crescentic) glomerulonephritis represents a medical emergency; immunosuppressive therapy and plasma exchange can attenuate the process and prevent the progression to end-stage renal failure and dialysis. The antineutrophil cytoplasmic antibody (ANCA) provides a sensitive marker for detecting ARF due to Wegener's granulomatosis, polyarteritis nodosa, and approximately 80% of cases previously called *idiopathic crescentic glomerulonephritis*. ANCA reacts with antigens within the cytoplasm of neutrophils and monocytes and may have a pathogenic role in activating leukocytes and the accompanying inflammatory injury.

j. **AIN.** In a patient with ARF, a history of all the medications taken during the last 6–12 months should be obtained. Physical findings with acute drug-induced interstitial nephritis may be lacking, although fever and a maculopapular or petechial skin eruption may occur with any of the agents, particularly the penicillin derivatives and allopurinol. Laboratory findings (e.g., eosinophilia, eosinophiluria) are more helpful in making this diagnosis. Proteinuria with nephrotic syndrome is a feature of the AIN caused by NSAIDs. The two major forms of drug-induced AIN are described in Table 9-1.

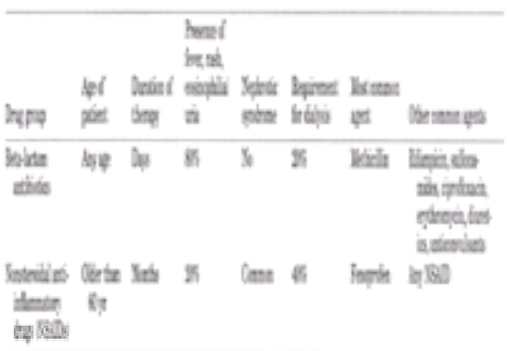

Table 9-1. Two major forms of acute allergic interstitial nephritis

k. **Aminoglycoside nephrotoxicity.** Nonoliguric ARF (more than 400 mL of urine per day despite a rising BUN and serum creatinine) is characteristic of azotemia that develops after aminoglycoside nephrotoxicity. Frank azotemia secondary to aminoglycosides may develop for the first time after the drug has been discontinued; conversely, recovery of renal function after discontinuation of the nephrotoxic aminoglycoside is often delayed and may require weeks to months to be complete. ARF occurs in 10% to 25% of patients on aminoglycosides, even with careful dosing and therapeutic plasma levels. Nephrotoxicity correlates better with total cumulative dose than with plasma levels. Predisposing factors are old age, preexisting renal disease, volume depletion, and combination with other agents (e.g., diuretics, cephalosporins, vancomycin). Nephrotoxicity is usually clinically apparent after 5 to 10 days of therapy; early findings are isosthenuria caused by nephrogenic diabetes insipidus, and magnesium and potassium wasting. Later findings include azotemia.

l. **Rhabdomyolysis** should be considered in patients with a predisposing cause (Table 9-2), muscle pain, and dark brown urine. However, rhabdomyolysis is frequently atraumatic, and up to 50% of patients have no muscular complaints. A presumptive diagnosis can be made in Hematest (+) urine with absence of red blood cells. Pigmented granular casts also can be found in the urine in the presence of an elevated serum creatine phosphokinase. Clues to diagnosis include a rapid rise of serum creatinine, disproportionate hyperkalemia, hyperphosphatemia, hyperuricemia, hypocalcemia early, and hypercalcemia during the recovery phase. Rhabdomyolysis can be prevented by vigorous volume replacement (200 to 300 mL of saline per hour) to achieve euvolemia followed by mannitol (12.5 to 25.0 g in 30 minutes).

Direct muscle damage (e.g., crush injuries, polymyositis)
Muscle ischemia (e.g., arterial occlusion or embolism)
Excess energy consumption (e.g., seizures, hyperthermia, delirium tremens)
Decreased energy production (e.g., severe hypophosphatemia, hypokalemia, myxedema, genetic defect)
Drugs and toxins (e.g., alcohol, heroin, cocaine, amphetamines, poisonous insect and snake bites)
Severe infections (e.g., tetanus, Legionnaire's disease, influenza)

Table 9-2. Causes of rhabdomyolysis

m. **Acute uric acid nephropathy** causes ARF due to intratubular deposition of uric acid crystals. A very high serum uric acid concentration is present. The condition typically occurs during induction chemotherapy for malignancies with high cell turnover (e.g., leukemias and lymphoproliferative malignancies). Acute uric acid nephropathy and ARF occur in the tumor lysis syndrome. Clinical features of acute uric acid nephropathy are hyperuricemia, hyperkalemia, hyperphosphatemia, and a urine urate to creatinine ratio higher than 2. Preventive measures include vigorous hydration and alkaline diuresis; allopurinol should be started several days before the chemotherapy.

n. **Postrenal azotemia.** Symptoms that suggest urinary tract obstruction are anuria or intermittent anuria, prostatic symptoms (frequency, urgency, dysuria, dribbling), pelvic malignancy or previous radiotherapy, and recurrent renal stones. Patients with diabetes mellitus, sickle cell anemia, and analgesic nephropathy are predisposed to papillary necrosis causing obstruction. The physical examination is also important in diagnosing postrenal azotemia, especially in the unconscious patient or in the confused patient in whom otherwise unexplained agitation may be the only clue to acute urinary retention. Careful abdominal examination may uncover a distended, tender bladder or bilaterally hydronephrotic kidneys. A digital examination of the prostate should be performed routinely in any azotemic male patient, and pelvic masses should be sought in female patients through a bimanual pelvic examination. In any patient in whom lower tract obstruction is suspected as the cause of acute azotemia, a sterile in-and-out diagnostic postvoid bladder catheterization should be performed as a routine part of the physical examination. The postvoid residual urine volume should be less than 50 mL. The urine volume should be recorded and the specimen saved for the studies described in section **III.B**. Bland urinalysis with progressive renal failure suggests urinary tract obstruction.

o. **ARF in patients with acquired immunodeficiency syndrome (AIDS).** The approach to the causes of ARF in AIDS patients is the same as that for other patients (i.e., classification into prerenal, intrinsic renal, and postrenal causes). ARF may develop in up to 20% of hospitalized patients with AIDS and is in most cases multifactorial (Table 9-3). ATN is seen in AIDS because the patients are acutely ill with multiple infections or malignancies. Their clinical course is often complicated by hypovolemia, multiorgan failure, compromised cardiovascular status, invasive diagnostic procedures complicated by bleeding, and the administration of multiple nephrotoxic drugs and radiocontrast agents. Although ATN is a major cause of morbidity and mortality in AIDS patients, it is also potentially reversible and treatable. All supportive measures, including dialysis, should be used as warranted by the clinical situation. Importantly, ATN is avoidable in some cases when preventative measures are used (e.g., maintaining adequate hydration before use of radiocontrast agents and during use of antibiotics and antiretroviral therapy that precipitates crystalluria).

Prerenal
Hypovolemia (diarrhea)
Hypotension (sepsis, bleeding)
Decreased arterial effective blood volume (hypoalbuminemia, cachexia, human immunodeficiency virus nephropathy)
Vasoconstriction (radiocontrast agents)
Renal
Acute tubular necrosis (shock, bacteremia, aminoglycosides, amphotericin)
Rhabdomyolysis (pentamidine, cidofovir)
Acute allergic interstitial nephritis (penicillins, sulfonamides)
Postinfectious glomerulonephritis
Hemolytic-uremic syndrome and thrombotic thrombocytopenic purpura
Plasmacytic interstitial nephritis
Postrenal
Tubular obstruction due to crystalluria (intravenous acyclovir, sulfadiazine, indinavir, saquinavir, ribavarin)
Extrinsic ureteral compression (lymph nodes, tumors)
Intrinsic ureteral obstruction (fungus balls)
Bladder obstruction (tumors, fungus balls)

Table 9-3. Acute renal failure in acquired immunodeficiency syndrome patients

p. **ARF in bone marrow transplant patients.** ARF is one of the most frequent and potentially life-threatening complications of bone marrow transplantation. Approximately 40% of these patients develop renal insufficiency early in the course of treatment. This incidence is higher in patients who receive allogeneic as opposed to autologous transplantation. Approximately 50% of the patients with ARF require dialysis. The incidence of ARF is high because of the life-threatening nature of the underlying diseases and the toxicity of the cancer drugs, immunosuppressive regimens, and antibiotics.

3. **Factors that predispose to ATN** are nausea, vomiting, and diarrhea due to radiochemotherapy or acute graft-versus-host disease; nephrotoxic drugs such as aminoglycosides and amphotericin; hemorrhagic and septic shock. Hepatic veno-occlusive disease, which is more common in allogeneic than autologous bone marrow transplants, is a syndrome that resembles the hepatorenal syndrome. A sodium retention state occurs and leads to weight gain, edema, and a low FE_{Na} of less than 1%, despite the use of diuretics. Progressive hyperbilirubinemia and nonoliguric ARF occur. By far, the most common period for development of ARF is 10 to 21 days after the transplant. The renal syndromes unique to bone marrow transplant patients are classified according to the time of presentation:
   a. Immediate (first few days)
      1. Tumor lysis syndrome
      2. Stored marrow toxicity
   b. Early (10 to 21 days)
      1. Hepatic veno-occlusive disease
      2. Sepsis
      3. ATN
   c. Late (6 weeks to 1 year)
      1. Bone marrow transplant–associated hemolytic-uremic syndrome
      2. Chronic cyclosporine nephrotoxicity

B. **Urine sediment.** Urinalysis should be regarded as an extension of the physical examination of the patient and as such should be performed on all patients with ARF. The only exception is in the anuric (producing less than 50 mL of urine per day) patient. In AIN, Hansel's secretion stain (methylene blue and eosin Y in methanol) for urine eosinophils is superior to Wright' ;s stain, because urinary eosinophils are readily identified by their brilliant red-pink granules. Hansel's stain is not influenced by urinary pH.

   Urine findings in the different causes of ARF

   1. **Prerenal:** Relatively high specific gravity, dipsticks normal, sediment bland.
   2. **Postrenal:** Specific gravity 1.010, bland sediment of hematuria (e.g., renal calculi).
   3. **Glomerulonephritis/vasculitis:** Variable specific gravity; hematuria, proteinuria, or both; granular cast, red blood cell casts, or both.
   4. **AIN:** Isotonic urine, white blood cells or white blood cell casts (sterile pyuria), eosinophils, hematuria (microscopical or macroscopic).
   5. **ATN:** Muddy brown urine, isotonic urine, hematuria or heme pigment, pigmented, coarsely granular casts, renal tubular epithelial cells.
   6. **Ethylene glycol intoxication:** ATN urine with calcium oxalate monohydrate crystals. Calcium oxalate monohydrate crystals may be mistaken for hippurate crystals.
   7. **Acute uric acid nephropathy:** ATN with uric acid crystals.
   8. **Obstructive uropathy due to sulfadiazine:** Crystalluria (crystals resemble shocks of wheat).
   9. **Rhabdomyolysis:** Heme-positive on dipstick (does not distinguish between hemoglobin or myoglobin), absence of red blood cells in sediment.

C. **Urine chemistry: laboratory studies.** Although physical findings are an important guide to the adequacy of the ECF volume, urinary diagnostic indices can

support the presence of prerenal azotemia. With prerenal azotemia, the specific gravity of the first-voided urine is often high (>1.020), whereas patients with postrenal failure and ARF (ATN) lose the ability to concentrate the urine and tend to have a urinary specific gravity similar to that of plasma (approximately 1.010). The BUN to serum creatinine ratio in healthy patients and in patients with established acute or chronic renal failure is ordinarily 10 to 1. In the presence of prerenal azotemia, this ratio tends to rise, reaching levels as high as 60 to 1. The first specimen of urine obtained from a patient with newly discovered acute azotemia may be particularly helpful in differentiating prerenal azotemia from other causes of renal failure (Table 9-4). The first-voided or catheterized specimen of urine of such a patient should be analyzed for sodium, creatinine, urea nitrogen, and osmolality. Determination of the various ratios and indices listed in Table 9-4 may help differentiate between prerenal failure and ARF. Intermediate values may occur in patients with postrenal failure or in those in transition from prerenal failure to ARF. Values with postrenal failure can also mimic exactly those in ARF. However, it is important to bear in mind that previous use of a potent diuretic agent (furosemide or mannitol) in an attempt to prevent or reverse ARF may totally invalidate the use of these diagnostic urinary indices for up to 24 hours.

Index	Prerenal azotemia	Acute tubular necrosis
Urine sodium (U_{Na}), mEq/L	<20	>40
Urine osmolality, mOsm/kg H_2O	>500	<350
Urine urea nitrogen to plasma urea nitrogen	>8	<3
Urine creatinine (U_{Cr}) to plasma creatinine (P_{Cr})	>40	<20
Fractional excretion of filtered sodium (FE_{Na}):	<1	>1

$$FE_{Na} = \frac{U_{Na} \times P_{Cr} \times 100}{P_{Na} \times U_{Cr}}$$

P_{Na}, plasma sodium.

Table 9-4. Urinary diagnostic indices

When time is a critical factor in determining the cause of acute azotemia, or not all of the desired tests are immediately available, prerenal azotemia may be strongly suspected if the urinary specific gravity is greater than 1.016, the urinary sodium concentration is less than 20 mEq per L, and the BUN to serum creatinine ratio is greater than 20 to 1. An elevated BUN to serum creatinine ratio may also be found in postrenal ARF. Exceptions are 20% of nonoliguric ATN, radiographic contrast nephropathy, hepatorenal syndrome, rhabdomyolysis, thrombotic thrombocytopenic purpura, acute glomerulonephritis, and early obstructive uropathy, in which low FE_{Na} may occur with oliguric ATN.

D. **Radiology**
   1. **Renal ultrasonography** is the procedure most widely used in ARF. It is useful in assessing kidney and bladder size. Small kidneys (less than 10 cm) suggest that the renal failure is chronic. Hydronephrosis or dilatation of the urinary tract suggests obstruction. In fact, the absence of hydronephrosis virtually excludes important urinary tract obstruction. Anatomic variants of the pyelocalyceal system, vesicoureteric reflux, and pregnancy may cause apparent hydronephrosis without true obstruction. Ultrasound does not assess the functional importance of the obstruction, and a furosemide isotope renogram provides functional information. Doppler ultrasound may be used to assess renal blood flow and to evaluate for renal vein thrombosis.
   2. **Excretory urography** may give additional information regarding renal anatomy, chronicity of the disease, and the site of urinary tract obstruction. However, renal ultrasonography, which is noninvasive, often gives equally valid information without the risk inherent in contrast administration.
   3. **Isotope renography** can be used to diagnose upper urinary tract obstruction. A radionucleotide is injected intravenously, followed by intravenous furosemide. The diuretic should cause rapid washout of the radionucleotide in a nonobstructed system. Persistence of the isotope suggests obstruction. Although the diuresis renogram is noninvasive, it is seldom the definitive test for obstruction. Poor renal function limits its usefulness because the diuretic response may be blunted, making interpretation of the test difficult. Urologic studies are often definitive for obstruction.
   4. **Computed tomography** of the kidneys, ureters, and abdomen is a useful noninvasive test for diagnosing the causes of obstruction. It is also useful for detecting clots in the renal vein or inferior vena cava.
   5. **Cystoscopy and retrograde or anterograde pyelography.** In instances of ARF with a high suspicion of urinary tract obstruction (e.g., calculi, pyogenic debris, blood clots, bladder cancer), cystoscopy and retrograde or anterograde pyelography should be performed, even if ultrasonography is negative for obstruction. Ureteral calculi extraction or placement of ureteral catheters or stents may relieve the obstruction and allow urinary drainage. It is particularly important to consider this diagnostic course in patients with acute or chronic renal failure, in whom even unilateral ureteral obstruction can lead to severe renal function deterioration.
   6. **Renal angiography.** When acute anuria develops as a consequence of acute renal embolization, renal angiography is usually warranted, because acute surgical intervention in selected cases may restore renal function. However, renal and other angiography studies that disturb the vascular endothelium are a major cause of renal atheroemboli. In less critical situations, a renal scan is often useful in determining whether renal blood flow to one or both kidneys is impaired.

E. **Renal biopsy** is performed in patients with prerenal azotemia or the typical features of ATN. However, important indications for a renal biopsy in a patient with ARF exist.
   1. **ARF of unknown etiology.** In most cases, a stepwise approach, as outlined in section **III.A**, section **III.B**, section **III.C**, section **III.D** and section **III.E**, will reveal a cause of the ARF. However, in some patients with ARF, the diagnosis is not clear.
   2. **Suspicion of glomerulonephritis, systemic disease (e.g., vasculitis), or AIN as the cause of ARF.** A renal biopsy in such circumstances may provide the basis and justification for aggressive and lifesaving therapy (e.g., high-dose steroids, cytotoxic agents, plasmapheresis).
   3. **ATN not recovering after 4 to 6 weeks of dialysis with no more recurrent insults.** A renal biopsy may determine that a less favorable condition, such as diffuse cortical necrosis, has developed and that chronic hemodialysis may need to be instituted.

IV. Management

A. **Prerenal azotemia**
   1. **Correction of underlying disorder**
      a. **Pure volume depletion.** When prerenal azotemia is due to deficits in ECF volume, therapy is directed to restoring fluids to the body that are similar to those lost. In gastrointestinal and other types of acute hemorrhage, packed red blood cells in saline are indicated. When blood has not been lost from the body, but plasma moves out of the intravascular compartment to a third space (e.g., crush injury with extensive edema formation in devitalized muscle, burns), isotonic saline approximates ECF tonicity and will restore blood volume and blood pressure. Gastrointestinal fluid losses vary widely in electrolyte content and tonicity, and laboratory analysis for sodium, potassium, and chloride concentrations is the most precise way to determine the type of replacement fluid. Ordinarily, gastric juices require replacement liter for liter with one-fourth- to one-half-strength normal saline containing 10 to 20 mEq per L of potassium chloride. Pancreatic, biliary, and small-bowel losses require replacement with isotonic saline. Diarrheal losses can be restored with a solution of 5% dextrose and water to which has been added one ampule of 7.5% sodium bicarbonate (45 mEq sodium bicarbonate) and 20 to 30 mEq of potassium chloride.
      b. **Ineffective arterial blood volume with edema.** Prerenal azotemia occurring in this setting usually represents a secondary problem overshadowed by a primary cardiac, hepatic, or renal disease.
         1. In **cardiac failure,** diuretic agents in combination with digitalis therapy may increase the cardiac output and improve renal perfusion, and thus lessen the azotemia. Cardiac unloading agents such as ACE inhibitors, nitrates, and hydralazine may also improve cardiac function. However, with advanced heart failure that is refractory or only partially responsive to these agents, the physician may be forced to accept mild to moderate prerenal azotemia as a tradeoff. Such azotemia rarely leads to ARF or symptomatic uremia.
         2. **Hepatic disease.** Prerenal azotemia associated with advanced hepatic cirrhosis, with or without the hepatorenal syndrome, is often refractory to attempts to improve intravascular volume. However, despite the presence of peripheral edema and ascites, renal function and renal excretion may improve in some of these patients in response to a saline challenge. Ordinarily, however, such patients are best treated with a sodium-restricted diet (1 to 2 g of salt), modest water restriction (1,500 to 2,000 mL per day), and an aldosterone antagonist (spironolactone, 100 to 200 mg b.i.d.), while the usually mild prerenal state is ignored. A potent diuretic agent such as furosemide (40 to 80 mg b.i.d.) is sometimes successful in causing a diuresis and improving renal function, but this therapy carries the risk of producing severe hypokalemia, worsening arterial underfilling, and precipitating hepatic coma or the hepatorenal syndrome. Paracentesis and albumin infusion may temporarily increase intravascular volume and improve urine flow. For selected compliant patients with intractable symptomatic ascites who have relatively good liver function, a peritoneovenous shunt (LeVeen shunt) may reduce ascites and improve renal function (see Chapter 1). Major complications of the peritoneovenous shunt are infections, disseminated

intravascular coagulation, pulmonary edema, variceal bleeding, and clotting of the shunt.

c. **Nephrotic syndrome.** Prerenal azotemia often occurs with nephrotic syndrome from any cause, particularly when it is accompanied by severe hypoalbuminemia (serum albumin lower than 2.5 g per L) and heavy proteinuria (10 to 20 g per day). As in the other states of prerenal azotemia associated with an expanded ECF but reduced effective arterial blood volume, success in reversing the prerenal state depends on correcting the primary disease state. Idiopathic nephrotic syndrome, especially in children, usually responds to short-term high-dose prednisone (1 to 2 mg per kg per day), but steroid resistance or frequent relapse may require the addition of cyclophosphamide (1 to 3 mg per kg per day).

2. **Monitoring therapy, non-ICU setting.** In most instances of prerenal azotemia secondary to volume depletion, the volume of fluid required to replace the deficit can be estimated from actual quantitation of fluid or blood losses or from changes in body weight. A useful rule is to replace no more than one-half to two-thirds of the total calculated deficit in the first 24 hours, especially in elderly patients or in patients with a compromised cardiovascular system. The simplest way to follow the patient's response to replacement therapy is by bedside evaluation, with frequent monitoring of orthostatic changes in blood pressure and pulse. The jugular venous pulsation is a gross indicator of pressure in the central venous area of the right heart. In a normovolemic patient, jugular venous pulsations are visible when the patient is supine but disappear when the patient assumes the sitting position. Jugular venous pulsations are not visible in the volume-depleted patient; thus, their reappearance following fluid administration suggests that the central venous pressure (CVP) has returned to normal. The heart and lungs should also be monitored regularly. The presence of basilar crackles or a third heart sound implies too-vigorous fluid replacement, with resultant cardiopulmonary congestion. In patients in whom vigorous resuscitation efforts are required, and cardiovascular tolerance to sudden fluid challenges is in doubt, some form of indwelling monitoring system is desirable.
3. **Monitoring therapy, ICU setting.** The maintenance of adequate hydration and effective intravascular volume is critical in sustaining adequate renal perfusion. The goal of therapy should be to maintain cardiac output, avoid vasoconstriction, and maintain renal blood flow. Urine output is an inaccurate index of renal perfusion; serum creatinine is also a poor marker of renal function in critically ill patients, because volume expansion is associated with dilution of serum creatinine, and it can take up to a week for a steady state of serum creatinine to be reached. Hemodynamic monitoring helps to avoid volume depletion and severe vasoconstriction.

a. **Central venous catheter.** When rapid fluid administration is required and severe heart or lung disease (or both) is absent, a catheter positioned in the central venous area of the right heart is a satisfactory guide to the speed of fluid administration. The CVP normally ranges between 2 and 12 cm of water. In volume-depleted states, values of zero or below can be expected. Before vigorous volume repletion is begun, a fluid challenge of 200 to 300 mL of normal saline should be attempted over a 10- to 20-minute period. In an otherwise uncomplicated volume-depleted patient, this amount of saline has little effect on the CVP reading. A CVP rise of more than 5 cm of water suggests cardiac failure, and the infusion should be immediately discontinued. Venous thrombophlebitis, a major late complication of central venous catheterization, can be avoided by removing the central line after resuscitation is complete or after a maximum of 36 hours.

b. **Swan-Ganz catheter.** When a volume deficit must be repaired in the presence of tricuspid stenosis, acute or chronic pulmonary disease, or an unstable cardiovascular system, the CVP does not give a reliable index of left ventricular performance. In this situation, a balloon-tipped Swan-Ganz catheter can be wedged in a pulmonary artery. This gives a measurement of pulmonary artery wedge pressure (PAWP), an indirect measurement of left ventricular end-diastolic pressure, and thus it is a better guide to the adequacy and speed of fluid replacement. Because of the complications of infection, pulmonary infarction, and hemopneumothorax, this device should be inserted and placed only by trained professionals and should be removed as early as possible. In patients with liver encephalopathy and ARF, clinical judgment of fluid balance may be difficult because of massive edema and ascites. Measurement of PAWP gives critical information about fluid balance: ARF in the presence of a low PAWP may respond to fluid administration; ARF in the presence of normal or high PAWP may point to a diagnosis of hepatorenal syndrome, which has a 95% mortality in the absence of liver transplantation.

B. **Renal or intrinsic ARF**

1. **Diuretics.** Osmotic diuresis with mannitol and the potent loop diuretics (furosemide and ethacrynic acid) has been used almost routinely to prevent or reduce the severity of ARF. However, no human studies clearly document that this therapy is effective. Available evidence suggests that these agents are effective only if given early in the initiation phase of ARF (e.g., immediately after a mismatched blood transfusion or crush injury with rhabdomyolysis). No data support their use in established ATN. In patients in whom volume deficits have been repaired with isotonic saline or its equivalent and oliguria persists, furosemide can be used. Furosemide has the advantage of not causing volume expansion. It is given intravenously in a dose of 80 to 400 mg. Doses higher than this are rarely effective and add the risk of ototoxicity. The chance of having a satisfactory diuretic response is small if ARF is more than 36 hours old, the 24-hour urine output is less than 200 mL per day, or the serum creatinine is greater than 5 to 6 mg per dL.

a. Rationale for use
   1. Convert oliguric to nonoliguric acute renal failure
   2. May make fluid management easier, but does not improve prognosis

b. Dosages
   1. **Mannitol:** Initially, 12.5 g (50 mL of 25% solution); repeat 12.5 g. Maintain with 5% mannitol solution.
   2. **Furosemide:** intravenous bolus, 80 to 400 mg

2. **Renal-dose dopamine.** Dopamine is a selective renal vasodilatator. It elicits profound natriuresis and increases urine output. The renal selective dose is 1 µg per kg per minute. No evidence suggests that renal-dose dopamine is beneficial in ARF. In fact, several studies have identified a deleterious effect. Unless dopamine is required for circulatory support, it should not be used for acute renal failure.
3. **Avoidance of nephrotoxic drugs.** Potentially nephrotoxic drugs and agents should be completely avoided in ARF—they perpetuate the renal injury. These agents and drugs include NSAIDs, ACE inhibitors, cyclosporine, tacrolimus, aminoglycosides, radiocontrast agents, amphotericin B, and chemotherapeutic agents.
4. **Adjustment of drug dosages.** Drug dosages should be based on the measured or best estimate of creatinine clearance, not merely on the serum creatinine.
5. **Fluid therapy**

a. **Oliguric ARF.** The use of dialysis therapy for oliguric ARF may permit fluid intakes of 1.5 to 2.0 L per day, depending on the status of the cardiovascular system. If hemodialysis or peritoneal dialysis is not immediately available, fluid balance usually can be maintained by replacing insensible losses (400 to 600 mL per day) with 10% dextrose in water and measured losses (e.g., urine, gastric drainage, diarrhea) liter for liter with 0.45% saline. If the plasma bicarbonate level falls below 20 mEq per L, one or two ampules of 7.5% sodium bicarbonate (45 mEq of bicarbonate per ampule) should replace an equivalent quantity of sodium chloride in these fluids. The best monitor of adequacy of fluid therapy is a bedside estimate of the ECF volume status and daily weights. A serum sodium determination every other day is helpful in deciding whether water intake is appropriate to solute intake (hyponatremia indicates excessive water intake, and hypernatremia indicates too little water intake). Because hypokalemia is rarely a problem with ARF, and because of the danger of cardiac arrhythmias from hyperkalemia, potassium chloride is not added to intravenous fluids.

b. In general, **nonoliguric ARF** represents a milder renal injury and requires dialysis less frequently. As a result, fluid management tends to be easier. These patients ordinarily should receive a volume of fluid each day that equals their urine output plus insensible losses. The salt content of their diets should be approximately equal to what is excreted in the urine and lost in other measurable bodily fluids.

6. **Parenteral hyperalimentation.** Nitrogen balance is extremely negative in ARF, especially ARF associated with the multiorgan dysfunction syndrome. A high protein catabolic rate is also present. Renal factors contributing to the negative nitrogen balance include uremia, acidosis, parathyroid hormone, inadequate protein intake, and protein losses. No sound rationale exists for protein restriction in the management of acutely ill patients with ARF. Nutritional supplementation should not be withheld to minimize azotemia and avoid renal replacement therapy. In fact, studies have demonstrated that aggressive protein administration is safe and easily achieved during renal replacement therapy and that it results in a detectable improvement in daily nitrogen balance. Previous studies did not demonstrate a beneficial effect of hyperalimentation and total parenteral nutrition on survival in ARF; however, significant advances have been subsequently made in dialysis and parenteral nutrition technology. In acutely ill patients, up to 1.5 g per kg per day of high biological value protein should be provided.
7. **Dialysis therapy**

a. The **indications to start dialysis** in ARF are not specific and should be individualized by nephrologic consultation. Some guidelines are given here. One criterion is grounds to start dialysis; if more than one criterion is met, dialysis is mandatory.
   1. Oliguria (less than 400 mL per day)
   2. Anuria (less than 50 mL per day)
   3. Serum creatinine higher than 6.7 mg per dL
   4. Plasma urea higher than 100 mg per dL
   5. Pulmonary edema unresponsive to conservative therapy
   6. Hyperkalemia (serum potassium higher than 6.5 mEq per dL)
   7. Symptomatic uremia (e.g., encephalopathy, pericarditis)
   8. Metabolic acidosis

b. The delivered **dose of dialysis** for ARF may be much higher than in the chronic setting, because ARF patients are often hypercatabolic, and most temporary catheters have a high recirculation rate. Early studies with bioincompatible dialysis membranes indicated that aggressive dialysis to keep the BUN below 60 dL did not improve mortality. Preliminary results of a more recent study using biocompatible dialysis membranes demonstrated that overall mortality improved in a group of ARF patients who received daily dialysis instead of alternative-day dialysis. This is the first study to show that the amount

of dialysis is an independent determinant of mortality in critically ill patients with ARF. In fact, the study suggests that the alternative-day dialysis regimen may be grossly inadequate. The dose of dialysis should be individualized for the patient in consultation with a nephrologist. For example, in severely catabolic patients (e.g., crush injury, burns), daily dialysis may be required. Until definitive studies confirm the benefits of more aggressive dialysis in ARF, a reasonable goal is that the adult predialysis BUN be maintained at less than 80 mg per dL.

c. The **main modalities of dialysis** that are presently used are intermittent hemodialysis (IHD) and continuous renal replacement therapy (CRRT), of which continuous venovenous hemodialysis (CVVHD) is the most widely used.
   1. In **IHD**, the patient is connected to a dialysis machine for 2 to 5 hours at a time, daily or every second day. Fluid removal and urea clearance for the day is achieved during the period of a few hours. Rapid removal of solutes and fluids leads to peaks and troughs in the BUN and serum creatinine and to hemodynamic instability. The technique requires a double-lumen catheter, tubing, a hemodialysis machine (blood pump, dialysate generation system, dialysate pump, and alarms and safety monitoring devices), a dialysis membrane, and a dialysis nurse. Daily treatment for 4 hours, with a blood urea clearance of 200 mL per minute, can achieve a weekly urea clearance of 350 L.
   2. In **CVVHD**, the patient undergoes continuous dialysis for 24 hours a day. Removal of solutes and fluid is slow, continuous, and gradual to avoid disequilibrium and hemodynamic instability caused by rapid solute and fluid removal. Minimization of hypotension theoretically avoids the perpetuation of renal injury. The technique requires a double-lumen catheter, tubing, a simple blood pump with safety devices, sterile replacement fluid, volumetric pumps to control replacement and ultrafiltration rate, and a high-flux dialysis membrane. CVVHD can achieve a weekly urea clearance of 340 L by use of any combination of ultrafiltration rate and dialysate flow rate that add up to 2 L per hour.
   3. **Intermittent versus continuous dialysis.** Many nonrandomized studies have compared IHD and CRRT. Prospective randomized studies are difficult to carry out, because hemodynamically unstable patients who cannot tolerate IHD are almost always started on CRRT. Alternatively, confining a mobile patient to bed to receive CVVHD may be unethical. Thus, randomization may be biased. CRRT is thought of as the modality of choice in very ill patients, and IHD is used in less ill patients. At present, IHD and CRRT are regarded as equivalent methods for the treatment of ARF. The choice of IHD or CRRT should be made in consultation with a nephrologist and tailored for the individual patient. The decision may also depend on facility-specific issues, such as experience, nursing resources, and technical proficiency. The cost of the procedures is roughly equivalent. Indications for CRRT in ARF at present include hemodynamic instability, cerebral edema, hypercatabolism, and severe fluid overload. Patients ideally suited for CRRT are those with hepatorenal syndrome who are awaiting liver transplantation, and critically ill patients in the bone marrow transplant unit who have ARF. A comparison of IHD and CRRT is given in Table 9-5. CRRT is similar in solute clearance to a GFR of 15 to 20 mL per min. A day of CRRT is roughly equivalent to one hemodialysis treatment. Thus, drug-dosing adjustments need to be made in CRRT.

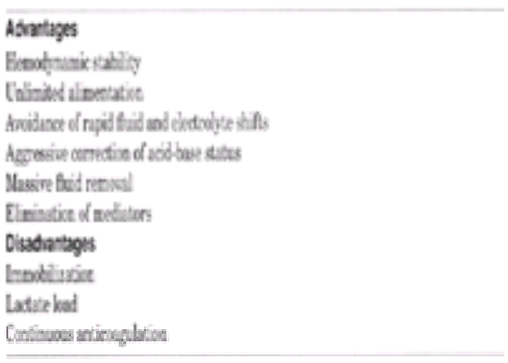

Table 9-5. Analysis of using continuous renal replacement therapy over intermittent hemodialysis

d. **Type of dialysis membrane.** Interaction between blood and artificial membranes may cause adverse effects. Adverse effects of bioincompatible cellulosic membranes (e.g., cellulose, cuprophane, hemophane, cellulose acetate) include activation of complement and hypotension. Biocompatible membranes are made of synthetic polymers and include polyamides, polycarbonate, and polysulfone. Studies have demonstrated that dialysis of ARF patients with biocompatible membranes is associated with improved mortality.
e. **Temporary vascular access.** The main vascular sites used for insertion of temporary catheters are the internal jugular vein, subclavian vein, and femoral vein. Internal jugular access is preferable when it does not pose additional life-threatening hazards for the patient. It is essential for a mobile patient. Femoral access is indicated in cases of emergency when the catheter has to be inserted rapidly or when the cardiopulmonary condition of the patient limits attempts at thoracic catheterization. It is useful in bedridden patients. Insertion of subclavian catheters entails a major risk of stenosis or thrombosis of the subclavian vein or its branches.
f. **Acute peritoneal dialysis** is not technically difficult and can be used with minimally trained staff and where IHD or CRRT is not available. It is indicated in patients with minimally increased catabolism without an immediate or life-threatening indication for dialysis. It is ideal for hemodynamically unstable patients. For short-term dialysis, a rigid dialysis catheter is inserted into the peritoneum, through the anterior abdominal wall, 5 to 10 cm below the umbilicus. Exchanges of 1.5 to 2.0 L of standard peritoneal dialysis solutions are infused into the peritoneum. The major risks are bowel perforation during insertion of the catheter and peritonitis. Acute peritoneal dialysis offers the same potential advantages to the pediatric patient that CRRT offers to the adult.

C. **Postrenal failure.** In large part, the therapy for urinary tract obstruction is surgical and requires early urologic consultation. Foley catheter drainage is usually successful for acute obstruction secondary to prostatic hypertrophy and can be followed in several weeks by prostatic resection. With ureteral obstruction, cystoscopy and placement of ureteral drainage catheters may allow passage of obstructing stones, sludge, or pus, but if this fails, operative intervention is required.
D. **Acute interstitial nephritis.** When a therapeutic agent is identified as the cause of acute interstitial nephritis, removal of the agent is the obvious first step in therapy. When renal impairment is minor, nothing more need be done. In more severe cases, high-dose, short-term prednisone therapy (60 mg per day for 1 to 2 weeks) may speed recovery of renal function and normalize urinary sediment. The extent and severity of the nonrenal manifestations (e.g., fever, dermal eruption) are also considerations in the decision to use corticosteroids.
E. **Primary renal disease: systemic and vascular diseases.** When renal failure develops in the course of a systemic or vascular disorder, it is usually a grave sign. However, experience with several of these disorders suggests that aggressive therapy may be warranted, and considerable recovery of renal function may occur in some patients. A comprehensive discussion of the treatment of these systemic and vascular disorders is beyond the scope of this chapter, but Table 9-6 outlines the diseases and usually recommended therapies. Management of such patients is often multidisciplinary and includes the joint participation of a rheumatologist or immunologist and a nephrologist.

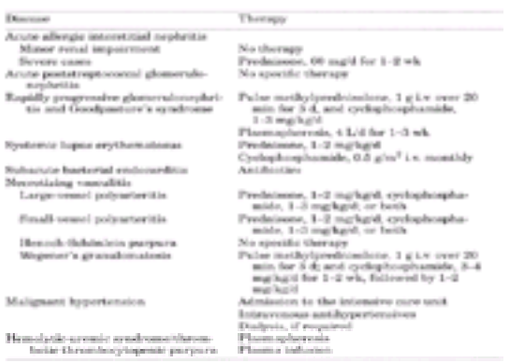

Table 9-6. Specific therapy for acute renal failure in primary renal, systemic, and vascular diseases

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Chapter 10 The Patient with Chronic Renal Disease

Bruce J. Fisch

Epidemiology and etiology
Risk factors
Natural history
Diagnosis
Initial evaluation
Treatment considerations

Chronic renal failure (CRF) is present when the glomerular filtration rate (GFR) is permanently decreased in association with the loss of functional nephron population . It is characterized by continuing attrition of nephrons and variable but usually unrelenting progression toward end-stage renal disease (ESRD). Although patients with CRF have an elevated serum creatinine (Scr), other uremic and metabolic derangements, such as hyperkalemia and acidosis, may be absent. In 1996, the United States Renal Data System (USRDS) reported an ESRD incidence of 268 per 1 million people per year, for a total prevalence of 283,000 patients. The prevalence of ESRD has increased by approximately 8% per year over the last decade, due to the combined effects of a rising incidence of renal disease in the 60-to-75-year age group and mortality rates that have remained nearly constant. More than 300,000 people will be treated for ESRD by the year 2000. CRF is costly: For dialysis patients, Medicare spends approximately $45,000 per patient per year, for a total of $10 billion annually. The cost of caring for non-ESRD patients with chronic renal disease is unknown.

I. Epidemiology and etiology Although relatively complete and accurate statistics on ESRD are available, limited epidemiologic data exists for CRF in general. The causes of CRF have been assumed to correspond proportionately to the causes of ESRD, though this was not proved until the 1990s. A contemporary, large-scale survey conducted in the U.S. population suggests that more than 3 million people have an Scr higher than 1.7 mg per dL. As detailed in section **IV.A**, however, Scr gives an imprecise estimate of renal function and may vary independently according to race, dietary intake, age, gender, and muscle mass.

Table 10-1 lists the most prevalent causes of ESRD. The majority of patients have diabetes mellitus, hypertension, or both. Studies suggest a synergism between hyperglycemia and elevated blood pressure in destroying nephrons. As a group, glomerular diseases are the third most common cause of ESRD; they include idiopathic disorders, such as focal and segmental glomerulosclerosis (FSGS) and membranous nephritis, and secondary nephritis due to systemic illness such as systemic lupus erythematosus and Wegener's granulomatosis. Interstitial disease, polycystic kidney disease, and obstructive uropathy each account for 3% to 5% of new cases. In contrast to hypertension and diabetes, which can cause CRF at any age, most other causes have a predilection for specific age groups. Idiopathic FSGS, lupus nephritis, and congenital anomalies of the urinary tract commonly lead to CRF before the age of 40. Polycystic kidney disease, idiopathic membranous glomerulonephritis, membranoproliferative glomerulonephritis (MPGN), and scleroderma lead to CRF and ESRD in the 40-to-55-year age group. In patients older than 55 years, cholesterol-emboli disease (blue-toe syndrome), analgesic nephropathy, multiple myeloma (including light-chain disease), ischemic nephropathy, and Wegener's granulomatosis are some of the common causes. The latest statistics from the USRDS indicate that diabetes, glomerulonephritis, secondary glomerulonephritis, vasculitis, and congenital diseases are overrepresented in the 20-to-64-year age group. Hypertension and renal neoplasms are more common in patients older than 64 years. Interstitial nephritis is seen more frequently in the youngest and oldest patients. Primary glomerulonephritis, hypertension, and neoplasms are more frequent in males, and secondary glomerulonephritis and diabetes are overrepresented in females.

Disease	Incidence in ESRD population (%)
Diabetes mellitus	40.3
Hypertension	27.1
Glomerulonephritis	12.9
Interstitial disease	4.2
Cystic/hereditary/congenital	3.4
Neoplasm/tumor	1.7
Other known cause	2.9
Unknown/missing	7.5

Table 10-1. Causes of end-stage renal disease (ESRD)

A. **Primary renal diseases** are confined to the kidneys and usually present with CRF or nephrotic syndrome without a history of systemic illness. Nonglomerular diseases such as obstructive uropathy, primary interstitial nephritis, and ischemic nephropathy are often identified during the workup for newly discovered hypertension or asymptomatic hematuria. Patients presenting with proteinuria or nephrotic syndrome but without evidence of infection, collagen-vascular disease, or malignancy are likely to have idiopathic glomerulonephritis. Because patients with primary renal disorders are either asymptomatic or have the nonspecific symptoms of chronic renal disease, renal biopsy is often necessary for diagnosis.
B. **Secondary renal diseases.** A complete history and physical examination accompanied by routine blood work uncovers the etiology of CRF in more than 60% to 70% of cases. Hypertension and diabetes are usually present for at least 10 years before they cause CRF. With hypertension leading to ESRD, uncontrolled and accelerated hypertension is most frequent. The history may reveal exposure to nephrotoxins such as analgesics or heavy metals, or evidence of systemic diseases such as lupus, sickle cell anemia, or malignancy. A recent history of arteriography involving the coronary arteries or aorta should prompt investigation for cholesterol emboli. In younger age groups, body imaging may reveal malformations of the urinary tract.

II. Risk factors

A. **Modifiable risk factors.** Diabetes mellitus is the single most common and potentially treatable risk factor for developing ESRD in the United States. Not only can early signs of diabetic renal disease be confidently detected with urinary microalbumin excretion (30 to 300 mg albumin per 24 hours), now pharmacologic therapy with angiotensin-converting enzyme (ACE) inhibitors is known to slow its progression at any stage. These drugs decrease proteinuria in addition to protecting nephrons from the deleterious effects of glomerular capillary hypertension. For this reason, all patients with diabetes mellitus should be assessed at least yearly for the presence of renal involvement. Glucose control itself has been demonstrated to decrease progression of incipient diabetic nephropathy and overt diabetic nephropathy. The other preeminent risk factor, hypertension, can act alone or in concert with other diseases to induce CRF, and although most patients with hypertension never develop significant renal disease, chronically elevated blood pressure is responsible for 25% of new cases. Population studies highlight a trend toward higher overall Scr in subgroups with hypertension. A number of other risk factors should alert the clinician to the possible presence of chronic renal disease and should be sought out in cases where renal failure is discovered but no cause is apparent. These include a history of analgesic abuse, malignancy (especially multiple myeloma), hepatitis, recent infection with *Streptococcus* species, a history of collagen vascular disease, massive obesity, human immunodeficiency virus infection, and peripheral vascular disease. Hepatitis C virus infection has been implicated in causing the majority of MPGN previously considered to be “idiopathic.” Chronic congestive heart failure and chronic liver failure can lead to a form of secondary, functional CRF. Hyperlipidemia may be a risk factor for progression of glomerular diseases.
B. **Nonmodifiable risk factors.** Age and race are the main nonmodifiable risk factors for the development of certain types of CRF. The most prevalent causes of ESRD, diabetes and hypertension, increase in incidence with advancing age. Moreover, older patients are likely to have lived with their diseases longer, resulting in more disease-years of exposure. In fact, the growing prevalence of ESRD over the past 10 years is attributed almost solely to greater attack rates in the over-65 age group. The incidence of renal failure in blacks is more than threefold that of whites, mainly due to a higher incidence of hypertensive nephropathy. The incidence of FSGS is ten times greater in blacks, making FSGS the single most common cause of ESRD in young black men. Sex is a risk factor for certain diseases. Although males have a slightly higher incidence and prevalence of ESRD overall, females are more frequently affected by the diseases that cause CRF, such as diabetes mellitus type II, interstitial nephritis, hemolytic-uremic syndrome, and systemic lupus erythematosus. Family history is important in two ways. Foremost, the risk for developing diabetic nephropathy is increased in the diabetic patient with a family history of diabetic nephropathy

and essential hypertension. Second, initial evaluation may reveal a history of hereditary diseases, including Alport's syndrome, polycystic kidney disease, and other, less common genetically transmitted diseases such as sickle cell anemia, medullary sponge kidney, Fabry's disease, and tuberous sclerosis.

III. Natural history. Most forms of CRF inevitably progress to ESRD over a 2- to 10-year period. As nephron mass is lost, the surviving nephrons hypertrophy and compensate by filtering more; these overworked nephrons eventually succumb to the increased workload, thus placing further functional strain on the fraction remaining. In diabetes mellitus, proteinuria is the harbinger of renal involvement. Microalbuminuria occurs in the first phase and may last for many years before evolving into overt proteinuria (more than 300 mg per day). By this time, the Scr is usually higher than 1.5 mg per dL. Although strict blood glucose control and the use of ACE inhibitors extends renal survival, once major proteinuria and elevated Scr are present, most such patients will have ESRD within 5 years. The progression of hypertension-induced CRF is not as clear, but again, once the Scr is twice the normal level—indicating a 50% or greater loss of GFR—relentless progression frequently ensues. Most other glomerular diseases that cause ESRD progress slowly over 5 to 10 years, featuring either continuous or intermittent glomerular injury. Idiopathic membranous nephropathy, lupus, MPGN, and immunoglobulin A nephropathy often take years to result in ESRD. Progression is not always insidious. Many of the aforementioned conditions (in addition to others, such as Wegener's granulomatosis, FSGS, and Goodpasture's syndrome) can manifest as the clinical entity of rapidly progressive glomerulonephritis, which leads to ESRD in weeks to several months. In certain conditions in which the renal insult is short-lived and does not recur, such as traumatic nephrectomy and toxic exposures, renal function is lost but then stabilizes without further decline. Disease states that can lead to stable CRF include autosomal dominant polycystic kidney disease (ADPKD), interstitial nephritis (without recurrence), and obstruction (once the obstruction is relieved). Elderly patients who lose a kidney due to infection, neoplasm, trauma, or vascular accident often experience an abrupt rise in Scr that plateaus over the long term. Likewise, normalization of blood pressure in patients with malignant hypertension may lead to doubling of the Scr, which then may revert to baseline, or at least improve, in the ensuing months. Many nephrologists advocate plotting 1/Scr against time as an index of progression, especially for glomerular disease. The 1/Scr should decline linearly, and by extending the line into the future, physician and patient can approximate when the Scr will reach 10 mg per dL (1/Scr of 0.1). In addition, patients who have mild or moderate CRF are at risk for acute renal failure (ARF) due to acute insults such as volume depletion. The 1/Scr line helps in these instances because when a patient “falls off the line” (i.e., when the slope abruptly increases), a second disease process may be at work.

IV. Diagnosis. Demonstrating decreased GFR, significant proteinuria, or abnormal urinary sediment of renal parenchymal origin establishes the clinical diagnosis of chronic renal disease.

A. **Decreased GFR.** Elevated Scr concentration is the most widely used indicator of a decreased GFR in clinical medicine. It is imprecise because of the influence of non-GFR factors on steady-state creatinine concentration. Muscle mass, metabolism characteristics, and absorption of dietary creatinine from meat can affect serum levels, and certain medications (cimetidine, trimethoprim) can affect Scr concentrations by inhibiting tubular secretion. Although such factors affect Scr, they do not alter GFR. Furthermore, changes in Scr are not linearly related to changes in GFR: Minor elevations in Scr often reflect large decreases in GFR (see Fig. 10-1). When using Scr to screen for CRF, the influences of race, sex, and age should be kept in mind. Males and non-Hispanic blacks have levels 0.1–0.2 mg per dL higher than their white counterparts. Hispanics have slightly lower Scr levels in all age and sex groups compared with non-Hispanic whites and non-Hispanic blacks. Muscle mass tends to decline with age; thus, a normal Scr level in an elderly individual may disguise renal impairment. Despite its shortcomings, in persons free of acute illness and who have experienced no recent changes in diet or exercise, Scr can be used as a gross index of kidney function.

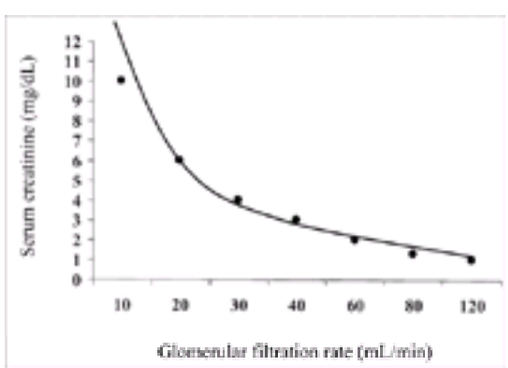

Figure 10-1. Nonlinear relationship between serum creatinine and glomerular filtration rate.

Once CRF is suspected, several tests are used to quantitate the decrement in renal function. The simplest method uses creatinine clearance (ClCr) as a surrogate for GFR. ClCr is determined by collecting the urine over a 24-hour period and measuring the total volume and creatinine concentration of the specimen. These values are used in the equation: ClCr = (U × V)/P, where U is the concentration of creatinine in the urine, V is the volume of urine per 24 hours, and P is the plasma concentration of creatinine. Like GFR, ClCr is reported in mL per minute, so a factor is used to convert days to minutes:

$$\text{ClCr (mL/min)} = \left(\frac{\text{U (mg/dL)} \times \text{V (mL/day)}}{\text{P (mg/dL)}} \right) \times \left(\frac{1 \text{ day}}{1{,}440 \text{ min}} \right)$$

As renal mass is lost, the remaining nephrons compensate by increasing tubular secretion of creatinine, thereby adding to overall ClCr in the face of decreasing GFR. Some have employed the creatinine-secretion blocking properties of cimetidine and trimethoprim to eliminate this effect at the time of ClCr determination. The equation of Cockcroft and Gault is an alternative and reasonably accurate method of estimating GFR based on Scr, age, and weight.

$$\text{ClCr} = \left(\frac{(140 - \text{age})}{72 \times \text{P}_{\text{cr}}} \right) \times \text{weight (kg)} \qquad \text{(Multiply by 0.85 for female patients.)}$$

However, when making critical medical decisions requiring an accurate estimate of ClCr, the 24-hour urine method may be best.

B. **Other indicators of chronic renal disease.** Due to its lack of sensitivity early in the course of disease, Scr may be normal in a significant number of patients who have parenchymal renal disease. Such patients may manifest proteinuria, hematuria, or other urinary sediment abnormalities for several years before Scr rises. Because Scr may not rise detectably until 50% of GFR is lost, these urinary findings are relied on to gauge disease activity.
   1. **Proteinuria.** The dipstick test for urinary protein has been used to screen for renal disease, and in some cases proteinuria is the only manifestation of chronic renal injury. When the dipstick result is positive but less than 2+ in younger patients, benign proteinuria is likely, as long as no other history or physical signs indicate the presence of or risk for chronic renal disease. However, if proteinuria persists at a low level (as in early diabetic nephropathy), or is greater than 2+ (or 100 mg per dL) on repeat analysis, clinically significant renal disease may be present: Of 10,000 college students screened for urinary protein, persistent proteinuria was found in 185. Of these, 35 were diagnosed as having renal disease. During 45 years of follow-up, six of the students, all among the 35 initially identified as having proteinuria, died of renal disease. The amount of protein in a 24-hour collection of urine can differentiate glomerular from nonglomerular diseases. Most glomerular diseases are accompanied by proteinuria of more than 2.5 g per day, whereas interstitial, vascular, and obstructive conditions feature less than 1.5 g of protein per day. This should be held as a general rule and not be considered diagnostic in and of itself. For example, diabetic patients commonly have very low-grade proteinuria early in the course of their glomerular disease, and certain vascular diseases, such as ischemic nephropathy, can present with high-grade proteinuria.
   2. **Hematuria.** A positive dipstick test for blood can occur in many forms of parenchymal renal disease and diseases of the urinary collecting system. Therefore, it is important to examine the urinary sediment microscopically to determine the quantity and characteristic of the blood in the urine. Occasionally, the dipstick indicates hemoglobin, but no red blood cells are seen, as in myoglobinuria or even hemoglobinuria. When more than 5 to 10 red blood cells are detected on repeated examinations and the cells are morphologically normal in fresh urine, common conditions such as nephrolithiasis, urinary tract infection, and prostatitis should be sought out and excluded. In the absence of these urologic causes, effort should be made to determine whether the hematuria is associated with proteinuria, cellular casts, renal cystic disease, or renal failure. A percentage of patients with isolated persistent hematuria without proteinuria have so-called thin basement membrane disease and require no further workup. Hematuria is one of the most common abnormalities seen in all forms of glomerulonephritis, in addition to being prominent in vascular diseases of the kidney.
   3. **Urinary sediment.** Glomerular diseases are often associated with microscopic hematuria (sometimes misshapen red blood cells), urinary white blood cells, casts, and lipid. Red blood cell casts almost always indicate glomerulonephritis, whereas white blood cell casts and waxy casts are less specific. A significant percentage of patients with MPGN, FSGS, and minimal change diseases have normal urinary sediment. The urinary findings of chronic interstitial disease

are usually not prominent, with fewer cells and rare white blood cell casts. Finding eosinophils free or in casts is suggestive of allergic interstitial nephritis. Of note, patients with functional CRF from cardiac failure or liver disease can have either completely normal sediment or hyaline casts, which indicate precipitation of normal tubular proteins in a highly concentrated milieu.

4. **Hypertension.** Patients with active glomerular disease accompanied by proteinuria and renal failure are prone to develop hypertension. A negative past medical history of hypertension in a patient presenting with proteinuria and renal failure suggests that the glomerular disease is the cause of the elevated blood pressure, rather than viceversa. Essential hypertension is always present for many years before it causes renal disease. Malignant hypertension often presents with a sudden increase in blood pressure and Scr, making it difficult to determine which came first. In ADPKD, the patient may present with hypertension years before CRF occurs and so may be misdiagnosed as having essential hypertension. Review of the family history, palpation for the presence of enlarged, cystic kidneys, and renal ultrasound usually establish the diagnosis in the presence of otherwise normal renal function.

V. Initial evaluation Renal diseases can be classified as acute or chronic based on the rate of decline in GFR, and as prerenal, postobstructive, or parenchymal based upon the proximal events that led to CRF. Acuity is easily determined early in the course of renal disease, but may be difficult to establish if the GFR is markedly decreased at the time of presentation. History may uncover a recent acute illness or recent decline in urine output suggesting acute, reversible renal failure. The presence of anemia, normokalemia, calcium-phosphate abnormalities, and malnutrition is evidence for CRF, whereas in ARF, hyperkalemia, fluid overload, and normal-sized kidneys are seen. Although most patients with CRF and ESRD have small, shrunken kidneys, conditions leading to CRF with normal or large kidneys include amyloidosis, ADPKD, diabetes, and chronic obstruction. Even when the indicators of CRF are present on initial evaluation, ruling out an additional decline in GFR from a superimposed process such as acute volume depletion, nephrotoxic drugs, infection, obstruction, cardiac failure, or accelerated hypertension is important. This is sometimes referred to as *acute-on-chronic renal failure* and is critical to consider because patients with CRF are at risk for many of the conditions causing ARF. Once chronicity is established and prerenal and obstructive factors have been ruled out, the focus is on intrarenal causes by group: glomerular, vascular, and interstitial. Table 10-2 lists features helpful in distinguishing the glomerular from the nonglomerular causes of CRF.

Clinical finding	Glomerular disease	Nonglomerular, interstitial, vascular, obstructive disease
24-hr urinary protein	>2.5 g	<1.5 g
Sediment	Mixed, with cellular casts, fat bodies, oval fat bodies	Few cells and casts
Hypertension	+++	±
Renal failure at time of diagnosis	±	+

+, present often; ±, may or may not be present; +++, usually present, may be severe.

Table 10-2. Glomerular versus nonglomerular disease

A. **Obstruction causing CRF.** Chronic partial urinary tract obstruction is seen in young people with congenital anomalies of the genitourinary system and in adults due to prostate disease, malignant tumors, and stones. Obstruction can be diagnosed with 95% confidence using ultrasound that demonstrates hydronephrosis, hydroureter, dilatated bladder, or a combination of such. One exception is retroperitoneal fibrosis, in which fibrotic tissue encapsulates the urinary collecting system and causes obstruction while preventing dilatation. In this scenario and other conditions in which a malignancy is suspected, computed tomography aids in diagnosis. Furosemide-assisted radionuclide renography offers a third approach to diagnosing obstruction and can usually differentiate true obstruction from an atonic dilatation of the collecting system. The postvoid residual (PVR) urine volume is a simple test that detects urethral obstruction by inserting a bladder catheter after voluntary voiding. A PVR greater than 50 mL suggests significant obstruction between the bladder neck and urethral meatus. Relief of partial obstruction may result in recovery of GFR, depending on the duration and severity of the obstruction. Even when obstruction is not suspected, renal ultrasound is useful in the setting of CRF to demonstrate the presence of two kidneys and to document renal size.

B. **Prerenal factors leading to CRF.** Severe cardiac failure and hepatic cirrhosis can lead to chronic decreases in effective arterial blood volume that can subacutely cause or worsen CRF. When these diseases are advanced to the point of secondarily triggering renal failure, they are clinically apparent with overt ascites, peripheral edema, or pulmonary edema. Optimizing renal function and preventing further declines in GFR are a matter of treating the underlying organ dysfunction. Because the kidneys are often functionally normal in these settings, urinary sediment is benign and proteinuria is usually minimal.

C. When **glomerular disease** is identified based on the presence of persistent, high-grade proteinuria (with or without hematuria, renal failure, or nephrotic syndrome), establishing a specific diagnosis is critical. If diabetes has been present for many years preceding the onset of renal abnormalities, little further workup is generally indicated. However, in older diabetic patients, multiple myeloma may need to be excluded with serum and urine protein electrophoresis, even when diabetes is the presumptive cause of the proteinuria. In most other conditions in which the etiology is unknown, renal biopsy is indicated for pathologic diagnosis and prognosis. Renal biopsy is a safe procedure with a low incidence of complications and can be performed during a single-day admission or on an outpatient basis. Occasionally, serologic tests such as antinuclear antibody, cryoglobulins, anti–streptolysin O titer, antinuclear cytoplasmic antibody, and anti–glomerular basement membrane antibody titer lead to a presumptive diagnosis. However, tissue examination is often necessary in these circumstances to establish histologic severity, confirm indirect serologic markers of disease, and guide therapy. Moreover, histologic results may raise the suspicion of other occult diseases such as hepatitis (when MPGN is found), malignancy (when membranous nephropathy is found), amyloidosis, plasma cell dyscrasias, and oxalosis. When CRF is advanced, as evidenced by an Scr higher than 4 to 5 mg per dL, renal biopsy results are usually nonspecific, and treatments are rarely able to reverse this degree of chronic glomerular injury, regardless of the etiology. Therefore, extensive renal workup including biopsy is usually only indicated when renal functional impairment is less severe. With normal renal size and a clinical picture of rapidly progressive glomerulonephritis or vasculitis, renal biopsy may be helpful, even with advanced disease (Scr higher than 4 or 5 mg per dL).

D. **Vascular disease.** Hypertensive nephrosclerosis, renal artery stenosis, and atheroembolic disease account for the majority of vascular diseases that cause CRF. History is critical in suggesting these diagnoses. These conditions are commonly associated with significant atherosclerotic vascular disease at other sites, including the coronary arteries, carotid arteries, aorta, and cerebrovascular system. Blacks have a manyfold higher risk of developing hypertensive renal disease progressing to ESRD than whites. For this reason, in black patients with long-standing uncontrolled essential hypertension, there is little reason to search for other causes unless significant abnormalities of the urinary sediment are present. This holds true even in the absence of clinical atherosclerosis. Contemporary data show that although a strong association exists between atherosclerosis and hypertensive ESRD in older white patients, the association is not as strong in blacks. Renal artery stenosis, which can lead to a form of CRF designated *ischemic nephropathy*, should be suspected in young white women with new-onset hypertension and in older patients with diffuse atherosclerosis, body imaging showing a significant discrepancy in renal size, a history of “flash” pulmonary edema, or a sudden rise in Scrafter administration of ACE inhibitors. Selection of the noninvasive screening test of choice, such as nucleotide renography or magnetic resonance angiography, is dictated by local expertise. Most experts suggest proceeding directly to renal arteriography when the suspicion of renal vascular disease is high. Percutaneous treatments including angioplasty and stent placement—again, locally variable—appear to be successful in most cases. Atheroembolic disease, also known as *cholesterol-emboli syndrome*, presents with gradual, progressive renal insufficiency associated with livedo reticularis, blue-toe syndrome, retechrae, hypocomplementemia, and eosinophilia. It usually begins days to weeks after a vascular diagnostic procedure or aortic surgery. When no such recent history is evident, renal biopsy may be necessary for diagnosis.

E. **Tubulointerstitial disease.** Patients with interstitial nephritis usually excrete less than 1.5 g of protein in the urine each day. Finding of this degree of proteinuria in association with sterile pyuria and occasionally white blood cell casts strongly suggests the diagnosis. Other clues to the presence of interstitial disease include renal salt wasting, a history of exposure to heavy metals, and renal tubular acidosis. In the past, analgesic preparations containing combinations of nonsteroidal antiinflammatory drugs and the acetaminophen precursor phenacetin were the causes of most cases of interstitial nephritis. Clinical evidence of renal disease occurs after the ingestion of 2 to 3 kg of each analgesic compound. The incidence of analgesic nephropathy has fallen subsequent to the removal of these preparations from the market. If a toxic substance such as lead, cadmium, oxalate, lithium, or analgesics is identified from the medical history, renal biopsy is usually of no value, because treatment is supportive and mainly involves avoiding the specified toxin. In young patients with CRF and nonglomerular proteinuria, a history of recurrent urinary tract infection suggests the diagnosis of vesicoureteral reflux with subsequent chronic pyelonephritis. Ultrasound and intravenous pyelography should be included in the initial evaluation of these patients. Other easily identifiable factors associated with tubulointerstitial disease and CRF include the use of cyclosporine, hyperuricemia, hypercalcemia, ADPKD, multiple myeloma, and sarcoidosis.

VI. Treatment considerations Three basic principles guide the approach to patients with CRF:

A. **Avoid renal insults.** CRF and its associated conditions predispose patients to additional renal injury both before they encounter health care providers and after they begin treatment in the acute setting. Volume depletion with acute prerenal azotemia commonly develops in CRF patients during an intercurrent illness

because of the diseased kidney's suboptimal ability to acutely conserve sodium and water. Although such patients are not overt salt-wasters, they can effectively attenuate negative salt balance only at the expense of a decreased GFR. Thus, early in the course of sodium depletion, ongoing renal sodium losses continue unabated until hemodynamically apparent extracellular fluid volume depletion develops. A trial of intravenous normal saline is usually safe and necessary to determine whether an acute rise in Scr from a historical baseline will improve. On the other hand, in patients with CRF and known cardiac disease, worsening cardiac decompensation can compromise effective arterial blood volume, leading to acute-on-chronic renal failure. Judicious use of salt restriction and diuretics is indicated when physical signs such as peripheral edema, pulmonary edema, and elevated jugular venous pressure are present.

During the course of medical treatment, the patient may be exposed to various nephrotoxins capable of causing reversible ARF. Commonly used agents such antimicrobials and antitumor drugs , including amphotericin, *cis*-platinum, and aminoglycosides can cause ARF in patients without a history of CRF; those with CRF are at higher risk. Radiocontrast media have been carefully studied, and it is evident that, although patients with CRF are at increased risk of developing ARF after a contrast procedure, the risk can be minimized by ensuring euvolemia and avoiding concomitant administration of other nephrotoxins, such as aminoglycoside antibiotics and nonsteroidal antiinflammatory drugs. For euvolemic patients, experts recommend administering intravenous 0.45 normal saline at a rate of 1 mL per kg per hour for several hours preprocedure and continuing for up to 24 hours postprocedure. Isotonic saline infusion may lead to volume overload and is not recommended. Additionally, contrast volume should be kept to a minimum. Finally, nonionic agents are preferable to less expensive ionic compounds in high-risk patients: One large, randomized trial of 1,196 cases supports the use of nonionic agents to minimize the risk to patients with CRF. Nonionic contrast agents are not indicated in patients with normal renal function. For most CRF patients, and especially those with diabetic nephropathy, other prophylactic maneuvers, including the use of mannitol, furosemide, atrial natruretic peptide, dopamine, theophylline, and calcium channel blockers, are still controversial.

Patients with impaired renal function are at increased risk for adverse drug events that are harmful, costly, and preventable. Standard of care in CRF includes the compulsory use of various readily available information systems to proactively determine appropriate drug dosing and administration interval modifications (see Chapter 12). For example, insulin therapy becomes more hazardous with advancing CRF, due to its increased half-life.

B. **Preventing or delaying progression of renal disease** is perhaps the main goal in treating CRF. Increasing evidence suggests that the following tools can retard the tempo of disease progression.
   1. **Blood pressure control.** In comparison with the established value of blood pressure control for stroke and heart disease prevention, little is known about the beneficial effect of treatment on the progression of all causes of renal disease. However, it is now believed that good control can retard the rate of decline of GFR in specific diseases, especially diabetic nephropathy and other conditions featuring significant proteinuria. ACE inhibitors are the drug class of choice, based on sound evidence that they have renoprotective properties that appear to extend beyond the degree expected by blood pressure reduction alone. Data regarding the effect of blood pressure control on CRF progression in the black population with hypertensive nephrosclerosis are being accumulated. One large trial is under way to compare the renoprotective properties of beta blockers, ACE inhibitors, and calcium channel blockers. At this time, experts recommend controlling blood pressure, preferably with an ACE inhibitor, although other agents shown to be effective in reducing blood pressure can be used. When a specific patient's regimen includes multiple drugs, one of those drugs should be a diuretic.
   2. **Glucose control.** Prospective data demonstrate a clear role for tight control of blood glucose in preventing or delaying the onset of proteinuria in type 1 diabetic patients. Less is known about type 2 diabetic patients and those with established diabetic nephropathy, although results from a large European study demonstrate a significant decrease in microvascular complications with tight blood glucose control. A caveat to tight blood glucose control is that diabetic patients with advanced CRF are at higher risk for hypoglycemia due to the increased half-life of insulin when GFR is subnormal.
   3. **Hyperlipidemia management.** Hyperlipidemia may be a risk factor for progression of renal disease, although few prospective data are available to support the use of antihyperlipidemic agents in preventing progression. However, CRF patients commonly manifest lipid disorders and can be safely treated with lipid-lowering drugs. Of note, proteinuria is often associated with elevations in low-density lipoprotein, so treating patients with ACE inhibitors to lower protein excretion may have the collateral effect of reducing serum cholesterol and triglycerides.
   4. **Diet.** Dietary protein restriction to limit progression of renal disease remains a very controversial area. The combined evidence suggests little if any protective effect in lowering protein intake to 0.6 g per kg per day. Moreover, unsupervised dietary restrictions can lead to malnutrition, as reflected by decreased serum albumin concentration, which is the most powerful predictor of mortality in patients starting dialysis.

C. **Management of uremic syndrome.** As CRF progresses, each of the remaining nephrons assumes a proportionately greater functional role in maintaining fluid and metabolic homeostasis, so that day-to-day balance is essentially maintained until 95% of nephron mass is lost. This effect, known as the *magnification phenomenon*, allows most patients with moderate CRF to consume a normal American diet, making severe dietary restrictions unnecessary. Eventually, however, dietary modification (or dialysis, or both) is needed to prevent volume overload, hypertension, hyperkalemia, metabolic acidosis, and other dangerous metabolic states.
   1. **Fluid and electrolyte balance.** Loss of the ability to dilute and concentrate the urine accompanies CRF. This tends to constrain regulation of urine volume, making it dependent on osmolar and fluid volume intake. Thus, as long as patients take in the usual amounts of solute and water, they remain in balance. Acute increases or decreases in sodium intake may lead to edema or volume depletion, respectively. Likewise, the diseased kidney cannot maintain normokalemia during acute changes in potassium intake. Water balance is similarly constrained, making patients prone to hyper- and hyponatremia during intercurrent illnesses. In a sense, CRF is characterized by the lack of ability to adapt quickly to dietary changes, but it has little impact on everyday balance in the absence of intercurrent illness.
   2. **Acid-base homeostasis.** The kidney must produce and excrete ammonia to maintain acid-base balance and prevent accumulation of dietary acid. As this capacity declines, patients develop a positive acid balance, gaining approximately 30 mEq of acid per day. The excess is buffered by the skeleton, leading to osteopenia and an increase in urinary calcium excretion. Many nephrologists use oral $NaHCO_3$ (3 g per day, or 36 mEq) to mitigate this effect—an approach that usually has only minor influence on blood pressure and extracellular fluid volume and that may improve potassium excretion by enhancing distal sodium delivery.
   3. **Calcium/phosphate.** The kidney's ability to excrete phosphate declines with falling GFR, leading to increased serum phosphate levels. It has been theorized that early elevations in serum phosphate, although undetectable in the laboratory, cause recurrent, subtle depressions in calcium levels, which, in turn, induce increases in parathyroid hormone (PTH) levels. The increased PTH levels cause remaining nephrons to excrete more phosphate, thus restoring balance. This chain of events is called the *trade-off hypothesis*, because normal phosphate balance is achieved at the expense of ever-increasing PTH levels (secondary hyperparathyroidism of uremia). The trade-off cycle apparently succeeds until GFR is below 25%. Thereafter, patients typically have hyperphosphatemia and hypocalcemia. Additionally, decreased levels of $1,25(OH)_2$ vitamin D_3 (the active form of vitamin D) contribute to hypocalcemia by causing decreased gut absorption of calcium. Eventually, pre-ESRD patients develop sustained hypocalcemia, negative calcium balance, and bone disease consistent with hyperparathyroidism. Considering that hyperphosphatemia may be the instigating event, the mainstay of therapy is to limit gut absorption of phosphate through dietary restriction and by binding phosphate to oral calcium carbonate or calcium acetate. Administering these preparations with meals improves their effectiveness as phosphate-binders and minimizes the chances of hypercalcemia. Hyperparathyroid bone disease, in the form of osteitis fibrosa cystica, is the end result of uncontrolled hyperphosphatemia and elevated PTH. Other forms of renal osteodystrophy that are often associated with hypercalcemia through a different mechanism include adynamic bone disease (seen more frequently in diabetic patients) and osteomalacia due to aluminum. Aluminum-containing binder and severe phosphate restriction, which may be accompanied by protein restriction and malnutrition, should be avoided.
   4. **Anemia.** Declining renal function is accompanied by reduced erythropoietin production, decreased red blood cell half-life, and a tendency toward gastrointestinal bleeding. Of these, erythropoietin is the principal cause of the uremic anemia seen in the later stages of CRF. Past worries about treatment with recombinant erythropoietin (worsening blood pressure, accelerating progression of CRF, and cost) have limited its use in the pre-ESRD population. Although anemia is one of the main factors in the development of left ventricular hypertrophy, there is, as yet, no evidence that reversing anemia with erythropoietin lessens left ventricular hypertrophy. When the hematocrit falls to the low 20s, some improvement in symptoms (exercise capacity, sexual function) and coagulopathy may be gained by administering the hormone subcutaneously in doses of 50 to 60 IU per kg three times per week. Iron deficiency should be sought out and treated with oral iron supplementation, particularly in patients who appear resistant to erythropoietin administration.
   5. **Nutrition.** CRF patients should see a nutritionist and become acquainted with a diet that provides adequate energy and protein in the range of 1.2 g per kg per day to prevent malnutrition. Protein-energy malnutrition may be evident when the Scr is 2 to 3 mg per dL, especially in the setting of inflammatory or wasting conditions.

D. **Early referral to a nephrologist.** The National Institutes of Health Consensus Statement on Morbidity and Mortality of Dialysis (1993) recommends that referral to a nephrologist occur when the Scr reaches 1.5 mg per dL in women and 2.0 in men. In addition to this consensus opinion, ample outcomes evidence during the modern era of renal replacement therapy has shown that early referral, defined as referral to a nephrologist 1 to 3 months before the initiation of dialysis, decreases cost and hospital days, improves overall mortality, and preserves serum albumin levels at the onset of dialysis. This recommendation assumes that the earlier opportunity for referral (at an Scr of 1.5 to 2.0) was missed. Additional arguments for early referral include leaving sufficient time to educate the patient about ESRD treatment options and optimizing the timing for access surgery. Arteriovenous fistula placement may be more successful when performed 6 months before dialysis, rather than at the start.

E. **Initiating renal replacement therapy.** The classic dilemma facing caregivers is whether to initiate dialysis before the onset of clinically significant malnutrition (i.e., when the patient is still feeling well). Waiting until the serum albumin is less than 3.5 mg per dL is discouraged. Yet, by the time the patient exhibits nausea, anorexia, or dysgeusia, he or she may already be malnourished. Moreover, following Scr is perilous, because as malnutrition worsens, the Scr may stop rising or actually decline (as muscle mass declines), creating a false sense of security. Of note, an elevated Scr level at start of dialysis does not predict a poor outcome.

The converse is true: The higher the Scr, the better for the dialysis patient. Low serum albumin, lean body mass below the ideal, and low protein catabolic rate—all indicators of malnutrition—are the strongest predictors of mortality. Despite a lack of rigorous randomized trials, the best evidence-based approach is to follow ClCr using repeated 24-hour urine collections and to consider initiating dialysis at a ClCr of 9 to 14 mL per minute. If no uremic signs or symptoms are present and nutritional status is excellent, monthly follow-up to assess uremic symptomatology is appropriate. The ClCr should not be allowed to fall to 5 mL per minute, because such poor residual renal function at the initiation of dialysis has been associated with higher mortality. Evidence points to somewhat greater ambiguity in the indicators for initiation of dialysis in the black population. In this group, none of the traditional parameters, including blood urea nitrogen, Scr, albumin, or uremic symptomatology, are associated with changes in survival rates. Other indications for dialysis in patients with advanced CRF include volume overload, intractable itching, cognitive impairment, resistant hyperkalemia, and serositis.

Suggested Reading

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Chapter 11 Renal Replacement Therapy: Dialysis and Transplantation

David M. Spiegel

Preparing for ESRD
Modality selection
Renal replacement therapy
Transplantation
Mortality comparison
Expense comparison

The number of individuals kept alive by either hemodialysis (HD) or peritoneal dialysis (PD) in the United States continues to grow by 7% each year. These life-prolonging techniques continue to make end-stage renal failure the only major organ-system failure that does not result in certain death without organ transplantation. However, the morbidity and mortality associated with end-stage renal disease (ESRD) remains high and renal transplantation remains the therapy of choice for many patients.

ESRD is the point of irreversible renal functional deterioration beyond which life can no longer be sustained. As renal function deteriorates toward ESRD, a number of physiologic alterations occur, many of which are detrimental. Renal replacement therapy is indicated when these changes can no longer be controlled by medications or diet, or when the accumulation of waste products starts to interfere with life functions. Importantly, appropriate pre-ESRD care ensures that patients are in the best overall condition when they start dialysis.

I. Preparing for ESRD.

Figure 11-1 traces the course of CRF leading up to ESRD.

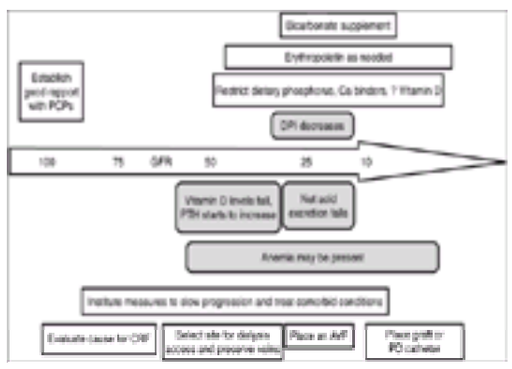

Figure 11-1. Timeline shows the course of chronic renal failure (CRF) leading to end-stage renal disease. (AVF, arteriovenous fistula; Ca, calcium; DPI, dietary protein intake; GFR, glomerular filtration rate; PCP, primary care provider; PD, peritoneal dialysis; PTH, parathyroid hormone.)

A. **Elective presentation and pre-ESRD care.** In general, patients should be referred to a nephrologist early in the course of progressive chronic renal failure (CRF). From the initial visit onward, the nephrologist should play an active role in the care of these patients. Initial visits should be directed at elucidating the cause of CRF and initiating specific therapy, if available (see Chapter 10). Later therapy should be directed at treating comorbid conditions and addressing the derangements specific to the pathophysiology of CRF. As CRF progresses, subsequent visits should address patient and family education and dialysis modality selection. The following factors should be carefully addressed:

1. **Comorbid conditions**
   a. **Hypertension** not only accelerates the progression of all forms of CRF but also is a major risk factor for cardiovascular disease, the major cause of death in dialysis patients. Most patients who start dialysis have significant cardiac hypertrophy, an independent risk factor for cardiovascular death (1). Adequate control of hypertension, especially with the use of an angiotensin-converting enzyme inhibitor, is generally agreed not only to slow the progression of CRF, but also to improve the long-term survival of patients reaching ESRD.
   b. **Lipid control.** Hypercholesterolemia, primarily low-density-lipoprotein cholesterol, is a major risk factor for cardiovascular disease in the general population. Because cardiovascular disease remains the most common cause of death in dialysis patients, aggressive treatment of lipid disorders is prudent. Such therapy should be instituted early in the course of CRF, following guidelines for the general population with appropriate medication dose adjustment where needed for chronic renal insufficiency.
2. **Disorders unique to CRF**
   a. The **anemia** of CRF almost certainly plays a role in the cardiac hypertrophy seen in patients with CRF. Early treatment with erythropoietin (EPO) can prevent severe anemia and hopefully improve the long-term survival of patients with ESRD. Although the target hematocrit for dialysis patients is currently 33% to 36%, the ideal hematocrit for dialysis and pre-ESRD patients has not been definitively determined.
   b. **Phosphate control** in the pre-ESRD patient is important to preserve the bone mineral content and avoid hyperparathyroidism. Calcium-containing phosphate binders should be instituted when the glomerular filtration rate (GFR) falls below 30 to 50 mL per minute. The use of vitamin D analogs, primarily 1,25$(OH)_2$ vitamin D_3 is more controversial. It can clearly help suppress parathyroid gland overactivity, but often at the expense of higher serum phosphate levels and the risk of hypercalcemia, both of which can worsen extraskeletal calcifications.
   c. **Acid-base control.** Acidosis is common in almost all forms of CRF. This net positive acid balance results in dissolution of bone, ultimately worsening uremic osteodystrophy. Early treatment of acidosis with oral bicarbonate therapy may help prevent some of the bone disease of chronic uremia. Care must be taken, however, not to precipitate or worsen hypertension with the added sodium intake.
3. **Access placement.** For dialysis to be performed, access to either the circulation (HD) or peritoneal cavity (PD) must be secured.
   a. For **HD** permanent access consists of either an arteriovenous fistula (AVF) or an artificial graft. Both types of accesses are placed surgically. When possible, an AVF is always preferable to an artificial graft, because AVFs have a significantly lower incidence of infection and a longer event-free survival. AVFs can take 2 to 6 months to mature and therefore should be placed 6 to 12 months before dialysis is anticipated. For artificial grafts, surgery should be performed 1 to 2 months before the anticipated start of dialysis. Access is usually placed in the nondominant arm in the most distal position available.
   b. **PD.** PD catheters are surgically inserted into the peritoneal cavity. Several types of catheters are now available, and the time from placement to first use may vary greatly. Most nephrologists allow 5 to 7 days before using a catheter that is externalized. Some PD catheters are left in a subcutaneous tunnel for several months before being externalized. This option may allow better ingrowth of the catheter in a sterile environment and allows for externalization at the time of training.
4. **Education and psychological adjustment.** In addition to the above considerations, psychological factors have been shown to have a major impact on the successful outcome of dialysis. Patients with flexible and adaptable lifestyles and strong family support systems adapt more successfully to life on dialysis. Patients must be educated regarding their disease process and the means available to slow its progression. The patients must be enlisted as partners in their own health care in order to achieve control of blood pressure, phosphate, acid-base, and lipids. Patients must be informed about dialysis and life with ESRD. Dialysis itself requires a major change in a patient's lifestyle. Whether HD or PD, patients must spend a significant amount of time either in a dialysis facility or performing PD or HD at home. In general, dialysis patients do not feel or function as well as normal individuals. However, the more the patient knows about the disease, the better the overall adjustment to the chronic illness and the subsequent quality of life.

B. **Emergency presentation**

1. **Acute renal failure leading to CRF.** Although acute renal failure requiring dialysis is not uncommon in critically ill patients, most recover renal function. Only a small percentage must remain on dialysis. These patients generally go through the same adjustment period as patients with known chronic renal insufficiency, but because it is more compressed in time, the adjustment may be more difficult. Acceptance of a chronic illness is often difficult, and patient education is crucial. Education must often be delayed until the patient is well enough to understand the issues.
2. **No previous medical care.** Many patients present with symptoms and signs of uremia with little or no previous medical care. For these individuals, dialysis

therapy must be instituted emergently, and the educational process begun after the patient is stabilized. As described above, the sudden disruption of lifestyle by ESRD often makes adjustment to dialysis initially very difficult.

3. **Access for acute dialysis.** When emergency HD is needed, a temporary dialysis catheter must be placed. To avoid puncturing the subclavian veins, use of either the femoral vein or the internal jugular vein is recommended. Increasing evidence suggests that use of the subclavian approach for temporary HD access predisposes to stenosis of the subclavian vein, often precluding future use of that extremity for permanent access. Acute PD catheters can also be placed at the bedside for emergent PD.

II. Modality selection Research suggests that both PD and HD provide equal renal replacement therapy for most patients. Modality selection should be based on patient preference, which is largely related to lifestyle decisions. Proper education, starting long before dialysis is required, is the best means of ensuring that patients are able to make rational and educated decisions.

A. **HD**

1. **In-center HD.** The largest percentage of dialysis patients in the United States are dialyzed via this modality. Although most patients participate very little in their actual dialysis care, some facilities promote self-care, in which patients actively participate by taking their blood pressure, responding to machine alarms, and even performing needle placement. However, as dialysis machines have become more complex and automated, self-care is not practical for all units.
2. The number of patients on **home HD** continues to decrease in the United States. It requires a partner to help with the machine, especially in emergencies. The average training time before patients are able to perform HD at home is about 6 weeks. However, once trained, patients generally do quite well, having the lowest mortality rate of any group of U.S. dialysis patients. Part of this low mortality may be related to patient selection, since only the healthiest patients are generally selected for home HD.

B. **PD**

1. **Continuous ambulatory PD,** along with continuous cycler PD, accounts for about 18% of all dialysis in the United States. PD allows patients a flexible schedule, because the exchanges can be done around most work schedules. Another advantage of PD is that patients in remote areas do not have to travel to a dialysis center.
2. **Continuous cycler PD,** which involves using a machine to perform dialysis exchanges at night, allows patients even greater daytime flexibility. This is especially useful for people in school or for young children.

III. Renal replacement therapy The appropriate time to initiate dialysis has not been determined. Most nephrologists base their decisions on clinical laboratory data and a subjective patient assessment. By the time the GFR falls below 10% of normal, many patients require dialytic intervention. However, many patients appear to function quite well until the GFR approaches 5% of normal. As a general rule, diabetic patients require earlier intervention (GFR less than 15% of normal) than those with other etiologies for their renal failure. Clearly, dialysis needs to be initiated before the uremic signs of peripheral neuropathy, encephalopathy, malnutrition, or serositis including pericarditis occur. Although many of these complications resolve with adequate dialysis, peripheral neuropathy and malnutrition may be exceedingly difficult to reverse. Some nephrologists believe that early initiation with dialysis, especially PD, may improve long-term outcome.

A. **HD**

1. **Technical aspects.** The basic principles of HD include diffusion-based mass transfer of solute and pressure-driven water removal. Most patients dialyze three times per week. For each treatment, two large-bore needles are inserted into the vascular access for removal and return of blood. The patient must remain confined to the dialysis machine for the duration of the treatment. Today, many dialysis units use volumetric machines designed to remove a precise amount of fluid. These volumetric machines permit the use of larger, highly porous dialyzers with high water and solute permeability. This new design not only allows for significantly more removal of larger molecules than older dialyzers, but also increases the efficiency of urea removal.
2. **Adequacy.** What constitutes optimal HD remains controversial. Urea kinetic modeling is a useful tool to quantify dialysis and thereby prevent underdialysis. Care must be taken to ensure that the modeling is based on delivered dialysis. Additionally, as dialysis times are shortened, plasma urea rebound due to delayed intercompartmental shifts must be considered. A delivered dialysis dose of less than 65%, as measured by urea removal, or a Kt/V of less than 1.2 (where *K* is the dialyzer clearance of urea, *t* is the treatment time, and *V* is the urea volume of distribution) is considered inadequate (2).
3. **Blood pressure control.** Cardiovascular mortality remains the number-one cause of death in ESRD patients. Although a patient's condition at the start of dialysis clearly plays a role in long-term outcome, optimal blood pressure control while on dialysis remains critical. Among dialysis patients in the United States, 50% to 80% are receiving antihypertensive therapy. Some evidence suggests that many of these patients could have their blood pressure adequately controlled without antihypertensive medications if adequate dialysis was provided along with vigilant control of fluid volume.
4. Chronic **anemia** occurs in most dialysis patients and almost certainly contributes to cardiac hypertrophy. Studies have shown that the anemia of ESRD is largely due to a deficiency of EPO and can be corrected by administration of exogenous EPO. Adequate iron stores are also required. Studies have shown an improvement in patient quality of life and exercise physiology. Short-term studies have shown a decrease in cardiac hypertrophy when the anemia of CRF was partially corrected (1). As with hypertension, some data suggest that adequate dialysis is associated with improved hematocrits and a decreased need for EPO.
5. **Nutritional aspects.** Large-scale studies have demonstrated that the nutritional state of a patient when HD therapy is begun has a major impact on long-term survival. However, many patients waste after years of HD therapy. It is clear that a significant number of patients on HD ingest too little protein and calories to maintain lean body mass. A low serum albumin concentration is the strongest predictive factor for increased mortality and may indicate inadequate dialysis. However, albumin is now recognized to be an important inverse acute-phase reactant. The usefulness of a low serum albumin as a marker of mortality may reflect either nutritional deficiencies or the presence of an active inflammatory process. Whether all the malnutrition seen in dialysis patients is secondary to inadequate dialysis or secondary to other causes, such as hypercatabolism induced by HD itself, remains to be clearly delineated. However, identifying and correcting reversible causes of malnutrition is essential to maintaining adequate nutrition in patients with ESRD.
6. **Rehabilitation/psychosocial adjustment.** When compared with the normal U.S. population, patients on HD have a much lower employment rate and a much higher percentage of disability recipients. Efforts to improve these figures through vocational rehabilitation have only been marginally successful. However, on quality of life questionnaires, most HD patients rate their quality of life only slightly below the general population. Despite their overall high self-rating on quality-of-life questionnaires, many dialysis patients suffer from depression and anxiety disorders. A social worker is a critical member of all dialysis facility teams and can play a vital role in helping patients adjust to dialysis and deal with feelings of depression and anxiety.
7. **Complications.** Despite its lifesaving nature, HD remains a poor substitute for normal renal function and is fraught with a number of complications, both technical and secondary to renal failure itself.
   a. Technical complications
      1. Despite advances, **vascular access** remains the Achilles' heel of HD. Some AVFs last 5 to 20 years. However, many patients have poor native vessels and therefore must rely on artificial grafts. These grafts are predisposed to thrombosis, aneurysm formation, and infection. The average survival of new grafts is about 2 years. Early intervention for failing grafts and new radiologic techniques have improved the average survival rate (3). Intervention can take several forms, including measurement of static or dynamic venous pressures and indirect measures of access blood flow rate.
      2. **Hypotension** remains a common problem in HD, despite improvements in dialysis equipment. Use of bicarbonate dialysis, higher sodium concentrations, and volumetric machines has helped to decrease its frequency. However, hypotension continues to occur for a number of reasons, including autonomic insufficiency, too-rapid ultrafiltration, and myocardial dysfunction.
      3. **Allergic reactions** to the dialyzer material or the sterilant can occur. They can range from mild itching to anaphylaxis.
      4. **Other.** Air embolism, ruptured dialyzer, and use of an improper dialysate mixture are rare but often life-threatening complications. Care and proper maintenance of dialysis machines, with special attention to the dialysis technique and to the safety and alarm mechanisms, helps prevent these complications.
   b. Complications associated with inadequate dialysis
      1. Although **uremic pericarditis** is often thought of as a predialysis problem, many HD patients develop it. This often occurs in the setting of an acute illness or a hypercatabolic state, or at a time of vascular-access difficulty, resulting in inadequate dialysis.
      2. **Uremic neuropathy** is overlooked by many nephrologists, because it is generally a peripheral neuropathy, starting in the feet or hands. It must be differentiated from diabetic neuropathy, which is common in the dialysis population. Because the two conditions can coexist, chronic inadequate dialysis must be considered a possible cause of any peripheral neuropathy.
   c. Long-term complications
      1. **Cardiovascular death** remains the major cause of mortality in patients with ESRD. Many factors contribute, including hypertension, anemia, cigarette use, hypercholesterolemia, and the presence of an arteriovenous shunt. Most of these factors are present long before the development of ESRD. Although aggressive treatment of these risk factors seems prudent, good clinical studies of its usefulness in ESRD patients are lacking.
      2. **Infections** remain a common cause of morbidity and mortality in HD patients. Infection of temporary catheters and artificial arteriovenous grafts are common. When infected, temporary catheters generally must be removed. However, some grafts can be salvaged with aggressive antibiotic treatment alone. Staphylococcal organisms remain the most common, followed by other gram-positive bacteria. Endocarditis is a very serious complication that may result from a catheter or graft infection. Native vein fistulas have a lower infection rate than all forms of temporary or artificial graft material and

are the access of first choice.

3. **Bone disease** is common in long-term dialysis patients. The morphology of the bone pathology has changed since the 1980s. Hyperparathyroid bone disease (osteitis fibrosa) remains the most common. It results from overactivity of the parathyroid glands as a result of hyperphosphatemia and low $1,25(OH)_2$ vitamin D_3 levels. Rapid bone turnover, increased osteoclast activity, and, ultimately, fibrosis of the marrow space characterize this bone disease. It can be mild to severe, pure or mixed with aluminum bone disease. Aluminum is directly toxic to bone. Dialysis patients acquire aluminum either through oral aluminum containing phosphate binders or through a contaminated water supply. It accumulates, due to lack of renal excretion, and deposits at the mineralization front of growing or remodeling bone. This impairs bone mineralization and leads to a condition of weakened bone with increased unmineralized matrix or osteoid known as *osteomalacia*. A histologic pattern increasingly found in bone biopsies from dialysis patients has been termed *adynamic bone*. This bone is characterized by very low bone turnover with few osteoblasts or osteoclasts. Although severe hyper-parathyroidism can cause hypercalcemia, both adynamic and aluminum bone disease also predispose patients to hypercalcemia. A final form of bone and osteoarticular disease seen in long-term dialysis patients is beta $_2$-microglobulin amyloidosis. Beta$_2$-microglobulin is a small protein that accumulates in the blood of dialysis patients and precipitates at osteoarticular surfaces, forming amyloid. Symptoms include pain, swelling, bone cysts, and fractures. Data suggest that highly permeable dialysis membranes may delay the onset of disease symptoms.
4. **Malnutrition.** The wasting seen in many dialysis patients results from loss of both lean body mass and fat mass. Insufficient protein and calorie intake, coupled with the catabolic stress of dialysis performed using poorly biocompatible membranes, leads to this debilitated state. In addition, inadequate dialysis also leads to decreased protein intake and malnutrition.
5. **Skin disorders.** Pruritus remains one of the most troubling complaints of dialysis patients. Causes include an elevated calcium-phosphorus product, dry skin, and hyperparathyroidism. Some relief may be achieved with antihistamines and phosphate control. Other skin conditions in dialysis patients include bullous dermatitis and porphyria cutanea tarda.
6. **Acquired renal cystic disease.** Many patients undergoing maintenance dialysis develop cysts in their native kidneys that tend to increase in size and number over time. Although these cysts are generally an incidental finding, complications including polycythemia, spontaneous rupture, and retroperitoneal bleeding have been reported. Dialysis patients with acquired renal cystic disease appear to have a 100-fold increase in the incidence of renal cell carcinoma (4). However, deaths from renal cancer remain quite uncommon in the ESRD population, and routine screening has not been advocated because of the high rate of false-positive studies, which might lead to unnecessary surgery in this high-risk population. Patients with hematuria, flank pain, or weight loss should be evaluated.

B. **PD.**

1. **Technical aspects.** Technically PD is much less complex than HD. A sterile electrolyte and dextrose solution (dialysate) is allowed to flow into the peritoneal cavity by gravity or via a low-pressure pump. After a specified period of time (dwell time), the fluid is drained out of the peritoneal cavity, and fresh fluid is again infused. The peritoneal lining acts as the semipermeable membrane across which diffusion occurs. The process of fluid infusion and drainage (exchanges) can be performed manually (continuous ambulatory PD) or by a machine (continuous cycle PD).
2. **Adequacy.** Unlike HD, no large prospective outcome studies that clearly address dialysis adequacy have been done for PD. Because the quantity of PD that can be delivered is limited by the fixed peritoneal membrane kinetics and the amount of dialysate that can be comfortably infused and carried, delivering as much dialysis as is reasonably possible seems prudent. Many experts have advocated minimum targets of 60 L per week of creatinine clearance or a weekly Kt/V urea of 2 for standard continuous ambulatory PD (2).
3. As with HD, **blood pressure control** is important for the long-term well-being of PD patients. Many patients on PD are able to discontinue their antihypertensive medications and maintain a normal blood pressure, which may be attributable to the steady-state volume control achieved by this continuous dialysis modality.
4. Correction of **anemia** with EPO is important in improving the quality of life for PD patients. EPO is generally administered subcutaneously in PD patients; adequate correction of anemia can generally be achieved with once- or twice-weekly injections. The lower overall dose of EPO needed to correct the anemia in PD patients compared with HD patients reflects the difference in routes of administration (subcutaneous is more effective than intravenous) and the small, ongoing blood losses in HD patients.
5. **Nutrition** is critically important in PD patients. Protein requirements for PD patients are considered to be slightly higher than for HD patients due to the ongoing loss of protein in the spent dialysate. Many patients on PD gain weight over the first year to 18 months. This phenomenon probably results from an increase in fat mass due to excess calorie intake, part of which comes from the high glucose content of the peritoneal dialysate solution. However, long-term PD patients, like HD patients, tend to lose lean body mass. How this relates to the adequacy of PD remains unclear.
6. **Rehabilitation/psychosocial adjustment.** Although PD allows individual patients more control over their health care and a more flexible dialysis schedule, the percentage of PD patients in the work force and the percentage on disability are not different than for HD. On quality-of-life questionnaires, PD patients as a group rate their quality of life about the same as HD patients. Unfortunately, no prospective studies are available, and the variability in patient selection is certainly a major factor in these outcomes.
7. Like HD, PD has a number of **associated complications,** which can be divided into two groups: infectious and long-term. However, unlike HD, inadequate PD tends to result in malnutrition and technique failure, with pericarditis and peripheral neuropathy being less common, although they do occur.
   a. **Infectious complications.** Peritonitis remains the most frequent complication of PD. Technical improvements, including disconnect “flush before fill” systems, have reduced the peritonitis rates in most centers. Most episodes of peritonitis are treatable in the outpatient setting, although severe infections require hospitalization and occasionally catheter removal. This is particularly true when peritonitis is caused by a fungal infection or *Pseudomonas aeruginosa*. Exit-site infections are also common in PD and usually result from gram-positive organisms. They can generally be treated with antibiotics and increased local care. However, some infections, particularly those secondary to *Staphylococcus aureus*, may require catheter removal. Although no consensus on proper exit-site care has emerged, most experts agree that the catheter should exit the skin in a downward direction. Tunnel infections usually result from exit-site infections and are frequently caused by *S. aureus*. Early diagnosis is often difficult. An episode of peritonitis with the same organism causing an exit-site infection may be the presenting symptoms. In some centers, ultrasound has been useful in detecting fluid around the subcutaneous tunnel that indicates a tunnel infection. Tunnel infections usually necessitate catheter removal.
   b. **Long-term complications.** Although acute hemodynamic complications are less frequent with PD, due to the continuous nature of the technique, cardiovascular disease remains the most common cause of death. Aggressive treatment of lipid abnormalities seems warranted, although outcome studies are not available. Renal osteodystrophy also occurs in PD patients. The morphology is similar to that seen in HD patients, with a slightly higher incidence of adynamic bone disease. Beta$_2$-microglobulin amyloidosis also occurs in PD patients, although theoretically its onset may be delayed due to the higher clearance of beta$_2$-microglobulin by the peritoneal membrane compared with that in conventional HD. Acquired renal cystic disease and renal cell cancer appear to have the same increased incidence in PD as in HD. A number of long-term complications are unique to PD, including a leak of PD fluid from the peritoneal space to either the pleural space or into the subcutaneous tissues, resulting in either pleural effusions or hernias, respectively. Sclerosing peritonitis resulting in ultrafiltration failure is an uncommon complication of PD, and when it occurs, it is usually in the setting of repeated episodes of peritonitis. A much more common cause of failure of patients on PD is gradual loss of residual renal function that results in a fall in total clearance, often leading to inadequate dialysis.

IV. Transplantation

Improvements in immunosuppression, along with better treatment and prophylaxis for infectious complications, have made renal transplantation the treatment of choice for most ESRD patients. The number of transplants in the United States is limited by the availability of donor organs.

A. **Patient selection.** Few absolute contraindications to renal transplant exist. The primary reasons include an incurable infection (e.g., acquired immunodeficiency syndrome) or cancer, severe untreatable cardiac disease, or advanced physiologic age. Relative contraindications include an active infection, active peptic ulcer disease, and an active immunologic,disease that has resulted in renal failure.

B. **Patient evaluation**

1. **Recipient.** Before renal transplantation, the patient undergoes an evaluation to rule out illnesses that would contraindicate a renal transplant and to determine the patient's immune status with regard to many chronic viral infections. The standard evaluation includes routine blood work; a test for human immunodeficiency virus, cytomegalovirus (CMV), and hepatitis; a cardiac evaluation; evaluation of the lower urinary tract; and a good history and physical examination, including routine screening studies appropriate for the patient's age. The cardiac evaluation may be simply a history and a physical examination in a young patient without symptoms, or it may include a cardiac angiogram in a diabetic patient with an abnormal electrocardiogram or a positive noninvasive test for cardiac ischemia. Evaluation of the lower urinary tract might consist of only a urinalysis or may require a voiding cystourethrogram. Once a patient is accepted for transplant, further evaluation, including ABO blood typing, HLA tissue typing (both HLA-A,B and HLA-DR), and screening for cytotoxic antibodies, is performed. The cytotoxic antibody screen involves testing the patient's serum against a random panel of lymphocytes to detect preformed antibodies against HLA antigens. Before a transplant takes place, a final crossmatch is performed. A crossmatch involves testing a patient's serum for lymphocytotoxic, antibodies against the donor's lymphocytes.
2. **Donor.** There is a tremendous shortage of kidneys available for transplant. Most of the organs come from cadaveric donors; most centers also pursue living related donors to variable degrees. Presently, there are about 20,000 patients waiting for a kidney transplant, and about 1,500 additional patients are added each year to the waiting list.
   a. The criteria for **cadaveric donation** include permission from the deceased and the next of kin. In addition, most donors are younger than 65 years, have a beating heart, and have been declared brain dead. The donor must be free of any potentially transferable diseases, including hepatitis B and C (unless

the recipient is also positive) and human immunodeficiency virus, and of malignancy and must have normal renal function without a history of renal disease or severe hypertension.

b. **Living donor.** Most living donors are blood relatives of the recipient; however, many centers are now performing living unrelated transplants, usually between spouses or from a stepparent to a child. Evaluation of the donor is thorough and designed to rule out any systemic disease, hypertension, cardiac disease, or any evidence of renal disease. ABO typing, HLA typing, mixed lymphocyte culture, and crossmatching are all performed. If all of the testing is acceptable, the donor undergoes evaluation of the renal arteries before donation.

C. In general, **transplant surgery** is relatively minor, and most patients are encouraged to be out of bed after 1 day. The kidney is placed in the extraperitoneal iliac fossa, and the renal artery and vein are anastomosed to the iliac vessels. The ureter is then implanted into the bladder, preferably using an antireflux technique, near the trigone.

D. **Immunosuppression protocols** vary widely among transplant programs. In general, immunosuppression can be divided into three phases: (a) induction—high dose immunosuppression for the first 5 to 14 days after transplant; (b) maintenance—immunosuppression at a level that can be tolerated for a lifetime while minimizing complications; and (c) rejection treatment—increasing or changing immunosuppression to treat a rejection episode.

1. **Induction protocols.** High-dose induction immunosuppression usually consists of high-dose intravenous steroids, mycophenolate mofetil (which has replaced azathioprine in many centers), and cyclosporin A (CSA) for all but HLA-identical transplants. The steroids are generally tapered to 20 to 30 mg per day by the time of hospital discharge at 7 to 10 days posttransplant. Mycophenolate mofetil is usually administered at 1,000 mg b.i.d. if gastrointestinal side effects can be tolerated. CSA may delay graft function, and an alternative regimen used by some centers includes high-dose steroids, mycophenolate mofetil, and an anti–T cell antibody for induction therapy. This therapy is also frequently used for high-risk transplants, second transplants, African-Americans, and patients with high reactive antibody panels. CSA is added at day 5 to 7, after the urine output has increased and the serum creatinine has fallen. The CSA is given for several days before the anti–T cell antibody is stopped.
2. Most **maintenance protocols** consist of oral prednisone and CSA with or without mycophenolate mofetil. Where possible, the prednisone is tapered to approximately 7.5 to 10.0 mg per day. CSA is reduced to about 3 to 4 mg per kg per day. CSA levels are followed routinely to adjust the dose based on variable absorption from the gastrointestinal tract.
3. **Treatment for rejection.** At the earliest signs of rejection, usually after a renal biopsy, treatment with antirejection medication is indicated. Many centers continue to use pulse intravenous methylprednisolone (500 mg) for 3 days and reserve monoclonal antibodies (OKT3) for severe rejection episodes or for patients who do not respond to high-dose steroids. Other centers use monoclonal antibodies for all but the mildest presentation of allograft rejection.

E. **Causes of graft loss**

1. **Rejection.** Chronic rejection remains the most common reason for ultimate loss of renal transplants. Whereas hyperacute rejection occurs within minutes to hours of transplant, most acute rejection episodes do not occur until approximately 7 to 14 days posttrans-plant. Acute rejection episodes are unusual after 2 years in a well-functioning transplant unless medications are withdrawn or the patient is noncompliant with therapy.
   a. **Hyperacute rejection** is rarely seen today with adequate crossmatching. It results from the presence of preformed antibodies to the transplanted organ and usually results in rapid graft loss.
   b. Most **acute rejection** episodes occur in the first 2 months after transplant. Traditionally, it was manifested by oliguria, fever, and pain over the transplanted kidney. However, CSA often masks these symptoms, and many patients present asymptomatically with a rise in their serum creatinine. On renal biopsy, the cellular infiltrate can be primarily perivascular, interstitial, or both. Most episodes of rejection respond to treatment. However, rejection episodes worsen the overall prognosis of the transplanted organ.
   c. **Chronic rejection** is a common cause for long-term graft loss. Along with acute rejection, it accounts for approximately 60% of all graft loss. Chronic rejection is thought to be an immunologically mediated process, but it does not respond to available antirejection protocols. Pathology reveals thickening of arterial walls and glomerular capillary basement membranes and interstitial fibrosis.
2. **Recurrent disease.** A number of systemic and primary glomerular diseases are known to recur in the renal allograft, but overall these account for less than 5% of graft failures. Recurrent glomerulonephritis, particularly dense deposit disease, anti–glomerular basement membrane disease, focal glomerulosclerosis, and membranous nephropathy can all recur and lead to graft failure. Some evidence suggests that when the initial glomerulonephritis is aggressive and results in rapid renal failure, the likelihood of recurrence in the transplant is increased, especially if the transplant is performed soon after the development of ESRD (5). Metabolic disorders such as diabetes and amyloidosis have a high incidence of recurrence in the transplanted organ but do not account for a significant incidence of graft failure.
3. **Hypertension** is very common after renal transplant. In the pre-CSA era, hypertension occurred in about one-third of all transplant recipients and was thought to result primarily from the presence of native kidneys. With the use of CSA, the prevalence of hypertension has increased to more than 50% of transplant patients. Much of the hypertension is mediated by the direct effect of CSA on salt retention. Aggressive treatment of hypertension in the transplant population seems warranted, because these patients have a solitary kidney and are predisposed to a number of renal insults.

F. **Complications**

1. **Technical complications** are unusual in renal transplantation. The most common is the development of a lymphocele or a urinoma due to either poor lymphatic drainage or a urinary leak, respectively. Acute renal vein thrombosis is unusual if not due to hyperacute rejection and, when it occurs early, it is usually secondary to a technical mishap at the time of surgery. Renal artery stenosis is a cause of worsening renal function or posttransplant hypertension. It is more common in living related transplants because a patch of aorta cannot be removed at the time of donor kidney harvesting.
2. **Drug-induced.** Many of the drugs used to prevent and treat transplant rejection have significant side effects. All of these drugs are immunosuppressive and lead to an increased incidence of infection (see section **IV.F.3**). Glucocorticoids have a number of other side effects, including lipid abnormalities, avascular necrosis of bone, cataracts, and central nervous system changes including psychosis or depression. Mycophenolate mofetil has significant gastrointestinal side effects and when used long term may significantly increase a patient's susceptibility to cancer. Azathioprine suppresses bone marrow and can lead to lymphopenia; some patients develop liver function abnormalities that can progress to cirrhosis. CSA has direct nephrotoxicity and central nervous system toxicity. It also results in hirsutism and tremor. The administration of OKT3 usually produces a febrile response accompanied by malaise and can produce acute pulmonary edema.
3. **Infections** occurring early in the postoperative course are the same as those following any surgical procedure and include urinary tract infections, wound infections, and pulmonary infections with common bacterial organisms. After the first month posttransplant, the incidence of infections due to opportunistic organisms increases. The most common of these include pneumocystis, CMV, and herpes virus infections. Prophylactic treatment with trimethoprim-sulfamethox-azole has decreased the incidence of pneumocystis. Early or prophylactic treatment with ganciclovir (especially during treatment with OKT3) has lessened the severity of CMV infections. Other organisms that cause disease are mycobacterium, legionella, listeria, nocardia, and aspergillus.
4. **Other.** The incidence of malignancy is significantly increased in transplant patients. The most common cancer is skin cancer, which can occur in up to one-fourth of patients in certain geographic areas. The second most common malignancy is lymphoproliferative disease. Many of these are polyclonal, present as a mononucleosis-like illness, and respond to withdrawal of immunosuppression, treatment with antiviral medications, or both. Other primary lymphomas, including isolated central nervous system lymphomas, also occur. These tumors are generally monoclonal and do not respond to the measures mentioned previously. Other cancers, especially colorectal, vaginal/cervical, and pharyngeal/esophageal cancer, occur at increased frequency.

V. Mortality comparison

Despite major advances in renal transplantation and the technology of HD and PD, the diagnosis of ESRD carries an increased mortality compared with age-matched controls. Although much of the increased mortality can be related to the underlying medical conditions that resulted in renal failure, some can be directly attributed to the current practice of dialysis and transplantation. Dialysis in any form provides only a very small percentage of the clearance achieved by the normal kidneys. Only recently have some of the hormones produced by the normal kidney, such as EPO and 1,25(OH)$_2$ vitamin D$_3$ become available. Optimal use of these medications remains to be determined. Immunosuppression for renal transplantation remains nonspecific and predisposes patients to infections and malignancies. The ultimate goal of specific tolerance remains elusive.

A. **HD versus PD.** In the United States, the gross annual mortality among dialysis patients is approximately 20% to 22% (6). This figure is 25% to 50% higher than is reported in much of Europe and Japan and has raised questions about the delivery of dialysis in this country, particularly related to treatment time and dialyzer reuse. However, differences in case mix remains a large confounding variable. The risk of death is higher for diabetic patients and with increasing age. For all age groups, the life expectancy on dialysis is significantly shorter than the general population (Table 11-1). However, most studies comparing survival on HD and on PD have found little difference in overall mortality.

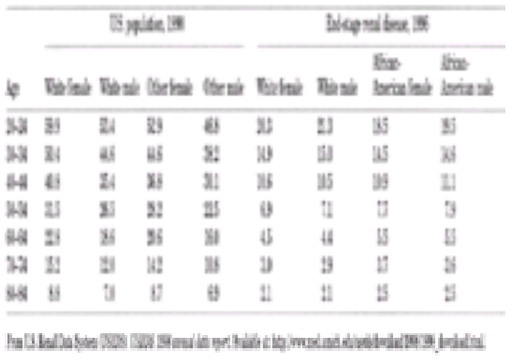

Table 11-1. Expected remaining lifetime in years for all end-stage renal disease patients (1996) compared with U.S. population (1990) by age, race, and sex

B. **Dialysis versus transplantation.** That a successful renal transplant improves an individual's quality of life and rehabilitation potential is not in doubt. For diabetic patients and the young, renal transplantation also significantly increases the average life expectancy of those with ESRD. Identical-twin transplant has the best outcome, followed by HLA-identical sibling transplant. In general, patients receiving other living related transplants have a better long-term survival than cadaveric transplants, although the difference at 2 years is becoming small due to improvements in cadaveric transplants. Because of the improved quality of life and long-term survival, renal transplantation remains the treatment of choice for most patients with ESRD.

VI. Expense comparison. The cost for each patient receiving dialysis in the United States is estimated to be approximately $44,000 per year (6). Most of this cost is paid by the Federal government through the Medicare ESRD program. In 1997, ESRD costs totaled approximately $15.6 billion, of which the Federal government paid approximately 72%. Renal transplantation is estimated to cost approximately $40,000 to $50,000. However, after a successful transplant, the average annual cost of caring for these patients falls to less than $10,000 per year, making transplantation the most cost-effective (means of caring for patients with ESRD.

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Chapter 12 Practical Guidelines for Drug Dosing in Patients with Renal Impairment

George R. Aronoff

A careful history and physical examination
Measurement of renal function
Calculation of the initial dose
Calculation of the maintenance dose
Use of the table
Drug dosing in dialysis patients
Adverse drug reactions
Therapeutic drug monitoring

Uremia influences every organ system and every aspect of drug disposition. The physiologic changes associated with renal disease have pronounced effects on the pharmacology of many drugs. The purpose of this chapter is to provide a rational schema for drug dosing in patients with decreased renal function and for those requiring renal replacement therapy.

Figure 12-1 is an outline of the approach to drug dosing in patients with renal disease. When possible, a specific diagnosis should be established before drug therapy is initiated. The use of fewer drugs and the recognition of potential drug interactions decreases adverse drug effects and the potential for drug interactions.

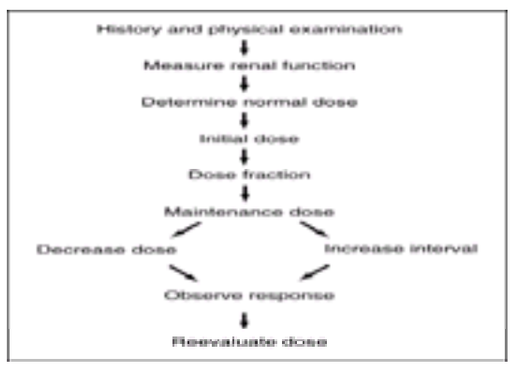

Figure 12-1. A schema for drug dosing in patients with impaired renal function.

I. A careful **history and physical examinatio**n are always the first steps in clinical evaluation of patients with renal disease. Particularly important for this purpose is the history of previous drug allergy or toxicity and the use of concurrent medications or recreational drugs. Physical assessment should include an estimate of the extracellular fluid volume. Edema or ascites increases the distribution volume of many drugs, while dehydration contracts this volume. Measurements of body weight and height are needed to tailor the dosage regimen. For obese patients, a calculated average of the ideal body weight (IBW) and the measured body weight is useful for estimating drug doses. Evidence of impaired function of other excretory organs should be sought. Stigmata of liver disease are clues that the drug dose may need to be altered.

II. Measurement of renal function The rate of elimination of drugs excreted by the kidneys is proportional to the glomerular filtration rate. The serum creatinine (Scr) or creatinine clearance (ClCr) is needed to determine renal function before prescribing any drug. The Cockcroft and Gault equation is useful for this purpose, as shown in the following formula:

$$\text{ClCr (mL/minute)} = \frac{(140 - \text{age}) \times (\text{IBW in kg})}{72 \times \text{Scr (mg/dL)}} \times (0.85 \text{ if female})$$

$$\text{IBW (men)} = 50 \text{ kg} + 2.3 \text{ kg/in. over 5 ft}$$
$$\text{IBW (women)} = 45.5 \text{ kg} + 2.3 \text{ kg/in. over 5 ft}$$

In cases of changing renal function, the Scr no longer reflects the true clearance rate. In these cases, a timed urine collection is needed to estimate renal function. The midpoint Scr is useful to calculate the ClCr for the collection period. If the patient is oliguric (less than 500 mL of urine per 24 hours), the ClCr is less than 5 mL per minute.

The Scr reflects muscle mass as well as glomerular filtration rate. Scr measurements within the “normal” range are frequently used to establish “normal” renal function. This erroneous assumption may cause serious overdose and resultant toxic drug accumulation in elderly or debilitated patients with decreased muscle mass.

III. Calculation of the initial dose The purpose of the initial dose is to achieve therapeutic drug concentrations rapidly. A loading dose should be considered when the half-life of a drug is particularly long in patients with impaired renal function and the clinical situation requires rapidly achieved therapeutic levels. When the physical examination suggests that the extracellular fluid volume is normal, the loading dose of a drug given to a patient with renal insufficiency is the same as the initial dose given to a patient with normal renal function. Initial doses for most drugs requiring loading are already known. However, the loading dose may be calculated using the following formula:

$$\text{Loading dose} = \text{Vd (L/kg)} \times \text{IBW (kg)} \times \text{Cp (mg/L)}$$

where *Vd* = volume of distribution of the drug and *Cp* = desired plasma drug level.

If the patient has edema or ascites, a larger loading dose may be required. Conversely, dehydrated or debilitated patients should receive smaller initial drug doses.

IV. Calculation of the maintenance dose Several methods can be used to decide subsequent doses. The following relationship is useful for calculating the fraction of the normal dose recommended for a patient with renal insufficiency:

$$\text{Dose fraction} = F\,[(\text{ClCr}/120) - 1)] + 1$$

where *F* = fraction of the drug excreted unchanged in the urine.

When F is not known, the ratio of the drug's half-life in patients with normal renal function to that measured in patients with renal failure may be substituted, as below:

$$\text{Dose fraction} = \frac{T_{1/2}\text{ normal}\,[(\text{ClCr}/120) - 1] + 1}{T_{1/2}\text{ renal failure}}$$

where $T_{1/2}$ = half-life of drug.

Table 12-1 lists commonly used drugs that require substantial dose alteration when used in patients with renal failure and suggestions for dose adjustment and for

dialysis.

V. Use of the table. Prolonging the dose interval is often a convenient and cost-effective method of altering the drug dose in patients with renal impairment. This method is particularly useful for drugs with wide therapeutic ranges and long plasma half-lives. Extended parenteral therapy can be completed without prolonged hospitalization when the dose interval can safely be lengthened to allow for home therapy. If the range between the therapeutic and toxic levels is too narrow, either potentially toxic or subtherapeutic plasma concentrations may result.

To maintain the same dose interval as holds for patients with normal renal function, decrease the amount of each individual dose administered to patients with renal impairment can be decreased. This method is effective for drugs with narrow therapeutic ranges and short plasma half-lives used in patients with renal insufficiency.

In practice, a combination of methods, involving modification of both the dose and dose interval, is often effective and convenient. For drugs with particularly long half-lives, in patients with impaired renal function, the total daily dose should be given as a single dose each day with an extended interval between days.

The decision to extend the dosing interval beyond a 24-hour period should be based on the necessity to maintain therapeutic peak or trough drug levels. When the peak level is most important, the dose interval should be prolonged. However, when the minimum trough level must be maintained, modification of the individual dose or a combination of the dose and interval methods may be preferred.

VI. Drug dosing in dialysis patients Drug removal by hemodialysis is most effective for drugs that weigh less than 500 d, are less than 90% protein bound and have small volumes of distribution. For many drugs, the dosage schedule should be altered so that the dose can be given at the end of the hemodialysis treatment, thus eliminating the need for a reloading dose. For example, aminoglycosides can be given to chronic hemodialysis patients as a postdialysis dose.

VII. Adverse drug reactions occur more frequently in patients with impaired renal function. Untoward effects may be the result of direct toxicity or additive effects of the drug or its metabolites. The lack of efficacy of the drug in patients with compromised renal function, or increased drug-induced metabolic load also causes adverse drug effects. The acute onset of any unexplained symptoms should alert clinicians to a possible adverse drug effect.

VIII. Therapeutic drug monitoring Measurement of plasma drug concentrations may be helpful in assessing a particular drug dosing regimen when efficacy or toxicity corresponds to drug levels. These measurements are most important for drugs with a narrow therapeutic range or for drugs whose pharmacologic effects are not easily measured.

Table 12-1. Drug dosing recommendations for patients with renal failure who are on hemodialysis (HD), chronic ambulatory peritoneal dialysis (CAPD), and chronic renal replacement therapy (CRRT)

A B C D E F G H I J K L M N O P Q R S T U V W X Y Z

Drug	Method	Renal failure dose	Dose after HD	Dose during CAPD	Dose during CRRT
Acarbose	D	Avoid	Unknown	Unknown	Avoid
Acebutolol	D	30–50%	None	None	50%
Acetazolamide	I	Avoid	Unknown	Unknown	Avoid
Acetohexamide	I	Avoid	Unknown	None	Avoid
Acetohydroxamic acid	D	Avoid	Unknown	Unknown	Unknown
Acetaminophen	I	q8h	None	None	q6h
Acetylsalicylic acid (aspirin)	I	Avoid	Dose after dialysis	None	q4–6h
Acrivastine	D	Unknown	Unknown	Unknown	Unknown
Acyclovir	D, I	2.5 mg/kg q24h	Dose after dialysis	Dose for renal failure	3.5 mg/kg/d
Adenosine	D	100%	None	None	100%
Albuterol	D	50%	Unknown	Unknown	75%
Alcuronium	D	Avoid	Unknown	Unknown	Avoid
Alfentanil	D	100%	Unknown	Unknown	100%
Allopurinol	D	25%	One-half dose	Unknown	50%
Alprazolam	D	100%	None	Unknown	NA
Alteplase (tissue plasminogen activator)	D	100%	Unknown	Unknown	100%
Altretamine	D	Unknown	Unknown	Unknown	Unknown
Amantadine	I	q7d	None	None	q48–72h
Amikacin	D, I	20–30% q24–48h	Two-thirds normal dose after dialysis	15–20 mg/L/d	30–70% q12–18h
Amiloride	D	Avoid	NA	NA	NA
Amiodarone	D	100%	None	None	100%
Amitriptyline	D	100%	None	Unknown	NA
Amlodipine	D	100%	None	None	100%
Amoxapine	D	100%	Unknown	Unknown	NA
Amoxicillin	I	q24h	Dose after dialysis	250 mg q12h	NA
Amphotericin	I	q24–36h	None	Dose for renal failure	q24h
Amphotericin B colloidal dispersion	I	q24–36h	None	Dose for renal failure	q24h
Amphotericin B lipid complex	I	q24–36h	None	Dose for renal failure	q24h
Ampicillin	I	q12–24h	Dose after dialysis	250 mg q12h	q6–12h
Amrinone	D	50–75%	Unknown	Unknown	100%
Anistreplase	D	100%	Unknown	Unknown	100%
Astemizole	D	100%	Unknown	Unknown	NA
Atenolol	D, I	30–50% q96h	25–50 mg	None	50% q48h
Atovaquone	—	100%	None	Unknown	Unknown
Atracurium	D	100%	Unknown	Unknown	100%
Auranofin	D	Avoid	None	None	None
Azathioprine	D	50%	Yes	Unknown	75%
Azithromycin	D	100%	None	None	None
Azlocillin	I	q8h	Dose after dialysis	Dose for renal failure	q6–8h
Aztreonam	D	25%	0.5 g after dialysis	Dose for renal failure	50–75%
Drug	**Method**	**Renal failure dose**	**Dose after HD**	**Dose during CAPD**	**Dose during CRRT**
Benazepril	D	25–50%	None	None	50–75%
Bepridil	—	Unknown	None	None	Unknown
Betamethasone	D	100%	Unknown	Unknown	100%
Betaxolol	D	50%	None	None	100%
Bezafibrate	D	25%	Unknown	Unknown	50%
Bisoprolol	D	50%	Unknown	Unknown	75%
Bleomycin	D	50%	None	Unknown	75%

Bleomycin	D	50%	None	Unknown	Unknown
Bopindolol	D	100%	None	None	100%
Bretylium	D	25%	None	None	25–50%
Bromocriptine	D	100%	Unknown	Unknown	Unknown
Brompheniramine	D	100%	Unknown	Unknown	NA
Budesonide	D	100%	Unknown	Unknown	100%
Bumetanide	D	100%	None	None	NA
Bupropion	D	100%	Unknown	Unknown	NA
Buspirone	D	100%	None	Unknown	NA
Busulfan	D	100%	Unknown	Unknown	100%
Butorphanol	D	50%	Unknown	Unknown	NA

Drug	Method	Renal failure dose	Dose after HD	Dose during CAPD	Dose during CRRT
Capreomycin	I	q48h	Give dose after HD only	None	q24h
Captopril	D, I	50% q24h	25–30%	None	75% q12–18h
Carbamazepine	D	100%	None	None	None
Carbidopa	D	100%	Unknown	Unknown	Unknown
Carboplatin	D	25%	50%	Unknown	50%
Carmustine	D	Unknown	Unknown	Unknown	Unknown
Carteolol	D	25%	Unknown	None	50%
Carvedilol	D	100%	None	None	100%
Cefaclor	D	50%	250 mg after dialysis	250 mg q8–12h	NA
Cefadroxil	I	q24–48h	0.5–1.0 g after dialysis	0.5 g/d	NA
Cefamandole	I	q12h	0.5–1.0 g after dialysis	0.5–1.0 g q12h	q6–8h
Cefazolin	I	q24–48h	0.5–1.0 g after dialysis	0.5 g q12h	q12h
Cefepime	I	q24–48h	1 g after dialysis	Dose for renal failure	Not recommended
Cefixime	D	50%	300 mg after dialysis	200 mg/d	Not recommended
Cefmenoxine	D, I	0.75 g q12h	0.75 g after dialysis	0.75 g q12h	0.75 g q8h
Cefmetazole	I	q48h	Dose after dialysis	Dose for renal failure	q24h
Cefonicid	D, I	0.1 g/d	None	None	None
Cefoperazone	D	100%	1 g after dialysis	None	None
Ceforanide	I	q24–48h	0.5–1.0 g after dialysis	None	1 g/d
Cefotaxime	I	q24h	1 g after dialysis	1 g/d	1 g q12h
Cefotetan	D	25%	1 g after dialysis	1 g/d	750 mg q12h
Cefoxitin	I	q24–48h	1 g after dialysis	1 g/d	q8–12h
Cefpodoxime	I	q24–48h	200 mg after dialysis only	Dose for renal failure	NA
Cefprozil	D, I	250 mg q24h	250 mg after dialysis	Dose for renal failure	Dose for renal failure
Ceftazidime	I	q48h	1 g after dialysis	0.5 g/d	q24–48h
Ceftibuten	D	25%	300 mg after dialysis only	Dose for renal failure	50%
Ceftizoxime	I	q24h	1 g after dialysis	0.5–1.0 g/d	q12–24h
Ceftriaxone	D	100%	Dose after dialysis	750 mg q12h	100%
Cefuroxime axetil	D	100%	Dose after dialysis	Dose for renal failure	NA
Cefuroxime sodium	I	q12h	Dose after dialysis	Dose for renal failure	1 g q12h
Celiprolol	D	75%	Unknown	None	100%
Cephalexin	I	q12h	Dose after dialysis	Dose for renal failure	NA
Cephalothin	I	q12h	Dose after dialysis	1 g q12h	1 g q8h
Cephapirin	I	q12h	Dose after dialysis	1 g q12h	1 g q8h
Cephradine	D	25%	Dose after dialysis	Dose for renal failure	NA
Cetirizine	D	30%	None	Unknown	NA
Chloral hydrate	D	Avoid	None	Unknown	NA
Chlorambucil	D	Unknown	Unknown	Unknown	Unknown
Chloramphenicol	D	100%	None	None	None
Chlorazepate	D	100%	Unknown	Unknown	NA
Chlordiazepoxide	D	50%	None	Unknown	100%
Chloroquine	D	50%	None	None	None
Chlorpheniramine	D	100%	None	Unknown	NA
Chlorpromazine	D	100%	None	None	100%
Chlorpropamide	D	Avoid	Unknown	None	Avoid
Chlorthalidone	I	Avoid	NA	NA	NA
Cholestyramine	D	100%	None	None	100%
Cibenzoline	D, I	66% q24h	None	None	100% q12h
Cidofovir	D	Avoid	Unknown	Unknown	Unknown, avoid
Cilastin	D	Avoid	Avoid	Avoid	Avoid
Cilazapril	D, I	10–25% q72h	None	None	50% q24–48h
Cimetidine	D	25%	None	None	50%
Cinoxacin	D	Avoid	Avoid	Avoid	Avoid
Ciprofloxacin	D	50%	250 mg q12h (200 mg if i.v.)	250 mg q8h (200 mg if i.v.)	200 mg i.v. q12h
Cisapride	D	50%	Unknown	Unknown	50–100%
Cisplatin	D	50%	Yes	Unknown	75%
Cladribine	D	Unknown	Unknown	Unknown	Unknown
Clarithromycin	D	50–75%	Dose after dialysis	None	None
Clavulanic acid	D	50–75%	Dose after dialysis	Dose for renal failure	100%
Clindamycin	D	100%	None	None	None
Clodronate	D	Avoid	Unknown	Unknown	Unknown
Clofazimine	—	100%	None	None	Unknown
Clofibrate	I	Avoid	None	Unknown	q12–18h
Clomipramine	D	Unknown	Unknown	Unknown	NA
Clonazepam	D	100%	None	Unknown	NA
Clonidine	D	100%	None	None	100%
Codeine	D	50%	Unknown	Unknown	75%
Colchicine	D	50%	None	Unknown	100%

Colestipol	D	100%	None	None	100%
Cortisone	D	100%	None	Unknown	100%
Cyclophosphamide	D	75%	One-half dose	Unknown	100%
Cycloserine	I	q24h	None	None	q12–24h
Cyclosporine	D	100%	None	None	100%
Cytarabine	D	100%	Unknown	Unknown	100%

Drug	Method	Renal failure dose	Dose after HD	Dose during CAPD	Dose during CRRT
Dapsone	—	Unknown	None	Dose for renal failure	Unknown
Daunorubicin	D	100%	Unknown	Unknown	Unknown
Delavirdine	—	100%	None	Unknown	Unknown
Desferrioxamine	D	100%	Unknown	Unknown	100%
Desipramine	D	100%	None	None	NA
Dexamethasone	D	100%	Unknown	Unknown	100%
Diazepam	D	100%	None	Unknown	100%
Diazoxide	D	100%	None	None	100%
Diclofenac	D	100%	None	None	100%
Dicloxacillin	D	100%	None	None	NA
Didanosine	I	q24–48h	Dose after dialysis	Dose for renal failure	Dose for renal failure
Diflunisal	D	50%	None	None	50%
Digitoxin	D	50–75%	None	None	100%
Digoxin	D, I	10–25% q48h	None	None	25–75% q36h
Dilevalol	D	100%	None	None	Unknown
Diltiazem	D	100%	None	None	100%
Diphenhydramine	D	100%	None	None	None
Dipyridamole	D	100%	Unknown	Unknown	NA
Dirithromycin	—	100%	None	Unknown	100%
Disopyramide	I	q24–40h	None	None	q12–24h
Dobutamine	D	100%	Unknown	Unknown	100%
Doxacurium	D	50%	Unknown	Unknown	50%
Doxazosin	D	100%	None	None	100%
Doxepin	D	100%	None	None	100%
Doxorubicin	D	100%	None	Unknown	100%
Doxycycline	D	100%	None	None	100%
Dyphylline	D	25%	One-third dose	Unknown	50%

Drug	Method	Renal failure dose	Dose after HD	Dose during CAPD	Dose during CRRT
Enalapril	D	50%	20–25%	None	75–100%
Epirubicin	D	100%	None	Unknown	100%
Ebastine	D	50%	Unknown	Unknown	50%
Erythromycin	D	50–75%	None	None	None
Esmolol	—	—	None	None	Unknown
Estazolam	D	100%	Unknown	Unknown	NA
Ethacrynic acid	I	Avoid	None	None	NA
Ethambutol	I	q48h	Dose after dialysis	Dose for renal failure	q24–36h
Ethchlorvynol	D	Avoid	None	None	NA
Ethionamide	D	50%	None	None	None
Ethosuximide	D	100%	None	Unknown	Unknown
Etodolac	D	100%	None	None	100%
Etomidate	D	100%	Unknown	Unknown	100%
Etoposide	D	50%	None	Unknown	75%

Drug	Method	Renal failure dose	Dose after HD	Dose during CAPD	Dose during CRRT
Famciclovir	I	50% q48h	Dose after dialysis	Unknown	Unknown
Famotidine	D	10%	None	None	25%
Fazadinium	D	100%	Unknown	Unknown	100%
Felodipine	D	100%	None	None	100%
Fenoprofen	D	100%	None	None	100%
Fentanyl	D	100%	Unknown	Unknown	100%
Fexofenadine	I	q24h	Unknown	Unknown	q12–24h
Flecainide	D	50–75%	None	None	100%
Fleroxacin	D	50%	400 mg after dialysis	400 mg/d	NA
Fluconazole	D	100%	200 mg after dialysis	Dose for renal failure	100%
Flucytosine	I	q24h	Dose after dialysis	0.5–1.0 g/d	q16h
Fludarabine	D	50%	Unknown	Unknown	75%
Flumazenil	D	100%	None	Unknown	NA
Flunarizine	D	100%	None	None	None
Fluorouracil	D	100%	Yes	Unknown	100%
Fluoxetine	D	100%	Unknown	Unknown	NA
Flurazepam	D	100%	None	Unknown	NA
Flurbiprofen	D	100%	None	None	100%
Flutamide	D	100%	Unknown	Unknown	Unknown
Fluvastatin	D	100%	Unknown	Unknown	100%
Fluvoxamine	D	100%	None	Unknown	NA
Foscarnet	D	6 mg/kg	Dose after dialysis	Dose for renal failure	15 mg/kg
Fosinopril	D	75–100%	None	None	100%
Furosemide	D	100%	None	None	NA

Drug	Method	Renal failure dose	Dose after HD	Dose during CAPD	Dose during CRRT
Gabapentin	D, I	300 mg q.d.	300-mg load, then 200–300 mg	—	300 mg q12–24h
Gallamine	D	Avoid	NA	NA	Avoid
Ganciclovir	I	q48–96h	Dose after dialysis	Dose for renal failure	2.5 mg/kg/d
Ganciclovir—oral	D, I	500 mg q48–96h	Dose after dialysis	Dose for renal failure	NA

Drug	Method	Renal failure dose	Dose after HD	Dose during CAPD	Dose during CRRT
Gemfibrozil	D	100%	None	Unknown	100%
Gentamicin	D, I	20–30% q24–48h	Two-thirds normal dose after dialysis	3–4 mg/L/d	30–70% q12h
Glibornuride	D	Unknown	Unknown	Unknown	Avoid
Gliclazide	D	Unknown	Unknown	Unknown	Avoid
Glipizide	D	100%	Unknown	Unknown	Avoid
Glyburide	D	Avoid	None	None	Avoid
Gold sodium thiomalate	D	Avoid	None	None	Avoid
Griseofulvin	D	100%	None	None	None
Guanabenz	D	100%	Unknown	Unknown	100%
Guanadrel	I	q24–48h	Unknown	Unknown	q12–24h
Guanethidine	I	q24–36h	Unknown	Unknown	Avoid
Guanfacine	D	100%	None	None	100%
Haloperidol	D	100%	None	None	100%
Heparin	D	100%	None	None	100%
Hexobarbital	D	100%	None	Unknown	NA
Hydralazine	I	q8–16h	None	None	q8h
Hydrocortisone	D	100%	Unknown	Unknown	100%
Hydroxyurea	D	20%	Unknown	Unknown	50%
Hydroxyzine	D	Unknown	100%	100%	100%
Ibuprofen	D	100%	None	None	100%
Idarubicin	—	Unknown	Unknown	Unknown	Unknown
Ifosfamide	D	75%	Unknown	Unknown	100%
Iloprost	D	50%	Unknown	Unknown	100%
Imipenem	D	25%	Dose after dialysis	Dose for renal failure	50%
Imipramine	D	100%	None	None	NA
Indapamide	D	Avoid	None	None	NA
Indinavir		100%	None	Dose for renal failure	Unknown
Indobufen	D	25%	Unknown	Unknown	NA
Indomethacin	D	100%	None	None	100%
Insulin	D	50%	None	None	75%
Ipratropium	D	100%	None	None	100%
Isoniazid	D	50%	Dose after dialysis	Dose for renal failure	Dose for renal failure
Isosorbide	D	100%	10–20 mg	None	100%
Isradipine	D	100%	None	None	100%
Itraconazole	D	50%	100 mg q12–24h	100 mg q12–24h	100 mg q12–24h
Kanamycin	D, I	20–30% q24–48h	Two-thirds normal dose after dialysis	15–20 mg/L/d	30–70% q12h
Ketamine	D	100%	Unknown	Unknown	100%
Ketanserin	D	100%	None	None	100%
Ketoconazole	D	100%	None	None	None
Ketoprofen	D	100%	None	None	100%
Ketorolac	D	50%	None	None	50%
Labetalol	D	100%	None	None	100%
Lamivudine	D, I	25 mg q.d. (50 mg first dose)	Dose after dialysis	Dose for renal failure	50–150 mg q.d. (full first dose)
Lamotrigine	D	100%	Unknown	Unknown	100%
Lansoprazole	D	100%	Unknown	Unknown	Unknown
L-dopa	D	100%	Unknown	Unknown	100%
Levofloxacin	D	25–50%	Dose for renal failure	Dose for renal failure	50%
Lidocaine	D	100%	None	None	100%
Lincomycin	I	q12–24h	None	None	NA
Lisinopril	D	25–50%	20%	None	50–75%
Lispro insulin	D	50%	None	None	None
Lithium carbonate	D	25–50%	Dose after dialysis	None	50–75%
Lomefloxacin	D	50%	Dose for renal failure	Dose for renal failure	NA
Loracarbef	I	q3–5d	Dose after dialysis	Dose for renal failure	q24h
Lorazepam	D	100%	None	Unknown	100%
Losartan	D	100%	Unknown	Unknown	100%
Lovastatin	D	100%	Unknown	Unknown	100%
Low-molecular-weight heparin	D	50%	Unknown	Unknown	100%
Maprotiline	D	100%	Unknown	Unknown	NA
Meclofenamic acid	D	100%	None	None	100%
Mefenamic acid	D	100%	None	None	100%
Mefloquine	—	100%	None	None	Unknown
Melphalan	D	50%	Unknown	Unknown	75%
Meperidine	D	50%	Avoid	None	Avoid
Meprobamate	I	q12–18h	None	Unknown	NA
Meropenem	D, I	250–500 mg q24h	Dose after dialysis	Dose for renal failure	250–500 mg q12h
Metaproterenol	D	100%	Unknown	Unknown	100%
Metformin	D	Avoid	Unknown	Unknown	Avoid
Methadone	D	50–75%	None	None	NA
Methenamine mandelate	D	Avoid	NA	NA	NA

Methicillin	I	q8–12h	None	None	q6–8h
Methimazole	D	100%	Unknown	Unknown	100%
Methotrexate	D	Avoid	None	None	50%
Methyldopa	I	q12–24h	250 mg	None	q8–12h
Methyl prednisolone	D	100%	Yes	Unknown	100%
Metoclopramide	D	50%	None	Unknown	50–75%
Metocurine	D	50%	Unknown	Unknown	50%
Metolazone	D	100%	None	None	NA
Metoprolol	D	100%	50 mg	None	100%
Metronidazole	D	50%	Dose after dialysis	Dose for renal failure	100%
Mexiletine	D	50–75%	None	None	None
Mezlocillin	I	q8h	None	None	q6–8h
Miconazole	D	100%	None	None	None
Midazolam	D	50%	NA	NA	NA
Midodrine	—	Unknown	5 mg q8h	Unknown	5–10 mg q8h
Miglitol	D	Avoid	Unknown	Unknown	Avoid
Milrinone	D	50–75%	Unknown	Unknown	100%
Minocycline	D	100%	None	None	100%
Minoxidil	D	100%	None	None	100%
Mitomycin C	D	75%	Unknown	Unknown	Unknown
Mitoxantrone	D	100%	Unknown	Unknown	100%
Mivacurium	D	50%	Unknown	Unknown	Unknown
Moricizine	D	100%	None	None	100%
Morphine	D	50%	None	Unknown	75%
Moxalactam	I	q24–48h	Dose after dialysis	Dose for renal failure	q12–24h

Drug	Method	Renal failure dose	Dose after HD	Dose during CAPD	Dose during CRRT
Nabumetone	D	100%	None	None	100%
N-Acetylcysteine	D	75%	Unknown	Unknown	100%
N-Acetyl-procainamide	D, I	25% q12–18h	None	None	50% q8–12h
Nadolol	D	25%	40 mg	None	50%
Nafcillin	D	100%	None	None	100%
Nalidixic acid	D	Avoid	Avoid	Avoid	NA
Naloxone	D	100%	NA	NA	100%
Naproxen	D	100%	None	None	100%
Nefazodone	D	100%	Unknown	Unknown	NA
Nelfinavir	—	Unknown	Unknown	Unknown	Unknown
Neostigmine	D	25%	Unknown	Unknown	50%
Netilmicin	D, I	10–20% q24–48h	Two-thirds normal dose after dialysis	3–4 mg/L/d	20–60% q12h
Nevirapine	D	100%	None	Dose for renal failure	Unknown
Nicardipine	D	100%	None	None	100%
Nicotinic acid	D	25%	Unknown	Unknown	50%
Nifedipine	D	100%	None	None	100%
Nimodipine	D	100%	None	None	100%
Nisoldipine	D	100%	None	None	100%
Nitrazepam	D	100%	Unknown	Unknown	NA
Nitrofurantoin	D	Avoid	NA	NA	NA
Nitroglycerine	D	100%	Unknown	Unknown	100%
Nitroprusside	D	100%	None	None	100%
Nitrosourea	D	25–50%	None	Unknown	Unknown
Nizatidine	D	25%	Unknown	Unknown	50%
Norfloxacin	I	Avoid	NA	NA	NA
Nortriptyline	D	100%	None	None	NA

Drug	Method	Renal failure dose	Dose after HD	Dose during CAPD	Dose during CRRT
Ofloxacin	D	25–50%	100 mg b.i.d.	Dose for renal failure	300 mg/d
Omeprazole	D	100%	Unknown	Unknown	Unknown
Ondansetron	D	100%	Unknown	Unknown	100%
Orphenadrine	D	100%	Unknown	Unknown	NA
Ouabain	I	q36–48h	None	None	q24–36h
Oxaprozin	D	100%	None	None	100%
Oxatomide	D	100%	None	None	NA
Oxazepam	D	100%	None	Unknown	100%
Oxcarbazepine	D	100%	Unknown	Unknown	Unknown

Drug	Method	Renal failure dose	Dose after HD	Dose during CAPD	Dose during CRRT
Paclitaxel	D	100%	Unknown	Unknown	100%
Pancuronium	D	Avoid	Unknown	Unknown	50%
Paroxetine	D	50%	Unknown	Unknown	NA
Para-amino-salicylate	D	50%	Dose after dialysis	Dose for renal failure	Dose for renal failure
Penbutolol	D	100%	None	None	100%
Penicillamine	D	Avoid	One-third dose	Unknown	Avoid
Penicillin G	D	20–50%	Dose after dialysis	Dose for renal failure	75%
Penicillin VK	D	100%	Dose after dialysis	Dose for renal failure	NA
Pentamidine	I	q48h	None	None	None
Pentazocine	D	50%	None	Unknown	75%
Pentobarbital	D	100%	None	Unknown	100%
Pentopril	D	50%	Unknown	Unknown	50–75%
Pentoxifylline	D	100%	Unknown	Unknown	100%
Pefloxacin	D	100%	None	None	100%
Perindopril	D	50%	25–50%	Unknown	75%
Phenelzine	D	100%	Unknown	Unknown	NA

Phenobarbital	I	q12–16h	Dose after dialysis	One-half normal dose	q8–12h
Phenylbutazone	D	100%	None	None	100%
Phenytoin	D	100%	None	None	None
Pindolol	D	100%	None	None	100%
Pipecuronium	D	25%	Unknown	Unknown	50%
Piperacillin	I	q8h	Dose after dialysis	Dose for renal failure	q6–8h
Piretanide	D	100%	None	None	NA
Piroxicam	D	100%	None	None	100%
Plicamycin	D	50%	Unknown	Unknown	Unknown
Pravastatin	D	100%	Unknown	Unknown	100%
Prazepam	D	100%	Unknown	Unknown	NA
Prazosin	D	100%	None	None	100%
Prednisolone	D	100%	Yes	Unknown	100%
Prednisone	D	100%	None	Unknown	100%
Primaquine	—	100%	Unknown	Unknown	Unknown
Primidone	I	q12–24h	1/3 dose	Unknown	Unknown
Probenecid	D	Avoid	Avoid	Unknown	Avoid
Probucol	D	100%	Unknown	Unknown	100%
Procainamide	I	q8–24h	200 mg	None	q6–12h
Promethazine	D	100%	None	None	100%
Propafenone	D	100%	None	None	100%
Propofol	D	100%	Unknown	Unknown	100%
Propoxyphene	D	Avoid	None	None	NA
Propranolol	D	100%	None	None	100%
Propylthiouracil	D	100%	Unknown	Unknown	100%
Protriptyline	D	100%	None	None	NA
Pyrazinamide	D	Avoid	Avoid	Avoid	Avoid
Pyridostigmine	D	20%	Unknown	Unknown	35%
Pyrimethamine	D	100%	None	None	None

Drug	Method	Renal failure dose	Dose after HD	Dose during CAPD	Dose during CRRT
Quazepam	D	Unknown	Unknown	Unknown	NA
Quinapril	D	75%	25%	None	75–100%
Quinidine	D	75%	100–200 mg	None	100%
Quinine	I	q24h	Dose after dialysis	Dose for renal failure	q8–12h

Drug	Method	Renal failure dose	Dose after HD	Dose during CAPD	Dose during CRRT
Ramipril	D	25–50%	20%	None	50–75%
Ranitidine	D	25%	One-half dose	None	50%
Reserpine	D	Avoid	None	None	100%
Ribavirin	D	50%	Dose after dialysis	Dose for renal failure	Dose for renal failure
Rifabutin	—	100%	None	None	Unknown
Rifampin	D	50–100%	None	Dose for renal failure	Dose for renal failure
Ritonavir	—	100%	None	Dose for renal failure	Unknown

Drug	Method	Renal failure dose	Dose after HD	Dose during CAPD	Dose during CRRT
Saquinavir	—	100%	None	Dose for renal failure	Unknown
Secobarbital	D	100%	None	None	NA
Sertraline	D	100%	Unknown	Unknown	NA
Simvastatin	D	100%	Unknown	Unknown	100%
Sodium valproate	D	100%	None	None	None
Sotalol	D	15–30%	80 mg	None	30%
Sparfloxacin	D, I	50% q48h	Dose for glomerular filtration rate <10	Unknown	50–75%
Spectinomycin	D	100%	None	None	None
Spironolactone	I	Avoid	NA	NA	Avoid
Stavudine	D, I	50% q24h	Dose after dialysis	Unknown	Unknown
Streptokinase	D	100%	NA	NA	100%
Streptomycin	I	q72–96h	One-half normal dose after dialysis	20–40 mg/L/d	q24–72h
Streptozotocin	D	50%	Unknown	Unknown	Unknown
Succinylcholine	D	100%	Unknown	Unknown	100%
Sufentanil	D	100%	Unknown	Unknown	100%
Sulbactam	I	q24–48h	Dose after dialysis	0.75–1.5 g/d	750 mg q12h
Sulfamethoxazole	I	q24h	1 g after dialysis	1 g/d	q18h
Sulfinpyrazone	D	Avoid	None	None	100%
Sulfisoxazole	I	q12–24h	2 g after dialysis	3 g/d	NA
Sulindac	D	100%	None	None	100%
Sulotroban	D	10%	Unknown	Unknown	Unknown

Drug	Method	Renal failure dose	Dose after HD	Dose during CAPD	Dose during CRRT
Tamoxifen	D	100%	Unknown	Unknown	100%
Tazobactam	D	50%	One-third dose after dialysis	Dose for renal failure	75%
Teicoplanin	I	q72h	Dose for renal failure	Dose for renal failure	q48h
Temazepam	D	100%	None	None	NA
Teniposide	D	100%	None	None	100%
Terazosin	D	100%	Unknown	Unknown	100%
Terbutaline	D	Avoid	Unknown	Unknown	50%
Terfenadine	D	100%	None	None	NA
Tetracycline	I	q24h	None	None	q12–24h
Theophylline	D	100%	One-half dose	Unknown	100%
Thiazides	D	Avoid	NA	NA	NA
Thiopental	D	75%	NA	NA	NA
Ticarcillin	D, I	1–2 g q12h	3 g after dialysis	Dose for renal failure	1–2 g q8h

Ticlopidine	D	100%	Unknown	Unknown	100%
Timolol	D	100%	None	None	100%
Tobramycin	D, I	20–30% q24–48h	Two-thirds normal dose after dialysis	3–4 mg/L/d	30–70% q12h
Tocainide	D	50%	200 mg	None	100%
Tolazamide	D	100%	Unknown	Unknown	Avoid
Tolbutamide	D	100%	None	None	Avoid
Tolmetin	D	100%	None	None	100%
Topiramate	D	25%	Unknown	Unknown	50%
Topotecan	D	25%	Unknown	Unknown	50%
Torsemide	D	100%	None	None	NA
Tranexamic acid	D	10%	Unknown	Unknown	Unknown
Tranylcypromine	D	Unknown	Unknown	Unknown	NA
Trazodone	D	Unknown	Unknown	Unknown	NA
Triamcinolone	D	100%	Unknown	Unknown	Unknown
Triamterene	I	Avoid	NA	NA	Avoid
Triazolam	D	100%	None	None	NA
Trihexyphenidyl	D	Unknown	Unknown	Unknown	Unknown
Trimethadione	I	q12–24h	Unknown	Unknown	q8–12h
Trimethoprim	I	q24h	Dose after dialysis	q24h	q18h
Trimetrexate	D	Avoid	Unknown	Unknown	Unknown
Trimipramine	D	100%	None	None	NA
Tripelennamine	D	Unknown	Unknown	Unknown	NA
Triprolidine	D	Unknown	Unknown	Unknown	NA
Tubocurarine	D	Avoid	Unknown	Unknown	50%

Drug	Method	Renal failure dose	Dose after HD	Dose during CAPD	Dose during CRRT
Urokinase	D	Unknown	Unknown	Unknown	Unknown

Drug	Method	Renal failure dose	Dose after HD	Dose during CAPD	Dose during CRRT
Valacyclovir	D, I	0.5 g q24h	Dose after dialysis	Dose for renal failure	Unknown
Vancomycin	D, I	500 mg q48–96h	Dose for renal failure	Dose for renal failure	500 mg q24–48h
Vecuronium	D	100%	Unknown	Unknown	100%
Venlafaxine	D	50%	None	Unknown	NA
Verapamil	D	100%	None	None	100%
Vidarabine	D	75%	Infuse after dialysis	Dose for renal failure	100%
Vigabatrin	D	25%	Unknown	Unknown	50%
Vinblastine	D	100%	Unknown	Unknown	100%
Vincristine	D	100%	Unknown	Unknown	100%
Vinorelbine	D	100%	Unknown	Unknown	100%

Drug	Method	Renal failure dose	Dose after HD	Dose during CAPD	Dose during CRRT
Warfarin	D	100%	None	None	None

Drug	Method	Renal failure dose	Dose after HD	Dose during CAPD	Dose during CRRT
Zafirlukast	D	100%	Unknown	Unknown	100%
Zalcitabine	I	q24h	Unknown	Unknown	Unknown
Zidovudine	D, I	100 mg q8h	Dose for renal failure	Dose for renal failure	100 mg q8h

D, decrease dose; I, prolong interval; NA, not avail-

Serum levels should be measured after administration of an appropriate loading dose. If no loading dose is administered, three or four doses of the drug should be given before serum levels are measured, to ensure that steady-state serum concentrations have been established. For some drugs, maximum and minimum concentrations are both relevant. Peak levels are most meaningful when measured after rapid drug distribution has occurred. For example, aminoglycoside peak concentrations should be measured 30 minutes after the end of the infusion; minimum concentrations are usually measured just before administration of the next scheduled dose. Appropriate pharmacokinetic application of drug level measurements can improve patient care and decrease cost.

Patients with renal disease are heterogeneous, and their responses to drug therapy are variable. Dosage nomograms, drug tables, and computer-assisted dosing recommendations should not be taken as a fixed approach to therapy in patients with decreased renal function. They are initial attempts to arrive at an effective dose regimen. Physicians using sound clinical judgment in caring for patients with renal disease evaluate each situation, choose a drug regimen based on all factors, and continually reevaluate the response to therapy.

Suggested Reading

Aronoff GR, Berns JS, Brier ME, et al. *Drug prescribing in renal failure: dosing guidelines for adults*. Philadelphia: American College of Physicians, 1999.

Chapter 13 The Patient with Kidney Disease and Hypertension in Pregnancy

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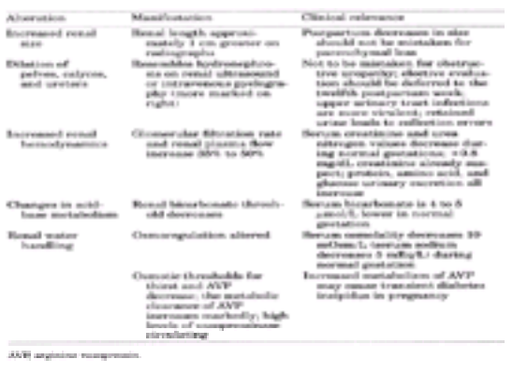
The kidney and blood pressure in normal pregnancy
Clinical evaluation of renal function in pregnancy
Renal disease in pregnancy
Hypertensive disorders of pregnancy

In most instances, pregnancy in women with renal disorders is successful, provided kidney function is well preserved and hypertension absent.

I. The kidney and blood pressure in normal pregnancy

The anatomy and function of the kidneys and lower urinary tract are altered in gestation. Physiologic alterations in volume homeostasis and blood pressure control also occur, and recognizing this is a prerequisite for the appropriate interpretation of data from pregnant patients with renal disease or hypertension (Table 13-1).



Alteration	Manifestation	Clinical relevance
Increased renal size	Renal length approximately 1 cm greater on radiographs	Purported decrease in size should not be mistaken for parenchymal loss
Dilation of pelves, calyces, and ureters	Reversible hydronephrosis on renal ultrasound or intravenous pyelography (more marked on right)	Not to be mistaken for obstructive uropathy; elective evaluation should be deferred to the twelfth postpartum week; upper urinary tract infections are more virulent; retained urine leads to collection errors
Increased renal hemodynamics	Glomerular filtration rate and renal plasma flow increase 30% to 50%	Serum creatinine and urea nitrogen values decrease during normal gestation; ≈0.8 mg/dL creatinine already suspect; proteinuria, amino acid, and glucosuria urinary excretion all increase
Changes in acid-base metabolism	Renal bicarbonate threshold decreases	Serum bicarbonate is 4 to 5 mEq/L lower in normal gestation
Renal water handling	Osmoregulation altered	Serum osmolality decreases 10 mOsm/L; [sodium, sodium decreases 5 mEq/L] during normal gestation
	Osmotic thresholds for thirst and AVP decrease; the metabolic clearance of AVP increases markedly; high levels of vasopressinase circulating	Increased metabolism of AVP may cause transient diabetes insipidus in pregnancy

AVP, arginine vasopressin.

Table 13-1. Renal changes in normal pregnancy

A. **Anatomic and functional changes in urinary tract.** Kidney length increases approximately 1 cm during normal gestation. The major anatomic alterations of the urinary tract during pregnancy, however, are seen in the collecting system, where calyces, renal pelves, and ureters dilatate, often giving the erroneous impression of obstructive uropathy. The dilation is accompanied by hypertrophy of ureteral smooth muscle and hyperplasia of its connective tissue, but whether bladder reflux is more common in gravidas is unclear. The cause of the ureteral dilation is disputed: Some researchers favor hormonal mechanisms, whereas other researchers believe that it is obstructive in origin. Clearly, as pregnancy progresses, assumption of a supine or upright posture may cause ureteral obstruction when the enlarged uterus entraps the ureters at the pelvic brim (Fig. 13-1). These morphologic changes have considerable clinical relevance. Stasis in the dilatated urinary tract may contribute to the propensity of pregnant women with asymptomatic bacteriuria to develop frank pyelonephritis. The widened ureters contain substantial volumes of urine, which may lead to collection errors in tests that require timed urine volumes. These errors may be avoided by the following simple protocol: Gravidas to be tested should receive a water load and remain in bed positioned in lateral recumbency for 1 hour before the start of the collection. This procedure minimizes inaccuracies by standardizing the procedures and by producing a modest water diuresis, so that residual urine is diluted and of recent origin. Acceptable norms of kidney size should be increased by 1 cm if estimated during pregnancy or the immediate puerperium, and reductions of renal length noted several months postpartum need not be attributed to renal disease. Rarely, ureteral dilation is of sufficient magnitude to cause a “distention” syndrome (characterized by abdominal pain, and on occasion small increments in serum creatinine levels presenting in late gestation, which resolve with the placement of ureteral stents). Also, because dilation of the ureters may persist until the twelfth postpartum week, elective ultrasonographic or radiologic examination of the urinary tract should be deferred, if possible, until after this time.

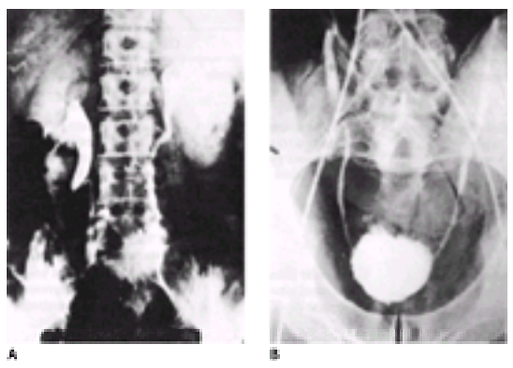


Figure 13-1. Intravenous pyelogram. **A:** Ureteral dilation of pregnancy. The right ureter is sharply cut off at the pelvic brim where it crosses the iliac artery (the iliac sign). **B:** Relationship between the ureters and iliac arteries can be demonstrated in postmortem studies. Note the iliac sign at the pelvic brim on the right. (From Dure-Smith P. Pregnancy dilation of the urinary tract. *Radiology* 1970;96:545. Reprinted with permission.)

B. **Renal hemodynamics.** The changes in renal hemodynamics in gestation are the most striking and clinically significant of all the urinary tract alterations of pregnancy.
   1. **Glomerular filtration rate (GFR) and renal plasma flow (RPF)**increase to levels 30% and 50% above nongravid values during pregnancy. Increments in GFR that are already present during the early days after conception reach a maximum during the first trimester. The basis for the increase in GFR and RPF is unknown. Animal studies suggest that renal vasodilation leading to increased glomerular plasma flow is a contributing, but not the sole, factor. RPF is greatest at midgestation, declining somewhat in the third trimester. Although increments in GFR measured by the infusion of insulin appeared to be sustained until term, 24-hour creatinine clearance declines during the last 4 weeks of pregnancy, accompanied by increases in serum creatinine levels of 15% to 20%. The increase in GFR has important clinical implications. Because creatinine production is unchanged during pregnancy, increments in its clearance result in decreased serum levels. Using the Hare method, one group of investigators observed that true serum creatinine, which averaged 0.67 mg per dL in nongravid women, decreased to 0.46 mg per dL during gestation [to convert to SI units (μmol/L), multiply serum creatinine (mg/dL) by 88.4]. In studies that also measured creatinine chromogen (which yielded results resembling those reported in most clinical laboratories), values were 0.83 mg per dL in nonpregnant women and decreased to 0.74, 0.58, and 0.53 mg per dL in the first, second, and third trimester of pregnancy, respectively. Thus, values considered normal in nongravid women may reflect decreased renal function during pregnancy. For example, in gravid women, concentrations of serum creatinine exceeding 0.8 mg per dL or of serum urea nitrogen that are greater than 13 mg per dL suggest the need for additional evaluation of renal function.
   2. **Other consequences of the increased renal hemodynamics.** Increased GFR and RPF also alter urinary solute content. For example, excretion of glucose, most amino acids, and several water-soluble vitamins increases, and these increments in the nutrient content of urine may be a factor in the enhanced susceptibility of gravidas to urinary tract infections. Urinary protein excretion also increases during gestation, but the fate of albumin excretion is more complex and disputed.

C. **Acid-base regulation in pregnancy.** Renal acid-base regulation is altered during gestation. The bicarbonate threshold decreases, and early-morning urines are often more alkaline than those in the nongravid state. In addition, plasma bicarbonate concentrations decrease approximately 4 μmol per L, averaging 22 μmol per L. This change most likely represents a compensatory renal response to hypocapnia, because pregnant women hyperventilate, and their Pco_2 averages only 30 mm Hg. The mild alkalosis (arterial pH averages 7.44) found in pregnancy is in accord with this view. Because steady-state P_{CO_2} and HCO_3 levels are already diminished, pregnant women are, in theory, at a disadvantage when threatened by sudden metabolic acidosis (e.g., lactic acidosis in

preeclampsia, diabetic ketoacidosis, or acute renal failure); however, they respond with appropriate increments in urinary titratable acid and ammonia after an acid load, and proton regeneration is already evident at blood pH levels higher than those in similarly tested nonpregnant women. Finally, when managing gravidas with pulmonary disorders, it should be noted that a Pco_2 of 40 mm Hg, normal in nonpregnant women, signifies considerable carbon dioxide retention in pregnancy.

D. **Water excretion.** After conception, a rapid decrease in plasma osmolality levels of 5 to 10 mOsm per kg below that of nongravid subjects occurs. If this decrease occurred in a nonpregnant woman, she would cease secreting antidiuretic hormone and enter a state of water diuresis; however, gravidas maintain this new osmolality, diluting and concentrating urine appropriately when the woman is subjected to water loading or dehydration. This suggests a resetting of the osmoreceptor system, and, indeed, recent data demonstrate that the osmotic thresholds for both thirst and arginine vasopressin (AVP) release are decreased in pregnant women. Furthermore, the plasma of pregnant women contains large quantities of a placental enzyme (vasopressinase) capable of destroying substantial quantities of AVP in vitro; moreover, the in vivo production and metabolic clearance of antidiuretic hormone are increased fourfold after midgestation.

   The changes in osmoregulation and AVP metabolism may be responsible for two unusual syndromes of transient diabetes insipidus that complicate pregnancy. One, in which polyuria is responsive to both AVP and deamino-8-D-arginine vasopressin (dDAVP), probably occurs in women with inapparent partial central diabetes insipidus whose disease is brought to the fore by the increment in hormonal disposal rates in late gestation. The other disorder, in which the marked polyuria continues despite large doses of AVP, is responsive to dDAVP, an analogue resistant to inactivation by vasopressinase. These gravidas may have excessively high circulating levels for increased activation of the aminopeptidase enzyme vasopressinase.

E. **Volume regulation.** Most healthy women gain approximately 12.5 kg during the first pregnancy and 1 kg less during subsequent pregnancies. Generations of physicians have considered these averages as upper limits of permissible weight gains, forgetting that a mean has plus and minus deviations. As a result, many gravidas were scolded for excessive weight gain, and their salt, calories, or both were restricted. Most of the increment is fluid, with total body water increasing 6 to 8 L, 4 to 6 L of which is extracellular. Plasma volume increases 50% during gestation, the largest rate of increment occurring during midpregnancy, whereas increments in the interstitial space are greatest in the third trimester. A gradual cumulative retention of approximately 900 mEq of sodium occurs in pregnancy that is distributed between the products of conception and the maternal extracellular space. These alterations in maternal intravascular and interstitial compartments produce apparent hypervolemia, yet the gravida's volume receptors sense these changes as normal, and when salt restriction or diuretic therapy limits this physiologic expansion, maternal responses resemble those in salt-depleted nonpregnant women. This is one compelling reason that a policy once common, whereby gravidas were sodium restricted and often given diuretics, is now condemned. Pregnant women are now advised to salt their food to taste, and some researchers believe that a liberal sodium intake is beneficial during gestation. The influence of humoral changes during normal pregnancy on renal sodium handling and volume regulation is incompletely understood. The increment in GFR means that up to 10,000 additional mEq of sodium must be reabsorbed by the renal tubules each day, a quantity considerably greater than the expected salt-retaining potency of several mineralocorticoids (aldosterone, desoxycorticosterone, estrogen), blood levels of which increase in pregnancy.

F. **Blood pressure regulation.** Mean blood pressure starts to decrease early in gestation, with diastolic levels in midpregnancy averaging 10 mm Hg less than measurements postpartum. In later pregnancy, blood pressure increases, gradually approaching nonpregnancy values near term. Because cardiac output rises quickly in the first trimester and remains relatively constant thereafter, the decrease in pressure is due to a marked decrement in peripheral vascular resistance. The slow rise toward nonpregnant levels after a midtrimester nadir is interesting, because it demonstrates that increasing vasoconstrictor tone is a feature of late gestation in normal women as well as in women in whom preeclampsia is developing. The cause of the decrease in peripheral resistance during pregnancy is obscure. Studies of arterial compliance in pregnancy demonstrate early rises, perhaps due to alterations in vessel ground substance. Elevations of plasma estrogen and progesterone to concentrations that may relax smooth muscle occur, and increments in vasodilating prostaglandins may also be present during gestation. Intriguing candidates for the increased vasodilation in pregnancy are endothelium-derived relaxing factors, mainly those relating to increased nitric oxide production. The role of these endothelial products in the physiology of pregnancy are under investigation. A unique feature of pregnancy is that despite lower blood pressure, levels of all components of the renin-angiotensin system are increased. Although gravidas are normally resistant to the pressor effects of angiotensin II, they may demonstrate exaggerated hypotensive responses to converting enzyme inhibitors, suggesting that the renin system is stimulated to help maintain blood pressure. Catecholamine levels appear to be unaltered in gestation.

   Lack of awareness of the fluctuation in blood pressure during normal gestation may lead to diagnostic errors. For example, certain women with mild essential hypertension experience the normal decrease in blood pressure during early pregnancy, and blood pressure may approach normal levels. They are then erroneously labeled preeclamptic in the last trimester, when frankly elevated pressures occur. Such errors can be avoided if diastolic levels of 75 mm Hg in the second trimester and 85 mm Hg in the third are considered to be upper limits of normal.

G. **Mineral metabolism.** Serum calcium levels decrease in pregnancy, in conjunction with a decrement in circulating albumin concentrations. Ionized calcium levels, however, remain in the normal nonpregnant range. Striking changes relating to calcium regulatory hormones also occur during normal pregnancy. Production of $1,25(OH)_2$ vitamin D_3 increases as early as the first trimester, reaching circulating levels that are approximately two times nonpregnant values. Gastrointestinal absorption of calcium increases, resulting in an “absorptive hypercalciuria,” with 24-hour urine excretion often exceeding 300 mg per day (in appropriately nourished individuals). Intact parathyroid hormone levels are lower during normal pregnancy.

II. Clinical evaluation of renal function in pregnancy

A. **Examination of the urine.** The association of proteinuria with eclampsia was first noted in the 1840s, and the science of prenatal care advanced dramatically when physicians began to systematically examine the urine of gravidas, primarily for albuminuria. In certain instances, latent renal disease is first uncovered by the detection of excessive protein excretion or microscopical hematuria during a routine prenatal evaluation.

   Healthy nonpregnant women excrete considerably less than 100 mg of protein in the urine daily, but due to the relative imprecision and variability of testing methods used in hospital laboratories, proteinuria is not considered abnormal until it exceeds 150 mg per day. During pregnancy, protein excretion increases, and excretion up to 300 mg per day (some authors accept 0.5 g per day) may still be normal. On occasion, a healthy gravida can excrete more than that amount. The problem is compounded by the fact that approximately 5% of healthy adolescents and young adults have postural proteinuria, which may become apparent only during pregnancy. In addition, postural proteinuria may increase near term, when gravidas tend to assume a more lordotic posture, which augments protein excretion. Another cause of increased proteinuria in pregnancy may be compression of the renal veins by the enlarged uterus, especially when gravidas lie supine. Thus, when the gravida is tested for postural proteinuria (see chapter 8), she should be positioned in lateral recumbency.

   Few attempts have been made to quantitate the urine sediment in pregnancy. The excretion of both red and white blood cells may increase during normal gestation, and 1 to 2 red blood cells per high-powered field is acceptable in a urinalysis.

B. **Renal function tests.** The clearance of endogenous creatinine, the most satisfactory approximation of GFR in nongravid subjects, is equally useful for assessing renal function in gravidas. Gravidas, as well as nonpregnant women, show little variation (approximately 10% per day) in urinary creatinine excretion and, presumably, in creatinine production, which in a given woman is similar both during and after gestation. The lower limit of normal creatinine clearance during gestation should be 30% greater than the average of 110 to 115 mL per minute for nongravid women.

   Acid excretion and urinary concentration and dilution are similar in gravid and nonpregnant women. Thus, tests such as ammonium loading (rarely indicated in gestation) give values similar to those in nongravid women. When examining urinary diluting ability, the clinician should be aware that supine posture can interfere with this test. Therefore, studies to detect minimal urinary osmolal concentrations should be performed with the patient lying on her side. However, although lateral recumbency is the required position for prenatal measurement of most renal function parameters, this posture interferes with tests of concentration. For example, a urine osmolality that was 800 mOsm per kg after overnight dehydration may decrease to 400 mOsm per kg within 1 hour by fluid mobilization from the extremities during bed rest, resulting in volume-induced inhibition of AVP secretion, a mild osmotic diuresis, or both. These observations demonstrate the importance of upright posture, such as quiet sitting, when maximum urinary concentration is measured in pregnancy.

C. **Role of renal biopsy in pregnancy.** Percutaneous renal biopsy is seldom performed during gestation. In fact, pregnancy was once considered a relative contraindication to the procedure because of early reports of excessive bleeding and other complications in gravid women. This view, however, stemmed from the period when many of the biopsies were performed in hypertensive patients at a time predating understanding of the coagulation abnormalities that may occur in preeclamptic women. It is now evident that if the renal biopsy is performed in women with well-controlled blood pressure and normal coagulation indices, morbidity is similar to that of nonpregnant patients.

   Although some authorities suggest that renal biopsies be performed in all pregnant women with undiagnosed hematuria, proteinuria, or both, claiming that such a policy has important relevance for management and prognosis, we believe such indications to be too broad and recommend the procedure very infrequently during gestation. Our indications are as follows.

   Renal biopsy should be considered when renal function suddenly deteriorates and no obvious cause is present; certain forms of rapidly progressive glomerulonephritis, when diagnosed early, may respond to aggressive treatment such as steroid pulses and, perhaps, plasma exchange. Another situation in

which biopsy is recommended is symptomatic nephrotic syndrome. Although some might consider a therapeutic trial of steroids in such cases, we prefer to determine beforehand whether the lesion is likely to respond to steroids, because pregnancy is itself a hypercoagulable state prone to worsening by such treatment. On the other hand, proteinuria alone in a normotensive woman with well-preserved renal function who has neither marked hypoalbuminemia nor intolerable edema would lead us to examine the patient at more frequent intervals and defer the renal biopsy to the postpartum period. This is because the consensus among most investigators is that prognosis is determined primarily by the level of renal function and the presence or absence of hypertension rather than by the type of renal lesion (see section **II.D**). We take a similar position in the management of pregnancies with asymptomatic microscopical hematuria alone, when neither stone nor tumor is suggested by ultrasonography. Finally, renal biopsies should not be performed after gestational week 32, because at this stage the fetus will probably be delivered in any case, and the decision usually has to be made quickly and independent of biopsy results.

D. **Clinical application.** Some of the normal morphologic and physiologic adjustments that affect the kidneys during pregnancy, and the application of such information to detecting disease, are illustrated in the following case report.

Example.A 25-year-old multipara with known hypertension was hospitalized at 31 weeks' gestation with a blood pressure of 200/140 mm Hg. Treatment included a single 20-mg dose of hydralazine, 2 mg trichlormethiazide daily for 3 days, bed rest in the position of lateral recumbency, and restriction of dietary sodium. After 2 weeks, weight decreased 4.6 kg and diastolic blood pressure now averaged 90 to 100 mm Hg. Unfortunately, urine volumes declined, and the creatinine clearance decreased from 106 mL per minute on the sixth hospital day to 82 mL per minute on the sixteenth (Table 13-2). Simultaneously, serum urea nitrogen increased from 8 to 25 mg per dL [to convert to SI units (µmol/L), multiply mg/dL by 0.357]. Interruption of gestation was considered, because deteriorating renal function was regarded as a sign of superimposed and progressing preeclampsia. However, a diagnosis of salt depletion was also entertained. A trial period in which sodium intake was increased to 206 mEq per day followed. After sodium intake was liberalized, weight increased 1.5 kg, but diastolic blood pressure remained between 90 and 100 mm Hg, and the creatinine clearance increased to 118 mL per minute. Serum creatinine and urea nitrogen decreased to 0.9 and 16 mg per dL respectively. The gestation was allowed to continue until labor ensued spontaneously (1).

Function	Day 6	Day 16	Day 26
Creatinine clearance (mL/min)	106.0	82.0	118.0
Serum creatinine (mg/dL)	1.1	1.3	0.9
Serum urea nitrogen (mg/dL)	8.0	25.0	16.0
Maximum urine flow (mL/min)	–	2.3	8.7

Table 13-2. Renal function during hospitalization

Several points are illustrated here. Alterations in serum creatinine mirrored changes in its clearance, whereas this relation was less clear in the case of urea nitrogen. The GFR was low for pregnancy—serum creatinine values of 0.9 to 1.3 mg per dL are acceptable in nonpregnant women but abnormal during gestation. On the other hand, plasma urea nitrogen was normal on admission, perhaps reflecting poor nutrition. How easily this patient became dehydrated is also interesting (a fact not appreciated by many who manage pregnant women). With dehydration and oliguria, the concentration of urea increased threefold, whereas the creatinine clearance decreased only 23%. However, when GFR increased to values greater than those measured on admission, serum urea nitrogen was still 16 mg per dL, probably reflecting a good hospital diet.

III. Renal disease in pregnancy

A. **Asymptomatic bacteriuria.** Urinary tract infection is the most common renal problem occurring in pregnancy. The urine of gravidas supports bacterial growth better than that of nonpregnant women because of its increased nutrient content. This, as well as ureteral dilation, stasis, and occasional obstruction, would be expected to increase the susceptibility of pregnant women to urinary tract infection. Surprisingly, this is not the case, and, with the exception of certain high-risk groups (diabetic patients and gravidas with sickle cell trait), the prevalence of asymptomatic bacteriuria during gestation varies between 4% and 7%, a value similar to that in sexually active nonpregnant women. The natural history of asymptomatic urinary tract infections is, however, quite different in pregnancy.

Although in the nonpregnant state asymptomatic bacteriuria is quite benign, progression to overt cystitis or pyelonephritis occurs in up to 40% of affected gravidas. Therefore, screening all pregnant women for the presence of asymptomatic bacteriuria and treating those with positive urine cultures is important.

1. **Method of urine collection.** Pregnant women contaminate midstream urine specimens more frequently. The incidence can be reduced by the use of multiple vulval washings combined with carefully supervised collection procedures. In some women, suprapubic aspiration is required to differentiate contamination from true infection. Pregnancy is not a contraindication to this procedure.

   If the urine is sterile at the beginning of pregnancy, it usually remains so until term. Still, a small number (1% to 2%) of gravidas whose original urine cultures are negative subsequently have bacteriuria. Abnormal urinalysis and the presence of dysuria do not differentiate between contamination and true infection. For example, dysuria occurs in 30% of gravidas whose urines are sterile, and the urine may be infected and still contain fewer than two leukocytes per high-power field.
2. **Method of treatment.** The optimum way to manage asymptomatic urinary tract infections in pregnancy has not been precisely defined. In the earlier literature, some authors recommended continuous antibiotic treatment from the time the bacteriuria was detected until delivery. This was based on the belief that the relapse rate was high, and that most bacteriuric women have renal parenchymal involvement as opposed to bladder infection. However, it is now apparent that one-half of these infections involve only the bladder, and the majority of these patients are cured by standard short-course (or even single-dose) therapy. More than 90% of the uropathogens involved are aerobic gram-negative rods, usually *Escherichia coli*, and we recommend a 10- to 14-day course of the antibiotic to which the cultured organism is sensitive, preferably a short-acting sulfa drug or a nitrofurantoin derivative, reserving the more potent agents for treatment failures or for symptomatic infections. This approach, when combined with surveillance for recurrent bacteriuria, has been shown to be quite effective.
3. **Importance of postpartum evaluation.** Asymptomatic urinary tract infection has been linked to premature labor, hypertension, and anemia during gestation, but these assertions have not been proved. On the other hand, an increased incidence of occult urinary tract pathology is present in these gravidas. Therefore, women with bacteriuria during pregnancy may benefit from evaluation of their urinary tract postpartum, especially those in whom the infection is resistant to therapy.

B. **Symptomatic bacteriuria.** The clinical approach to symptomatic urinary tract infection during gestation differs from that for asymptomatic bacteriuria.
1. **Acute pyelonephritis.** Pyelonephritis was a cause of maternal death in the preantibiotic era, and 3% of pregnant patients in a more recently reported series developed septic shock. At one time, symptomatic urinary tract infections complicated almost 2% of all gestations, but prenatal screening combined with rapid treatment of asymptomatic bacteriuria has reduced this incidence to approximately 0.5%. The bacteriology of these infections resembles that in asymptomatic patients (predominantly *E. coli*), and most of the cases present after midpregnancy. The clinical presentation of pyelonephritis in pregnancy can be dramatic. As noted before, the disease caused maternal deaths in the preantibiotic era, and upper urinary tract infections in gravidas are associated with exaggerated effects of endotoxemia, including shock, respiratory distress syndrome, marked renal dysfunction, and hematologic and liver abnormalities. Symptomatic urinary tract infections have also been implicated in the etiology of intrauterine growth retardation, prematurity, congenital anomalies, and fetal demise. Thus, although treatment of cystitis may take place in an outpatient setting, treatment of pyelonephritis should be aggressive and is best performed in the hospital.

   Most patients with pyelonephritis respond quickly, with defervescence within 48 to 72 hours. However, in contrast to patients with cystitis or asymptomatic bacteriuria, these women are likely to experience relapse. Thus, gravidas with acute pyelonephritis should receive the therapeutic dose of antibiotics for 3 to 6 weeks. Subsequently, we recommend continuous suppressive therapy during the remainder of pregnancy and for the first 2 weeks of the puerperium, because up to 60% of the patients will have a recurrence of pyelonephritis if left untreated. Antibiotic suppression is preferable to drugs such as methenamine mandelate (because urinary “sterilization” does not seem to be effective during gestation). An alternative approach, frequent surveillance for recurrent infection with prompt treatment when significant bacteriuria is identified, has been claimed to be as effective as suppressive therapy.

2. **Perirenal abscess and renal abscess formation or carbuncle,** although infrequent complications of gestation, should be considered in the differential diagnosis of postpartum fever. It is important to recognize that a high incidence of positive urine cultures occurs in the postpartum period—perhaps 17% to 20% in the first few days after delivery, decreasing to 4% after the third postpartum day. These cases, which resolve spontaneously, may reflect a temporary breakdown in the normal host antibacterial mechanisms in the immediate postpartum period rather than true infection. Thus, when pyrexia is evaluated during the first 72 hours of puerperium, suprapubic aspiration of urine is preferable to midstream specimens.
3. **Antibiotic use in pregnancy.** The first-choice antibiotic for symptomatic infections changes from decade to decade because of the rapid emergence of resistant strains, resulting in the use of drugs that have not yet withstood the test of time for safety in pregnancy. We continue to recommend starting treatment with cephalosporins, because a significant percentage of community-acquired *E. coli* infections are resistant to ampicillin. For routine cystitis, nitrofurantoin is often effective, and it is acceptable during pregnancy.

   The physician should also be aware of problems specific to the use of antibiotics in obstetrics and anticipate the potential fetal toxicity of agents that cross the placental barrier. (Information concerning safety during pregnancy is listed in the *Physicians' Desk Reference* which is updated annually.) In brief, sulfa drugs should not be used near term, because they may precipitate kernicterus in the newborn. The anti–folic acid activity of trimethoprim has been associated with anomalies such as cleft palate in animals, and this combination drug should also be avoided, at least before midpregnancy.

   Aminoglycosides should also be prescribed sparingly, because streptomycin has been associated with fetal ototoxicity and nephrotoxicity. Fluoroquinolones are classified by the U.S. Food and Drug Administration as Pregnancy Category C (should be used only if benefit exceeds risk, may be associated with deleterious effects). They cross the placenta and should be avoided if possible. Tetracyclines are contraindicated because they deposit in fetal bones and teeth and may cause severe reactions in the mother, including hepatic failure.

C. **Acute renal failure**

1. **Incidence.** Before 1970, the incidence of acute renal failure in pregnancy severe enough to require dialytic therapy was estimated at between 1 in 2,000 and 1 in 5,000 gestations, and it represented a considerable proportion of cases reported in large series. Since then, the number of patients with acute renal failure from obstetric causes has declined markedly, and the incidence is now estimated to be less than 1 in 20,000 pregnancies. This trend, attributed to liberalization of abortion laws and improvement of prenatal care, has not been shared by the poorer and less industrialized nations, in which such patients compose up to 25% of referrals to dialysis centers and in which renal failure in pregnancy continues to be an important cause of maternal and fetal mortality.

   The frequency distribution of acute renal failure during gestation was bimodal, with one peak early in pregnancy (12 to 18 weeks) comprising most of the cases associated with septic abortion, and a second peak between gestational week 35 and the puerperium, primarily due to preeclampsia and bleeding complications, especially placental abruption.
2. **Causes.** Acute renal failure in pregnancy can be induced by any of the disorders leading to renal failure in the general population, such as acute tubular necrosis. Early in pregnancy, the most common problems are prerenal disease due to hyperemesis gravidarum, and acute tubular necrosis resulting from a septic abortion. Several different uncommon disorders can lead to acute renal failure later in pregnancy. Mild to moderately severe preeclampsia is not usually associated with renal failure, because renal function is generally maintained in the normal or near-normal range for a nonpregnant women. A variant of preeclampsia, the HELLP syndrome (*h*emolysis, *e*levated *l*iver enzymes, and *l*ow *p*latelet count; see section **IV.B**) may be associated with significant renal dysfunction, especially if not treated promptly.
   a. **Thrombotic microangiopathy.** An important and difficult differential diagnosis is that of acute renal failure in late pregnancy in association with microangiopathic hemolytic anemia and thrombocytopenia. Such cases are usually due to thrombotic thrombocytopenic purpura (TTP), postpartum hemolytic-uremic syndrome (HUS), or the HELLP syndrome, which is a variant of preeclampsia. The distinction of these syndromes is important for therapeutic and prognostic reasons, but considerable overlap exists in their clinical and laboratory features. Features that may be helpful in making the diagnosis include timing of onset and the pattern of laboratory abnormalities. Preeclampsia typically develops in the third trimester, with only a few cases developing in the postpartum period, usually within a few days of delivery. TTP usually occurs antepartum, with many cases developing in the second trimester, as well as the third. HUS is usually a postpartum disease. Symptoms may begin antepartum, but most cases are diagnosed postpartum.

      Preeclampsia is much more common than TTP/HUS, and it is usually preceded by hypertension and proteinuria. Renal failure is unusual even with severe cases, unless significant bleeding or hemodynamic instability, or marked disseminated intravascular coagulation (DIC) occurs. In some cases, preeclampsia develops in the immediate postpartum period, and when thrombocytopenia is severe, it may be indistinguishable from HUS. However, preeclampsia spontaneously recovers, whereas HUS only infrequently improves.

      In contrast to TTP/HUS, preeclampsia may be associated with mild DIC and prolongation of prothrombin and partial thromboplastin time. Another laboratory feature of preeclampsia/HELLP syndrome that is not usually associated with TTP/HUS is marked elevations in liver enzymes. The presence of fever is more consistent with a diagnosis of TTP than preeclampsia or HUS. The main distinctive features of HUS are its tendency to occur in the postpartum period and the severity of the associated renal failure. Treatment of preeclampsia/HELLP syndrome is delivery and supportive care. More aggressive treatment is rarely indicated. Treatment of TTP/HUS includes plasma infusion/exchange and other modalities used in nonpregnant patients with these disorders.
   b. Bilateral **renal cortical necrosis** may be induced by abruptio placenta or other severe complications associated with obstetric hemorrhage. Both primary DIC and severe renal ischemia have been proposed as the initiating events. Affected patients typically present with oliguria or anuria, hematuria, and flank pain. Ultrasonography or computed tomographic scanning may demonstrate hypoechoic or hypodense areas in the renal cortex. Most patients require dialysis, but 20% to 40% have partial recovery of renal function.
   c. **Acute pyelonephritis.**Some pregnant women may develop acute renal failure in association with pyelonephritis.
   d. **Acute fatty liver of pregnancy** (fatty infiltration of hepatocytes without inflammation or necrosis) is a rare complication of pregnancy that is associated with significant azotemia. Women with this disorder often complain of anorexia and occasionally of abdominal pain in the third trimester. Clinical features suggesting preeclampsia, including hypertension and proteinuria, are not uncommon. Laboratory tests reveal elevations in liver enzymes, hypoglycemia, hypofibrinogenemia, and prolonged partial thromboplastin time. Delivery is indicated, and most patients improve shortly afterwards.
   e. **Urinary tract obstruction.**Pregnancy is associated with dilation of the collecting system, which is not usually associated with renal dysfunction. Rarely, complications such as large uterine fibroids that enlarge in the setting of pregnancy can lead to obstructive uropathy.

      Rarely, acute urinary tract obstruction in pregnancy is induced by a kidney stone. Diagnosis can usually be made by ultrasonography. Often the stones pass spontaneously, but occasionally cystoscopy is necessary for insertion of a stent to remove a fragment of stone and relieve obstruction, particularly if there is sepsis or a solitary kidney.
3. The **management** of acute renal failure occurring in gestation or immediately postpartum is similar to that in nongravid subjects (see Chapter 9), but several points peculiar to pregnancy deserve emphasis. Because uterine hemorrhage near term may be concealed and blood loss underestimated, any overt blood loss should be replaced early. Gravidas should be slightly overtransfused to forestall the development of acute tubular or cortical necrosis. Both peritoneal dialysis and hemodialysis have been successfully used in patients with obstetric acute renal failure. Neither pelvic peritonitis nor the enlarged uterus is a contraindication to the former method. In fact, this form of treatment is more gradual than hemodialysis and thus less likely to precipitate labor. Because urea, creatinine, and other metabolites that accumulate in uremia traverse the placenta, dialysis should be undertaken early, with the aim of maintaining the blood urea nitrogen at approximately 50 mg per dL. In essence, the advantages of early dialysis in nongravid patients are even more important for the pregnant patient, making arguments for prophylactic dialysis quite compelling. Excessive fluid removal should be avoided, because it may contribute to hemodynamic compromise, reduction of uteroplacental perfusion, and premature labor. Some obstetricians and perinatologists recommend continuous fetal monitoring during hemodialysis treatments, starting at midpregnancy. Finally, the physician should be aware of potential dehydration in the neonate, because the newborn usually undergoes a brisk urea-induced diuresis.

D. **Pregnancy in women with preexisting renal disease.** The current approach to pregnancy in women with chronic renal disease is primarily based on retrospective studies, and more definitive views must await prospective data from large series in which clinical, pathologic, and functional observations are correlated. Nevertheless, several generalizations can be made and some guidelines presented regarding gestation in women with chronic kidney dysfunction (Table 13-3 and Table 13-4).

Disease	Comments
Chronic glomerulonephritis and focal glomerular sclerosis (FGS)	Increased incidence of high blood pressure occurs late in gestation, but usually no adverse effect results if renal function is preserved and hypertension absent before gestation. Some changes, including that complement changes in pregnancy resemble disease, especially membranoproliferative glomerulonephritis, and FGS.
Systemic lupus erythematosus	Controversial; prognosis is most favorable if disease is in remission 6 mo or more before conception.
Pyelonephritis cystitis and reflux disease	Both fetal and maternal prognosis is poor. Therapeutic abortion should be considered.
Diabetic nephropathy	No adverse effect on the renal lesion. Increased frequency of infections. High incidence of toxemia, pyelonephritis and hypertension seen here.
Chronic pyelonephritis (reflux nephropathy, tubulointerstitial disease)	Bacteriuria in pregnancy may lead to exacerbations.
Polycystic kidneys	Few problems when function is preserved and hypertension is absent. However, the incidence of preeclampsia is increased.
Urolithiasis	Ureteral dilation and stasis do not seem to affect natural history, but infections can be more frequent. Stents have been successfully placed during gestation.
Reflux nephropathy	Prognosis disputed. We believe such pregnancies have a good outcome, although urinary infection may be more common.
Previous urologic surgery	Urinary tract infection is common with urinary diversion, and renal function may undergo irreversible decline. Cesarean section might be necessary to avoid disruption of the continence mechanism of urethral sphincters or reconfigure have been constructed.
Adult polycystosis, solitary pelvic kidneys	Pregnancy is well tolerated. Might be associated with either malpresentation of the urogenital tract. Ptosis can occur rarely with a pelvic kidney.

[a]Glomerulopathies that occur with only mild renal dysfunction (serum creatinine level = 1.5 mg/dL) and without hypertension are excluded.

Table 13-3. Summary of pregnancy in women with preexisting renal disease[a]

Prospects	Category		
	Mild (Cr <1.5 mg/dL)	Moderate (Cr 1.5–3.0 mg/dL)	Severe (Cr >3.0 mg/dL)
Pregnancy complications	25%	47%	86%
Successful obstetric outcome	96% (65%)	90% (59%)	47% (9%)
Long-term sequelae	<3% (9%)	25% (71%)	50% (92%)

Cr, creatinine clearance.
[a]Estimates are based on 1,682 women with 3,799 pregnancies (1933–1992) and do not include collagen diseases. Numbers in parentheses refer to prospects when complication(s) develop before 28 weeks' gestation.
From Davison JM, Lindheimer MD. Renal disorders. In: Creasy RK, Resnick RK, eds. Maternal-fetal medicine, 3rd ed. Philadelphia: Saunders, 1994. Reprinted with permission.

Table 13-4. Pregnancy and renal disease: functional renal status and prospects [a]

1. **Prognosis.** Counseling and managing women with chronic renal disease is based on the following general approach: Fertility and ability to sustain an uncomplicated pregnancy relate to the degree of functional impairment, whether hypertension is present, and not to the underlying disorder.
   a. **Degree of impairment.** Patients are arbitrarily considered in three categories: preserved or mildly impaired renal function (serum creatinine less than or at 1.4 mg per dL), moderate renal insufficiency (creatinine 1.5 to 3.0 mg per dL), and severe renal insufficiency (creatinine higher than or equal to 3 mg per dL). Table 13-4 summarizes the maternal and fetal prognosis in each category, and Table 13-5 depicts the improvement in pregnancy outcomes that has occurred since the 1950s, reflecting advances in prenatal and neonatal care. We generally counsel avoidance of conception in women who have moderate or severe renal dysfunction, because up to 40% of pregnancies in the former category are complicated by either hectic hypertension or sudden declines in GFR, which may not reverse after delivery. An even higher incidence of serious maternal problems occurs when renal insufficiency is severe. This is especially true for women receiving dialytic therapy, in whom fewer than 50% of the gestations succeed, and problems of extreme prematurity plague many of those that do. Notably, although we base prognosis primarily on the degree of functional impairment, the underlying disease may also play a role. Thus, all authorities recommend against pregnancy in women with scleroderma and periarteritis nodosa, and some have reservations concerning patients who have lupus erythematosus, immunoglobulin A nephropathy, or focal glomerular sclerosis.

Renal disease	Pregnancy outcome	Morbidity and mortality (%)			
		1960s	1960s	1970s	1980s
Mild (Cr <1.5 mg/dL)	Preterm delivery	8	10	19	25
	Perinatal mortality	18	15	7	<5
Moderate (Cr 1.5–3.0 mg/dL)	Preterm delivery	15	21	40	52
	Perinatal mortality	58	45	23	10
Severe (Cr >3.0 mg/dL)	Preterm delivery	100	100	100	100
	Perinatal mortality	100	91	58	53

Cr, creatinine
[a]Estimates are based on 2,952 women with 4,011 pregnancies (1954–1990) and do not include cases of lupus erythematosus.
From Davison JM, Lindheimer MD. Renal disorders. In: Creasy RK, Resnick RK, eds. Maternal-fetal medicine, 3rd ed. Philadelphia: Saunders, 1994. Modified with permission.

Table 13-5. Renal disease and pregnancy: improvements in perinatal mortality over four decades [a]

   b. **Level of blood pressure.** The blood pressure level at time of gestation is an important prognostic index. In the absence of hypertension, the natural history of most established renal parenchymal disease is unaffected by gestation (although preeclampsia may occur more readily). In contrast, when renal disease and hypertension coexist, the gestation is more likely to be complicated, either by severe increments in blood pressure or by additional reductions in renal function. We permit women with well-controlled blood pressures and only mild renal dysfunction to conceive or continue gestation, but these gravidas must be seen frequently and should understand that their gestation must be terminated if renal function deteriorates or if their blood pressure becomes difficult to control.
   c. **Proteinuria.** Urinary protein excretion, which increases in normal pregnancy, may increase markedly in pregnant women with underlying parenchymal renal disease. In one large series, one-third of the patients with preexisting renal disease developed nephrotic-range proteinuria during gestation. These increments do not necessarily reflect worsening of the underlying kidney disease.
   d. **Renal hemodynamics.** Gravidas with kidney disorders who have only minimal renal dysfunction usually experience increments in GFR during gestation, even though levels do not reach those seen in normal pregnant women. Thus, a decrement in serum creatinine level early in pregnancy is a good prognostic sign. If serum creatinine levels before conception exceed 1.4 mg per dL, decrements during gestation are less common, and, as noted, the prognosis of such pregnancies is more guarded. Finally, Table 13-6 summarizes fetal and maternal outcomes of 906 pregnancies in women with various primary glomerular disorders. Of importance, the data are mainly retrospective, reflecting an important need for prospective observational studies.

Renal lesion	Pregnancies	Spontaneous abortion	Perinatal loss	Preterm delivery	Renal function decrease		Hypertension	
					Reversible	Progressive	Reversible	Permanent
Focal glomerulosclerosis	95	1	25	32	13	5	32	10
Membranous glomerulopathy	110	12	4	35	3	1	32	1
Membranoproliferative	105	17	9	39	6	1	30	12
Immunoglobulin A nephropathy	160	5	15	32	12	1	35	12
Mesangial proliferative	126	5	12	9	2	1	36	7
Minor	106	6	12	29	6	1	27	9

From Jungers P, Houillier P. Pregnancy and renal disease: prediction for fetal and maternal outcome. Contrib Nephrol 1990;81:155–162. Modified with permission.

Table 13-6. Maternal and fetal outcomes (%) in 558 women with primary glomerulopathies

2. **Glomerulonephritis.** Absence of gravidas in large epidemiologic surveys of poststreptococcal glomerulonephritis is remarkable and has led to speculations that pregnancy protects women from this disease. However, this form of immune complex nephritis does occur rarely in gestation, in which it may mimic preeclampsia. Its prognosis is favorable, because in those instances in which the occurrence of acute poststreptococcal glomerulonephritis during gestation was properly documented, renal function recovered rapidly and the pregnancy usually had a successful outcome.

The prognosis of chronic glomerulonephritis during pregnancy is difficult to evaluate because most reported cases are poorly documented, especially the prepregnancy level of renal function and blood pressure. Still, it appears that if proteinuria or abnormal urinary sediment is the sole manifestation of the disease, pregnancy proceeds normally. Some authorities disagree, claiming that women with membranoproliferative glomerulonephritis and immunoglobulin A nephropathy are more prone to exacerbations during pregnancy, a view we do not share. Although C3 nephritic factor may pass from mother to fetus, the neonate appears unaffected, and maternal complement levels may actually rise during gestation.

Hereditary nephritis is an uncommon disorder that may first be manifested during pregnancy, when women with this disease develop frank nephrotic syndrome. A variety of hereditary nephritis accompanied by platelet abnormalities has been described. Pregnancy in these women has been successful from a renal standpoint, but their gestations have been complicated by bleeding problems.

3. **Collagen vascular disease**
   a. **Lupus nephritis.** The effect of gestation in women with lupus erythematosus who have renal involvement is difficult to evaluate, in part because of the unpredictable course of the disease regardless of pregnancy. Activity of the disease in the 6 months before conception is often a useful prognostic guide (the longer the remission, the better the outlook). Although most pregnancies in the presence of preserved function proceed uneventfully or are accompanied by only transient functional declines, in approximately 10%, gestation appears to cause permanent renal damage and to accelerate the renal disease. Also, placental transmission of maternal autoantibodies is associated with an increased frequency of spontaneous abortion in these women, and certain anticytoplasmic antibodies (especially SS-A/Ro) cause a neonatal lupus syndrome characterized by congenital heart block, transient cutaneous lesions, or both. Women with systemic lupus erythematosus have a high incidence of detectable levels of antiphospholipid antibodies (anticardiolipin antibodies, lupus anticoagulant). High titers of these antibodies are associated with several complications of pregnancy, including spontaneous fetal loss, hypertensive syndromes indistinguishable from preeclampsia, and thrombotic events including deep vein thrombosis, pulmonary embolus, myocardial infarction, and strokes. Also, pregnant women with circulating antiphospholipid antibodies can manifest a rare form of rapid renal failure postpartum, associated with glomerular thrombi. Thus, women with systemic lupus erythematosus should be screened for antiphospholipid antibodies early in gestation. The therapeutic approach when gravidas manifest antiphospholipid antibodies is disputed, and many would not treat asymptomatic patients who manifest low titers. However, when titers are elevated [more than 40 GPL (immunoglobulin G antiphospholipid level)], most authorities prescribe aspirin (80 to 325 mg per day). Heparin in combination with aspirin is recommended for patients with a history of thrombotic events.

      Previously, patients with lupus nephropathy were believed to be prone to relapse in the immediate puerperium, and some physicians still start or increase steroid treatment during and after delivery. Such views of “stormy puerperium” are now disputed, and most authorities institute or change therapy only if signs of increased or de novo disease activity appear.
   b. Pregnancy in patients with **periarteritis nodosa and scleroderma with renal involvement** appears to be disastrous, possibly due to the associated hypertension, which frequently becomes malignant in nature. Not only is fetal prognosis dismal, but most reported cases end in maternal death. Although such a poor prognosis partly reflects the selectivity of a handful of case reports, prudence dictates that pregnancies of gravidas with these diseases be terminated at an early stage until more is known about their natural history during pregnancy.
4. **Diabetes mellitus** is among the more common medical disorders encountered in the prenatal clinic. Many of the patients are juvenile (type I, insulin-dependent) diabetics, who probably harbor early microscopical changes in their kidneys. Nevertheless, most gestations in diabetic patients with normal renal function succeed, especially if blood glucose levels are maintained close to the normal range during the prenatal period. These diabetic women, however, have an increased prevalence of bacteriuria and an increased susceptibility to symptomatic infection during pregnancy. With these exceptions, such women rarely have complications, although they seem to have a higher incidence of preeclampsia.

   The effects of gestation in diabetic patients with overt nephropathy are similar to those in women with other forms of renal parenchymal disease. Patients with the mildest functional impairment have little trouble (although more than 50% experience third-trimester hypertension and increased proteinuria, the latter sometimes massive), whereas the presence of hypertension before conception imparts a poorer prognosis. Older reports of frequent deteriorations reflect experience from centers in which the gravidas were managed with stringent salt restriction and prophylactic diuretics. Without such restrictions, women with biopsy-proven diabetic nephropathy actually display increases in GFR during gestation.
5. **Nephrotic syndrome.** The most common cause of nephrotic-range proteinuria (more than 3.5 g per day) in late pregnancy is preeclampsia, a diagnosis that may be missed when diastolic pressures are between 85 and 95 mm Hg. The fetal prognosis in preeclampsia with heavy proteinuria is poorer than in other preeclamptic states, but maternal prognosis is similar. Most of the usual causes of nephrotic syndrome, including membranous nephropathy, proliferative or membranoproliferative glomerulonephritis, lipoid nephrosis (nil disease), diabetic nephropathy, amyloidosis, and focal glomerulosclerosis have been described in gravidas. Many of these conditions do not respond to corticosteroids, and some may be aggravated by them, underscoring the importance of establishing a tissue diagnosis before starting therapy.

   One should not confuse physiologic changes during gestation with the exacerbation of a disease causing the nephrotic syndrome; many women with a variety of nonnephrotic renal disorders develop heavy proteinuria when pregnant. Such increments in urinary protein may relate to the increased renal hemodynamics, alterations in the glomerular barrier, and possibly a rise in renal vein pressure. Other alterations in pregnancy that simulate symptoms accompanying nephrotic syndrome include decrements in serum albumin (approximately 0.5 to 1.0 g per dL), increments in the levels of cholesterol and other circulating lipids, and edema, which can occur at one time or another in up to 80% of normal gestations. Accordingly, an entity once termed *cyclic nephrotic syndrome of pregnancy* reflects instances of quiescent mild renal disease, which becomes more apparent during gestation.

   Management of nephrotic pregnant patients includes dietary replenishment of urine protein losses (in rare instances, gestation has been sustained until an appropriate delivery date using albumin infusions). Although restriction of dietary protein has been recommended in certain forms of nephrotic syndrome in nonpregnant patients and has led to decrements in the excretion of and increments in levels of circulating albumin, such therapy should not be attempted in gravid women, because it could be deleterious to fetal development. Diuretics should be avoided, if possible, because these women are already oligemic, and further intravascular volume depletion might impair uteroplacental perfusion. Also, because blood pressure normally declines during pregnancy, diuretics might provoke more ready circulatory collapse or thromboembolic episodes. Exceptions to this, however, are certain nephrotics who also manifest salt-sensitive hypertension (mainly women with diabetic nephropathy). In such cases, modest salt restriction, combined with the judicious use of diuretics, may avoid termination in the early third trimester because of poorly controlled blood pressure.

   Prognosis in most nephrotic gravidas with preserved function is good, but some claim that fetal outcome is poorer if full-blown nephrotic syndrome is already present very early in gestation. In addition, hypoalbuminemia may be associated with small-for-date newborns. One disease of varied (and often unknown) etiology whose natural history during gestation remains disputed is focal segmental glomerulosclerosis. Some claim pregnancy leads to irreversible functional loss and hypertension-sustained postpartum; others find the natural history of this entity in pregnancy similar to that of most other disorders.
6. **Tubulointerstitial disease**
   a. **Chronic pyelonephritis.** Dilation and stasis in the urinary tract make chronic pyelonephritis in gravidas more prone to exacerbation. These women should have a high fluid intake and should be told to rest frequently on their sides. Prognosis of pregnant women with noninfectious interstitial nephritis seems similar to that of pregnant women with glomerular disease. Renal function deterioration may occur rapidly in this group of patients when they are inadvertently salt restricted during gestation.
   b. **Reflux nephropathy.** Some authors believe that pregnancy adversely influences the course of reflux nephropathy. Others note that patients who do poorly have preexisting hypertension and moderate functional insufficiency. Obviously, the propensity for urinary tract infection in these patients demands close scrutiny during pregnancy, including frequent urine cultures and prompt treatment when signs of urinary tract infection appear.
   c. **Polycystic kidney disease** may remain undetected in gestation. Careful questioning of gravidas for a family history of renal problems and judicious use of ultrasonography may lead to its earlier detection. Patients with minimal functional impairment have few complications, but a greater propensity toward preeclampsia exists. They are also prone to urinary tract infections, and it may therefore be prudent to culture their urines more frequently. Hypertension usually accompanies or antedates the onset of functional deterioration, and pregnancy in such gravidas is more hazardous.

      Some women with polycystic kidney disease manifest cysts in their livers that may enlarge with repeated pregnancy as well as with oral contraceptive use. A high incidence of cerebral aneurysms also occurs in certain affected families. When aware of such family clustering, usually identified by a history of subarachnoid hemorrhages amongst relatives, the patient should undergo screening using magnetic resonance imaging. If an aneurysm is detected, neurosurgical consultation should be obtained, and the obstetrician may wish to avoid natural labor. All these patients should undergo genetic counseling before pregnancy to ensure they are aware that 50% of their offspring are at risk. Finally, predicting the fetal outcome using molecular probes and linkage analysis on cells cultured from the amniotic fluid is possible.
   d. **Solitary and pelvic kidneys.** Women with solitary kidneys appear to tolerate gestation well. However, if the nephrectomy was performed for nephrolithiasis or chronic pyelonephritis, the remaining kidney is often infected. Patients with these conditions must be carefully scrutinized by frequent

examination and culture of the urine throughout pregnancy and in the puerperium.

Pelvic kidneys are apparently associated with decreased fetal survival, often due to the presence of other malformations of the urogenital tract of the mother. In addition, dystocia may occur when the kidney is in the true pelvis.

e. **Urolithiasis and hematuria.** The prevalence of urolithiasis in gestation varies between 0.03% and 0.35% in the Western hemisphere; many of the stones contain calcium, and some are infective in origin. The older literature tended to stress the dramatic complications that occur when calculi cause obstructive uropathy and infection supervenes, but more recent reports, including one survey of 148 gestations in 78 nonselected stone formers, suggest that pregnancy has little influence on the course of stone disease (although women with renal calculi may have an increased incidence of spontaneous abortions). It should be noted that most of the reported series focus on women whose calculi are mainly of the noninfective variety, and little is known of the natural history of the more serious struvite stones during gestation. In any event, urinary tract infection in the presence of nephrolithiasis requires prompt and prolonged treatment (3 to 5 weeks), followed by suppressive therapy through the immediate puerperium, because the calculus may represent a nidus of infection resistant to sterilization.

   Experience with cystinuria in pregnancy is limited, but most women with this disease also do well in gestation. d-Penicillamine as used in these patients appears to have no apparent adverse effects on mother or fetus.

   Renal calculi are among the most common causes of abdominal pain (of nonobstetric origin) requiring hospitalization during gestation, and, when complications suggest the need for surgical intervention, pregnancy should not be a deterrent to pyelographic x-ray examination. If the stone obstructs the ureter, surgery may be necessary, and in this respect approximately 30% of patients described in the literature have undergone an operative procedure such as open lithotomy and percutaneous nephrostomy. Also, rigid ureteroscopy (direct vision) performed under general anesthesia has been used early in gestation. More recently, however, a less invasive technique, the placement of a stent, has made it possible to manage gravidas through gestation, deferring more definitive surgical procedures to the postpartum period.

   Spontaneous gross or microscopical hematuria occasionally complicates an otherwise uneventful gestation. The differential diagnosis includes all causes of hematuria in nongravid patients (see Chapter 8), but frequently no etiology is demonstrable and the bleeding subsides postpartum. It has been suggested that these events are due to the rupture of small veins around the dilatated renal pelvis. Hematuria may or may not occur in subsequent gestations. In any event, investigation of the hematuria can often be deferred until after delivery, and noninvasive techniques such as ultrasound and magnetic resonance imaging are helpful in arriving at such decisions.

E. **Renal transplantation**

1. **Fetal and maternal complications.** Several thousand pregnancies have been reported in allograft recipients. As expected, prognosis is better when the transplanted kidney comes from a living donor. Most (more than 90%) gestations allowed to proceed beyond the first trimester succeed, but both maternal and fetal complications, due in part to the immunosuppressive therapy, can be anticipated; these include steroid-induced hyperglycemia, severe hypertension, urinary tract infection, septicemia, ectopic pregnancy, and uterine rupture. Fetal problems such as intrauterine growth retardation, congenital anomalies, prematurity, hypoadrenalism, hepatic insufficiency, thrombocytopenia, and serious infection have been reported.
2. **Suggested criteria for pregnancy.** The following relative criteria for transplant recipients wishing conception are suggested.
   a. Good health and stable renal function for 2 years after transplantation
   b. Stature compatible with good obstetric outcome
   c. Absent or at most minimal proteinuria
   d. No or easily managed hypertension
   e. No evidence of pelvicalyceal distention on an excretory urogram performed before attempting pregnancy
   f. Serum creatinine of 2 mg per dL or less, preferably less than 1.4 mg per dL
   g. Drug therapy: prednisone, 15 mg per day or less; azathioprine, 2 mg per kg per day or less, cyclosporine, less than 5 mg per kg per day

   Published experience with cyclosporine use in pregnancy is still somewhat limited. A national transplant registry (U.S.) was established in 1991 at the Department of Surgery, Jefferson Medical College, Philadelphia. Initial data suggest that the caveat of creatinine below 1.5 mg per dL and the absence of hypertension at conception impart the best prognosis in cyclosporine recipients as well. Of concern, however, was that approximately 50% of the first 114 women registered had prepregnancy hypertension, which may underlie the finding that a similar percentage bore growth-retarded or small-for-gestational-age infants. Still, 96% of the gestations that continued beyond the first trimester succeeded.

   Cyclosporine levels may decrease during pregnancy. No information on whether or not drug dosage should be increased is available, but we advise maintenance of therapeutic levels.

   Experience with tacrolimus (FK506) and mycophenolate mofetil during pregnancy is limited. Tacrolimus has been associated with growth restriction, as well as hyperkalemia and even anuria in an infant. A recent survey of 25 infants born to liver transplant recipients reported neonatal hyperkalemia and renal insufficiency. Published experience with mycophenolate mofetil in pregnancy is extremely limited. This drug has been reported to be embryotoxic in animals.

F. **Dialysis.** Fertility is reduced in dialysis patients, and few women conceive once they have started dialysis. Most pregnancies occur during the first few years on dialysis. Although previously the outcomes of such pregnancies were poor, with only approximately 25% resulting in surviving infants, new information suggests that pregnancy in dialysis patients is successful as often as 30% to 50% of the time in pregnancies that reach the second trimester. Considerable problems exist in such pregnancies, however, and we do not encourage women on maintenance dialysis to conceive.

   The National Registry for Pregnancy in Dialysis Patients has reported 318 pregnancies in women on dialysis. Prematurity is common, and approximately 85% of infants born to women who conceive after starting dialysis are born before 36 weeks' gestation. More than one-third of the infants reported by the registry weighed less than 1,500 g at birth, and growth restriction was common. Maternal complications are also common, including accelerated hypertension, and an increased maternal mortality rate. Management of pregnant women on dialysis should include attempts to minimize the uremic environment. In women with chronic renal disease, prophylactic dialysis should be considered when renal function is poor. In women already on dialysis, treatment time should be increased to five to seven dialysis sessions per week, with minimal heparinization and slow ultrafiltration to avoid dialysis hypotension and volume contraction. If peritoneal dialysis is being used, decreasing exchange volumes and increasing exchange frequency is recommended. Adequate calorie and protein intake should be encouraged and supplemental vitamins prescribed. Antihypertensive therapy should be adjusted to be appropriate for pregnancy. Anemia should be corrected with iron, folic acid, and erythropoietin. Adequate calcium supplements should be administered, and metabolic acidosis should be prevented. No evidence exists to support the superiority of one dialysis modality over another with respect to pregnancy outcome.

IV. Hypertensive disorders of pregnancy

Hypertension during gestation remains a major cause of morbidity and death in both mother and child.

A. Of the many **classifications** proposed for hypertension complicating pregnancy, that of the Committee on Terminology of the American College of Obstetricians and Gynecologists (1972) has been the most useful. The National High Blood Pressure Education Program in the United States endorsed this system in 1990 and, at the time of this writing, is in the process of reevaluating the classification system. It is unlikely that major changes in the current system will be made. The four categories of hypertensive disorders in pregnancy are

1. **Preeclampsia.** Preeclampsia, characterized by hypertension, proteinuria, edema, and, at times, coagulation and liver function abnormalities, occurs in late pregnancy (after 20 weeks), primarily in nulliparas. Third-trimester hypertension is defined as a blood pressure of 140/90 mm Hg or greater (Korotkoff V) sustained for 4 to 6 hours. Also, increments over earlier systolic and diastolic pressures exceeding 30 and 15 mm Hg, respectively, are considered abnormal.

   Attempts have been made to categorize this disease as severe (e.g., diastolic and systolic pressures of 110 and 160 mm Hg or greater, heavy proteinuria, oliguria, and neurologic symptoms) or mild. Because a seemingly mild preeclamptic patient (e.g., a teenage gravida with a systolic blood pressure of 140/85 mm Hg and trace proteinuria) may suddenly convulse (in which case the disease is called *eclampsia*, a complication associated with maternal mortality), terms such as *mild* and *severe* may be misleading. Hypertension during late pregnancy in a nullipara, whether or not other signs are present, is sufficient reason to consider hospitalization and treatment as if the patient were potentially preeclamptic .
2. **Chronic hypertension.** Most women in this category have essential hypertension, but in some the elevated blood pressure is secondary to such conditions as renal artery stenosis, coarctation of the aorta, renal disease, primary aldosteronism, and pheochromocytoma. Evidence of arteriolar disease and knowledge that hypertension was present before conception or early in gestation is helpful in establishing a diagnosis. Cocaine abuse may masquerade as chronic hypertension in pregnancy. Pheochromocytoma has a catastrophic outcome during pregnancy; thus, measurement of urinary catecholamines or vanillylmandelic acid excretion should be considered in all hypertensive gravidas not previously evaluated.

3. **Chronic hypertension with superimposed preeclampsia.** Hypertensive women are at increased risk for the development of superimposed preeclampsia, and, when this occurs, maternal and fetal morbidity and mortality are greater than when preeclampsia develops in a previously normotensive woman. Most of the maternal deaths attributable to hypertensive disease occur in previously hypertensive women with superimposed preeclampsia.
4. **Late or transient hypertension.** This category includes a number of patients otherwise difficult to classify. Some women develop hypertension only in the last trimester or the immediate puerperium, but blood pressure normalizes postpartum. Among nulliparas, some patients may be preeclamptics who have not manifested other signs of the disease. (However, managing all such primigravidas as if they were preeclamptic is prudent.) Some gravidas develop hypertension in two or more pregnancies and become normotensive after delivery. Patients with transient hypertension probably represent women destined to develop essential hypertension later in life.

   The physician should be aware of two forms of hypertension that complicate the puerperium. One entity is called *late postpartum eclampsia* (hypertension and convulsions 48 hours to weeks after delivery). This disorder may be elicited by administration of bromocriptine, a drug prescribed to suppress lactation. The second entity is postpartum hypertension in normotensive gravidas, presenting 2 weeks to 6 months after delivery, with normalization by the end of year 1. Its etiology is poorly understood.

B. **Pathophysiology of preeclampsia.** Preeclampsia is more than a hypertensive disorder; it is a systemic disease whose manifestations affect many organ systems, including brain, liver, kidney, blood vessels, and placenta. Thus, while the focus may be on hypertension and proteinuria, we must always be aware that such signs and symptoms may be minimal while other, life-threatening syndromes develop, including convulsions and liver failure, both often associated with thrombocytopenia, as well as signs of DIC.

   The mediators of hypertension in preeclampsia are not clearly understood. Evidence suggests that vasoconstriction results from a complex interplay of hormonal and vascular alterations. With respect to hormonal factors, the renin-angiotensin system is stimulated in normal pregnancy and relatively suppressed in women with preeclampsia. However, preeclamptic patients are more sensitive to the pressor effects of angiotensin II, and therefore this pressor peptide may be playing a role in their elevated blood pressure. Aldosterone levels are also lower in preeclamptic women than in women with normal pregnancies, but they are still higher than nonpregnant levels. Considerable evidence suggests that alterations in eicosanoid metabolism play a role in the pathophysiology of preeclampsia. Manifestations such as increments in vascular reactivity and hypertension, as well as coagulopathy, have been attributed to an imbalance between vascular prostacyclin and platelet thromboxane synthesis, resulting in a relative or absolute prostacyclin deficiency and increased thromboxane-mediated vasoconstriction and platelet aggregation. In this respect, a number of observations have been reported in which blood levels, renal excretion, or placental production of prostacyclin has been lower, or levels of thromboxane higher, in preeclampsia. Earlier reports that low-dose aspirin appeared to prevent the development of preeclampsia lent additional support to the role of altered prostaglandin metabolism in this condition.

   More recent evidence suggests that alterations in vascular endothelial cell function are important features of the pathophysiology of preeclampsia. Endothelial cells produce a variety of substances important in modulating vascular tone and coagulation (e.g., nitric oxide, prostacyclin, and endothelin). Of interest, therefore, is preliminary evidence that vascular endothelial damage is present in preeclampsia and may occur months before overt disease. The ensuing compromise of endothelial cell function is postulated to cause vasoconstriction, platelet aggregation, and increased intravascular coagulation, and it is consistent with observations of altered prostaglandin metabolism in preeclampsia (as prostacyclin is produced by the endothelial cell).

   The ability to excrete sodium may be impaired in preeclampsia, but the degree to which this occurs varies, as severe disease can occur in the absence of edema (the “dry preeclamptic” patient). Even when edema is marked, plasma volume is below that for normal pregnancy, and hemoconcentration is often present. This latter phenomenon may relate to the development of a “leaky” vasculature (thus, hypoalbuminemia in this disease may have three components: renal protein loss, liver dysfunction, and extravasation from the intravascular to the interstitial space). A decrement or suboptimal increase in intravascular volume also appears to precede the onset of overt hypertension.

   Cardiac output is often decreased, and central venous and pulmonary capillary wedge pressures are normal or low. Thus, high blood pressure is maintained by a marked increase in peripheral resistance. The alterations in cardiac output, combined with the decrements in intravascular volume, and the fact that placental perfusion is decreased in preeclampsia are major reasons that most authorities discourage use of diuretics in this disease.

   In one variant of preeclampsia, HELLP, coagulation abnormalities and liver dysfunction predominate, whereas hypertension and proteinuria may be minimal. This syndrome is life threatening, as platelet counts may plunge far below 100 × 103 per mm ^{3}, whereas transaminase and lactic acid dehydrogenase levels rise above 1,000 units per L, and evidence of a marked microangiopathic hemolytic anemia appears on the peripheral blood smear, all in less than 24 hours. Early recognition of this HELLP variant and prompt termination of gestation are important, and such action avoids substantial maternal morbidity.

   The placenta may be critically involved in the genesis of preeclampsia, and failure of trophoblastic invasion of the uterine spiral arteries is one of the earliest changes in this disorder. Thus, these vessels are not transformed into the dilatated sacs seen with normal placentation, an aberration that may underlie the poor placental perfusion and growth retardation characteristic of preeclampsia. The reason for the failure of the trophoblast to invade the uterine spiral arteries is obscure, and it is currently the focus of considerable research relating to immunogenetic causes of preeclampsia.

   The pathogenesis of the eclamptic convulsion is also poorly understood. Vasospasm, ischemia, and local hemorrhage may all play a role. The importance of hypertension per se in the genesis of the seizures is debated, because convulsions may be observed in women whose blood pressure is only mildly elevated.

C. **Kidney function and morphology in preeclampsia**
   1. **GFR and RPF.** Both GFR and RPF decrease in preeclampsia. The decrements approximate 25% in most instances, so that the GFR of preeclamptic women often remains above pregravid values. However, in rare instances, large decreases in function may occur and, on occasion, lead to acute tubular or cortical necrosis.
   2. **Uric acid.** Changes occur in the renal handling of urate in preeclampsia. A decrease in the clearance of uric acid, accompanied by increments in blood levels of this solute, may occur weeks before any clinical signs of the disease appear. In pregnancy, serum urate levels above 4.5 mg per dL are suspect [to convert to SI units (µmol/L), multiply mg/dL by 59.48]. The level of hyperuricemia also correlates with the severity of the preeclamptic renal lesion, as well as with fetal outcome.
   3. Increased **proteinuria,** which may be moderate or heavy, is a feature of preeclampsia, and the diagnosis is suspect in its absence. The magnitude of proteinuria does not appear to affect maternal prognosis, but protein excretion in the nephrotic range is associated with greater fetal loss.
   4. **Calcium.** Studies have demonstrated that renal calcium handling is altered in preeclampsia, and that in contrast to normotensive gravidas, or those with chronic or transient hypertension, patients with preeclampsia demonstrate marked hypocalciuria. The basis for this abnormality is unknown.
   5. Preeclampsia is accompanied by a characteristic histologic lesion: **glomerular capillary endotheliosis** (Fig. 13-2). In women diagnosed clinically as preeclamptic, this lesion is present in only about 85% of biopsies obtained from primiparas and in considerably fewer biopsies from multiparas. The remainder of patients have evidence of nephrosclerosis or another parenchymal disease. Some claim that preeclampsia is a cause of focal glomerular sclerosis, but others (including the authors) believe preeclampsia lesions to be completely reversible, the presence of focal glomerular sclerosis reflecting preexisting nephrosclerosis or primary renal disease. Women with glomerular endotheliosis alone tend to have uneventful subsequent gestations, but when focal glomerular sclerosis or alterations in the renal vessels are present, hypertension is more likely to recur in later pregnancies.

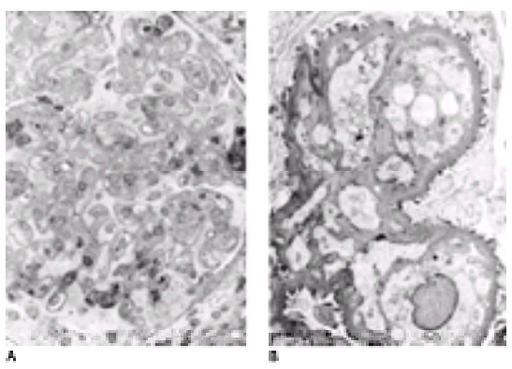
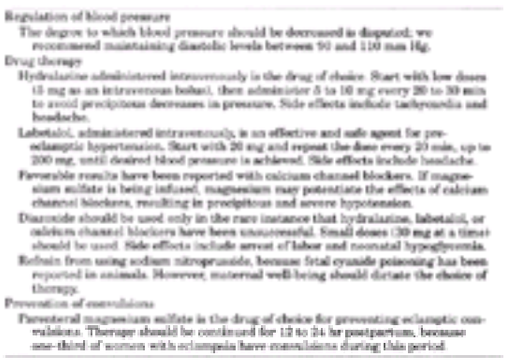


Figure 13-2. A: Electron micrograph demonstrating complete capillary obliteration by a swollen endothelial cell. Note, however, that the basement membrane is normal and the epithelial foot processes are intact. **B:** Micrograph showing glomerulus from a preeclamptic kidney. Swollen endothelial and mesangial cells that display prominent vacuolization encroach on the capillary lumina. (Courtesy of B. H. Spargo, M.D.)

D. **Management of preeclampsia**

1. **Hospitalization.** Ambulatory treatment is risky in the management of preeclampsia. Thus, suspicion of the disease is sufficient to consider hospitalization. Such an approach diminishes the frequency of convulsions and other consequences of diagnostic error. In general, fetal maturity is evaluated; if the gestation is near term, induction is the therapy of choice, whereas attempts to temporize are made if the pregnancy is at an earlier stage. Rest is an extremely important part of the therapeutic regimen, which must be prescribed rather than suggested. Termination of pregnancy should be considered when signs of impending eclampsia (e.g., hyperreflexia, headaches, epigastric pain) develop or persist; blood pressure cannot be controlled; serum creatinine, urea nitrogen, and uric acid rise; laboratory evidence suggests DIC or abnormal liver function (increased transaminases); or specific obstetric tests suggest fetal jeopardy. When signs of impending convulsions (eclampsia) are present, parenteral magnesium sulfate is the drug of choice.
2. **Treatment of hypertension.** The approach to treatment of high blood pressure in gravidas is disputed. As noted, morphologic examination of preeclamptic placentae demonstrates decreased trophoblastic invasion of the uterine spiral arteries, causing these vessels to be more constricted than normal. Thus, perfusion of the placenta is compromised. Therefore, we believe that reduction in maternal blood pressure decreases uteroplacental perfusion even further (i.e., poor autoregulation of uterine blood flow), and we caution against large decrements in the mother's mean pressure, especially in acute emergencies. Data on human pregnancy are limited, but they suggest that decrements in maternal pressure may indeed reduce placental perfusion. Others have argued that, based on evidence obtained from animal studies, uterine blood flow is autoregulated, and thus hypertension should be aggressively treated. Assuming that autoregulation of uterine blood flow exists, a critical but unanswered question is how quickly it takes place, because fetuses may be damaged by short periods of ischemia. In documented instances, precipitous decreases of pressure in response to diazoxide (even to diastolic levels above 85 mm Hg) were followed by immediate monitor signs of fetal distress. Thus, we prescribe the careful use of parenteral hydralazine or labetalol, in addition to close maternal scrutiny and fetal monitoring, when acute hypertension exceeds diastolic levels of 105 mm Hg (Table 13-7). This approach is successful in most gravidas. Calcium channel blockers have also been used to treat acute hypertension associated with preeclampsia. However, these agents should be considered only after hydralazine or labetalol has been unsuccessful, because anecdotal reports exist of precipitous decreases in blood pressure when calcium channel blockers have been used concomitantly with magnesium sulfate. Diazoxide can be used in rare resistant cases and should be administered only in small doses (30 mg at a time). Sodium nitroprusside should be avoided, because cyanide poisoning and fetal death have been observed in laboratory animals.



Regulation of blood pressure

The degree to which blood pressure should be decreased is disputed; we recommend maintaining diastolic levels between 90 and 100 mm Hg.

Drug therapy

Hydralazine administered intravenously is the drug of choice. Start with low doses (5 mg as an intravenous bolus), then administer 5 to 10 mg every 20 to 30 min to avoid precipitous decreases in pressure. Side effects include tachycardia and headache.

Labetalol, administered intravenously, is an effective and safe agent for pre-eclamptic hypertension. Start with 20 mg and repeat the dose every 10 min, up to 200 mg, until desired blood pressure is achieved. Side effects include headache.

Favorable results have been reported with calcium channel blockers. If magnesium sulfate is being infused, magnesium may potentiate the effects of calcium channel blockers, resulting in precipitous and severe hypotension.

Diazoxide should be used only in the rare instance that hydralazine, labetalol, or calcium channel blockers have been unsuccessful. Small doses (30 mg at a time) should be used. Side effects include arrest of labor and neonatal hyperglycemia.

Refrain from using sodium nitroprusside, because fetal cyanide poisoning has been reported in animals. However, maternal well-being should dictate the choice of therapy.

Prevention of convulsions

Parenteral magnesium sulfate is the drug of choice for preventing eclamptic convulsions. Therapy should be continued for 12 to 24 hr postpartum, because one-third of women with eclampsia have convulsions during this period.

Table 13-7. Guidelines for treating severe hypertension near term or during labor

3. **Treatment of the eclamptic convulsion.** A mistaken tendency to equate the eclamptic convulsion with hypertensive encephalopathy persists, although an eclamptic convulsion can arise in a seemingly stable patient manifesting only minimal blood pressure elevation. For this reason, many clinicians initiate prophylactic therapy when women with suspected preeclampsia are in labor, even if premonitory signs are absent. In the United States, parenterally administered magnesium sulfate is the drug of choice. (At the New York Hospital and at University of Chicago Lying-In Hospital, a loading dose of 4 g magnesium sulfate is infused over 15 minutes, followed by a sustaining infusion of 1 to 2 g per hour, aiming to achieve levels of 2 to 4 µmol per L.) Although in the past critics have claimed that this drug is ineffective because it is not an established anticonvulsant, two large clinical trials have demonstrated the superiority of magnesium sulfate compared with either phenytoin or diazepam. Whether prophylaxis is required remains to be established , because magnesium has not been compared with placebo in a large clinical trial. Nevertheless, standard practice in the United States is to administer magnesium routinely for prophylaxis.
4. **Prevention of preeclampsia.** Promising preliminary studies of small numbers of patients published in the mid-1980s suggested that low-dose aspirin (60 to 150 mg) prevented preeclampsia. The rationale for this approach was that platelet thromboxane A2 generation would be blocked, whereas vascular prostacyclin synthesis would be maintained, thus inhibiting platelet aggregation, an important step in the pathogenesis of preeclampsia. However, several large randomized, placebo-controlled multicenter trials have failed to identify a benefit of low-dose aspirin when prescribed to low-risk populations (primarily healthy nulliparas) or women with risk factors (e.g., patients with chronic hypertension, diabetic patients, women with multiple gestations, and women who manifested preeclampsia in a previous gestation).

   Another preventive strategy that has received considerable attention is calcium supplementation. Low calcium intake has been implicated in the pathogenesis of preeclampsia, and a trial of 1,094 nulliparous pregnant women, with several meta-analyses, suggested that calcium supplementation with 2 g of calcium carbonate daily can prevent preeclampsia. Again, a large National Institutes of Health multicenter randomized clinical trial of 4,589 women failed to support these earlier findings. However, subsequent trials conducted outside of the United States have continued to demonstrate a beneficial effect of calcium supplementation in the prevention of preeclampsia. A possible explanation for the discrepancy in these results is the dietary calcium intake in these populations. In the National Institutes of Health trial, the placebo and treated groups both had baseline calcium intake of more than 1,000 mg per day. In contrast, in those trials in which calcium was shown to be beneficial, the calcium intake in the population was well below the recommended dietary allowance for pregnancy. Thus, calcium supplementation may be beneficial in women with low calcium intake, but it may not be necessary if calcium intake is adequate.

   Other approaches to prevention, including fish oil, antioxidants, and magnesium, have not been successful. Nevertheless, although prevention of preeclampsia is not possible at present, avoidance of severe complications may be accomplished by early recognition of the disease before such complications develop. If early signs are detected, hospitalization should be strongly considered to permit close monitoring of the patient. If preeclampsia is detected early, bed rest and close monitoring of maternal and fetal condition may enable prolongation of pregnancy in some cases.

E. **The hypertensive patient without preeclampsia.** Increased risk is associated with pregnancy in women with chronic hypertension. Complications include superimposed preeclampsia, placental abruption, acute tubular and cortical necrosis, retardation of intrauterine growth, and midtrimester fetal death. Such events seem to correlate with the age of the gravida and the duration of her high blood pressure. Thus, the majority of these complications occur in women over the age of 30 or with evidence of end-organ damage. On the other hand, most women (approximately 85%) with essential hypertension have uncomplicated and successful gestations.

   Women with chronic hypertension often have reductions in blood pressure by midpregnancy, so that their blood pressure may not exceed that observed in normotensive pregnant women. The failure of this decrement to occur, or increases in blood pressure in early or midtrimester pregnancy, indicates a guarded prognosis for the gestation. Fetal outcome is poorer in hypertensive women with superimposed preeclampsia than in previously normotensive women with this complication, and the combination of chronic hypertension and preeclampsia seems responsible for most cases of cerebral hemorrhage in pregnancy. Patients with both conditions must be hospitalized and their hypertension controlled, but even with these precautions, most authorities consider delaying actions too risky and terminate the gestation.

F. **Antihypertensive therapy.** Whether mild degrees of hypertension during gestation should be treated is not generally agreed on. Although one group claimed that such therapy decreases the incidence of superimposed preeclampsia, most authorities would withhold treatment until diastolic levels are at least 15 mm Hg above borderline hypertension (defined in our clinics as 75 mm Hg in the second trimester and 85 mm Hg in late gestation). Very young gravidas, however, may require treatment at lower levels. Table 13-7 and Table 13-8 summarize current knowledge on the use of antihypertensive drugs in pregnancy. Only since the mid-1980s have serious efforts been undertaken to determine the safety and efficacy of these medications in pregnant women, and only a handful of these efforts have involved controlled trials. Future endeavors should increase the availability of this information.

Table 13-8. Antihypertensive drugs used to treat chronic hypertension in pregnancy

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Chapter 14 The Patient with Hypertension

Charles R. Nolan

Definition and classification of hypertension
Epidemiology of hypertension
Pathogenesis of hypertension
Clinical features of hypertension
Diagnostic evaluation of hypertension
Treatment of hypertension
Resistant hypertension
Evaluation of suspected renovascular hypertension
Treatment of hypertensive crises
Management of severe uncomplicated hypertension in the acute care setting

I. Definition and classification of hypertension The definition of hypertension is somewhat arbitrary, because blood pressure is not distributed bimodally in the population, making differences between normotensive and hypertensive groups unclear. Instead, the distribution of blood pressure readings in the population is unimodal, and an arbitrary level of blood pressure must be defined as the threshold above which hypertension can be diagnosed. The correlation between the levels of systolic blood pressure (SBP) and diastolic blood pressure (DBP) and cardiovascular risk has long been recognized. Increasing blood pressure clearly has an adverse effect on mortality over the entire range of recorded blood pressures, even those generally considered to be in the normal range. Lifespan and health are progressively reduced as blood pressure rises. The goal of identifying and treating high blood pressure is to reduce the risk of cardiovascular disease and associated morbidity and mortality. In this regard, classifying hypertension in adults is useful to identify high-risk individuals and to provide guidelines for follow-up and treatment of hypertension. The Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure has established criteria for the diagnosis and classification of blood pressure in adult patients. The optimal blood pressure in an individual who is not acutely ill is lower than 120/80 mm Hg. Normal blood pressure is defined as blood pressure lower than 130/85 mm Hg. High-normal blood pressure is in the range of 130–139/85–89 mm Hg. Though normotensive by definition, these patients should be rechecked annually to exclude the development of hypertension. Hypertension is arbitrarily defined as SBP of 140 mm Hg or greater or DBP of 90 mm Hg or greater, or by virtue of the patient taking antihypertensive medications. The stage of hypertension (1 through 3) is determined by the levels of both SBP and DBP (Table 14-1). This classification should be based on the average of two or more blood pressure readings at each of two or more visits after the initial blood pressure screening. When SBP and DBP fall into different categories, the higher category should be selected to classify the individual's blood pressure. Isolated systolic hypertension is defined as a SBP higher than or equal to 160 mm Hg with a DBP less than 90 mm Hg, and staged according to the level of SBP.

Table 14-1. Classification of blood pressure (BP) for adults [a,b]

A. **Risk stratification in hypertension.** The overall risk of cardiovascular morbidity and mortality in patients with hypertension is determined not only by the stage of hypertension, but also by the presence of other risk factors, such as smoking, hyperlipidemia, and diabetes, and by the existence of target-organ damage (TOD) or clinical cardiovascular disease (CCD) (Table 14-2). The empiric classification of hypertensive patients into risk groups based on risk factors, TOD, and CCD is used to guide therapeutic decision making. Patients in risk group A have no other risk factors and no TOD/CCD, whereas those in risk group B have at least one risk factor, not including diabetes, but no evidence of TOD/CCD. Risk group C includes all hypertensive patients with diabetes or with TOD or CCD (Table 14-3).

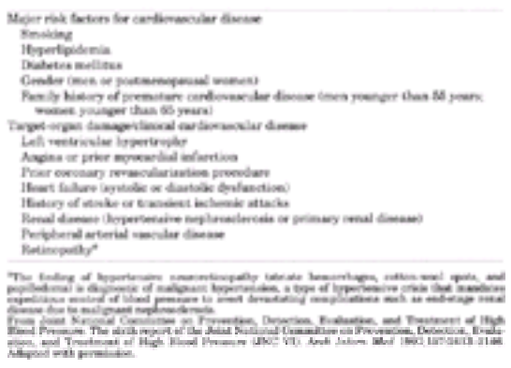

Table 14-2. Components of cardiovascular risk stratification in patients with hypertension

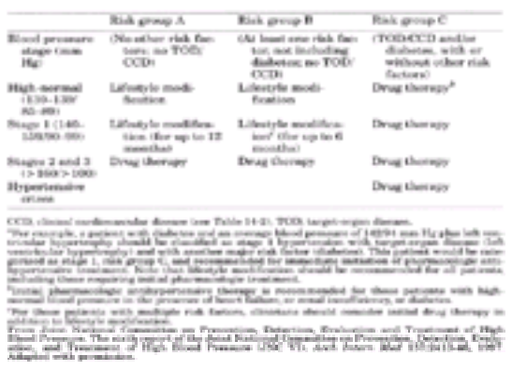

Table 14-3. Risk factor stratification and treatment guidelines [a]

B. **Benign versus malignant hypertension.** The classification of hypertension as benign or malignant is based on funduscopic examination (Table 14-4). The finding of hypertensive neuroretinopathy (HNR) is the clinical sine qua non for the diagnosis of malignant hypertension. In the absence of HNR, malignant hypertension cannot be diagnosed, regardless of the severity of the hypertension. HNR is defined by the presence of striate hemorrhages and cotton-wool spots

with or without papilledema. The clinical importance of the finding of HNR is that it signifies the presence of a systemic hypertensive vasculopathy with fibrinoid necrosis and obliterative Karteriopathy that, left untreated, will lead to end-stage renal failure or death within 1 year. But malignant hypertension is a relatively rare disorder, occurring in less than 1% of hypertensive patients. The term *benign hypertension* is clearly a misnomer, because although the clinical course is less dramatic and precipitous than that seen in patients with malignant hypertension, the eventual cerebrovascular and cardiovascular complications are quite devastating, and they represent a major cause of morbidity and mortality in the general population. In this regard, use of the term *nonmalignant hypertension* is probably more appropriate. Nonmalignant hypertension is defined based on the absence of HNR. Retinal arteriosclerosis and arteriosclerotic retinopathy (see Table 14-4), which are the characteristic funduscopic findings in nonmalignant hypertension, are of little clinical use, because they may be found in elderly normotensive individuals, and they have no predictive value with regard to the risk of cardiovascular or cerebrovascular complications.

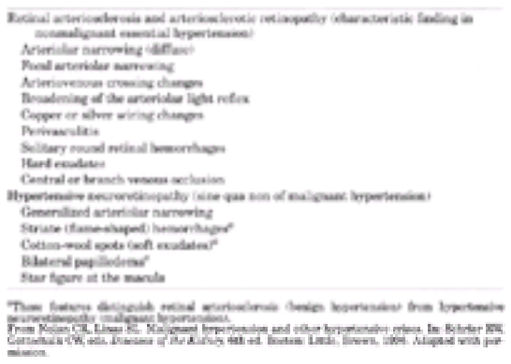

Table 14-4. Classification of hypertensive retinopathy

C. **Definition of hypertensive crises.** The vast majority of hypetensive patients are asymptomatic for many years until complications due to atherosclerosis, cerebrovascular disease, or congestive heart failure (CHF) supervene. In a minority of patients, this “benign” course is punctuated by a hypertensive crisis. A hypertensive crisis is defined as the turning point in the course of an illness at which acute management of the elevated blood pressure plays a decisive role in the eventual outcome. The haste with which the blood pressure must be controlled varies with the type of hypertensive crisis. However, the crucial role of hypertension in the disease process must be identified and a plan for management of the blood pressure successfully implemented if the patient's outcome is to be optimal. The absolute level of the blood pressure is clearly not the most important factor in determining the existence of a hypertensive crisis. For example, in children, pregnant women, and other previously normotensive individuals in whom mild to moderate hypertension develops suddenly, a hypertensive crisis can occur at a level of blood pressure that is normally well tolerated by adults with chronic hypertension. Furthermore, in adults with mild to moderate hypertension, a crisis can occur with the onset of acute end-organ dysfunction involving the heart or brain. The spectrum of hypertensive crises is outlined in Table 14-5.

Table 14-5. Clinical syndromes of severe hypertension

1. **Malignant hypertension** is a clinical syndrome characterized by marked elevation of blood pressure with widespread acute arteriolar injury (hypertensive vasculopathy). Funduscopy reveals HNR with flame-shaped hemorrhages, cotton-wool spots (soft exudates), and sometimes papilledema (Fig. 14-1). Regardless of the severity of blood pressure elevation, in the absence of HNR, malignant hypertension cannot be diagnosed. HNR is thus an extremely important clinical finding, indicating the presence of a hypertension-induced arteriolitis that may involve the kidneys, heart, and central nervous system. With malignant hypertension, a rapid and relentless progression to end-stage renal disease occurs if effective blood pressure control is not implemented. Mortality can result from acute hypertensive heart failure, intracerebral hemorrhage, hypertensive encephalopathy, or complications of uremia. Malignant hypertension represents a hyper tensive crisis; adequate control of blood pressure clearly prevents these morbid complications.

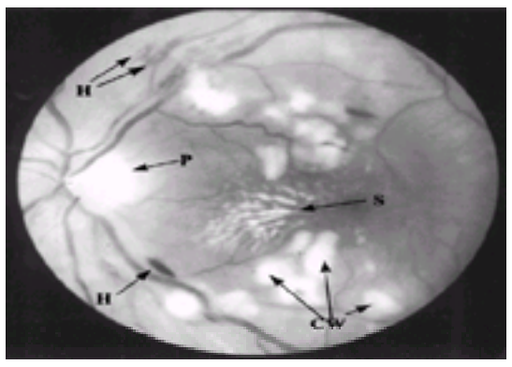

Figure 14-1. Hypertensive neuroretinopathy in malignant hypertension. Fundus photograph in a 30-year-old man with malignant hypertension demonstrates all of the characteristic features of hypertensive neuroretinopathy, including striate hemorrhages (H), cotton-wool spots (CW), papilledema (P), and a star figure at the macula (S).

2. **Hypertensive crises due to nonmalignant hypertension with acute complications.** Even in patients with nonmalignant hypertension, in whom HNR is absent, a hypertensive crisis may be diagnosed based on the presence of concomitant acute end-organ dysfunction. Hypertensive crises due to nonmalignant hypertension with acute complications include hypertension accompanied by hypertensive encephalopathy, acute hypertensive heart failure, acute aortic dissection, intracerebral hemorrhage, subarachnoid hemorrhage, severe head trauma, acute myocardial infarction or unstable angina, and active bleeding. Poorly controlled hypertension in a patient requiring surgery increases the risk of intraoperative cerebral or myocardial ischemia and postoperative acute renal failure. Severe postoperative hypertension, including post–coronary artery bypass hypertension and post–carotid endarterectomy hypertension, increases the risk of postoperative bleeding, hypertensive encephalopathy, pulmonary edema, and myocardial ischemia. The various catecholamine excess states can cause a hypertensive crisis with hypertensive encephalopathy or acute hypertensive heart failure. Preeclampsia and eclampsia represent hypertensive crises that are unique to pregnancy. Scleroderma renal crisis is a hypertensive crisis—failure to adequately control blood pressure with a regimen that includes an angiotensin-converting enzyme (ACE) inhibitor results in rapid irreversible loss of renal function. Hypertensive crises can also occur in quadriplegic patients due to autonomic hyperreflexia induced by bowel or bladder distention. The sudden onset of hypertension in this setting can lead to hypertensive encephalopathy or acute pulmonary edema.
3. **Hypertensive syndromes often misdiagnosed as hypertensive crises.** Notably, the finding of stage 3 hypertension (blood pressure higher than 180/110 mm Hg) does not necessarily imply the presence of a hypertensive crisis. In patients with severe uncomplicated hypertension (formerly known as *urgent hypertension*), in which severe hypertension is not accompanied by evidence of malignant hypertension or acute end-organ dysfunction, eventual complications due to stroke, myocardial infarction, or CHF tend to occur over a time frame of months to years rather than hours to days. Although long-term control of blood pressure can prevent these eventual complications, a hypertensive crisis cannot be diagnosed, because no evidence suggests that acute

reduction of blood pressure results in an improvement in short-term or long-term prognosis. Moreover, the presence of chronic hypertensive end-organ complications in a patient with stage 3 hypertension that is not accompanied by HNR (i.e., nonmalignant hypertension) does not imply the existence of a hypertensive crisis requiring rapid control of blood pressure.

II. Epidemiology of hypertension The prevalence of hypertension, defined as SBP greater than 140 mm Hg or DBP greater than 90 mm Hg, ranges from 20% to 30% of the entire adult population of the United States. The prevalence increases with advancing age, so that approximately one-third of patients in their fifties meet the criteria for hypertension or isolated systolic hypertension. Many hypertensive patients have a positive family history of parental hypertension. The mode of inheritance is complex and probably polygenic in most instances. Black men and women have a twofold higher prevalence of hypertension (30%) than white men and women (15%) in a sampling of almost 18,000 American adults aged 48 to 75 years in the National Health and Nutrition Examination Survey (NHANES). Prevalence appears to be equal in men and women in most surveys. Obese individuals have significantly more hypertension than thin individuals. In childhood, obesity is a major cause of hypertension. Proof of the significant relationship between body weight and blood pressure is found in the observation that blood pressure falls with weight reduction.

The intake of dietary salt (sodium chloride) has significant effects on blood pressure, especially in patients with other factors predisposing to the development of hypertension, such as advancing age, obesity, adult onset diabetes, positive family history of hypertension, black race, or underlying renal disease. Numerous epidemiologic studies have shown that the dietary intake of salt correlates with the average blood pressure in a population. Northern Japanese fisherman who ingest 450 mEq of sodium daily have a 40% prevalence of hypertension. In contrast, Alaskan Eskimos, and the Yanomamo Indians in Brazil and Venezuela, who have dietary intakes of 1 mEq of sodium daily, do not develop hypertension at any age. Intersalt, an international epidemiologic study, examined the relation between dietary sodium intake (based on 24-hour urinary sodium excretion) and blood pressure in more than 10,000 individuals aged 20 to 59 years from 52 countries around the world. The results demonstrate a significant correlation between median SBP and DBP and dietary sodium intake. These observations can be explained based on the role of abnormal renal sodium handling in the pathogenesis of hypertension, which is discussed in detail in section III. Therapeutic implications of these observations include dietary sodium restriction as part of nonpharmacologic therapy and the recommendation for use of thiazide diuretics as first-line drug therapy for the treatment of hypertension in most patients.

Despite the known cardiovascular risks of untreated hypertension, and the widespread availability of effective pharmacologic treatment, identification and effective control of hypertension remains a significant public health problem in the United States. From the 1976–1980 NHANES survey (NHANES II) to the 1988–1991 survey (NHANES III, phase 1), the percentage of hypertensive Americans who are aware that they have high blood pressure increased from 51% to 73%. Among persons with hypertension, the prevalence of treatment increased from 31% to 55% during the same time period. The number of persons with high blood pressure controlled to below 140/90 mm Hg increased from 10% in NHANES II to 29% in NHANES III. Alarmingly, more than 70% of patients with hypertension have inadequate control of their blood pressure. The continued high prevalence of hypertension and hypertension-related complications such as stroke, cardiovascular complications, heart failure, and endstage renal disease represents a major public health challenge.

III. Pathogenesis of hypertension Experiments with isolated, perfused kidneys demonstrate that the magnitude of urinary sodium excretion is a direct function of the renal arterial perfusion pressure. The level of perfusion pressure may alter sodium excretion by changing the peritubular hydrostatic pressure. Thus, an increase in perfusion pressure should increase peritubular hydrostatic pressure with a resultant decrease in sodium reabsorption. Micropuncture studies in the rat have shown an inverse relationship between renal perfusion pressure and proximal sodium reabsorption. It has been argued that if this pressure natriuresis mechanism was operating in a normal fashion, in the presence of hypertension, profound volume depletion would result. The fact that this does not occur suggests that in every hypertensive state, a shift in the pressure natriuresis curve must occur so that a higher perfusion pressure is required to achieve any given level of natriuresis. In this regard, this shift in the pressure natriuresis curve has been postulated to be actually a reflection of the underlying renal abnormality present in essential hypertension and virtually all secondary forms of hypertension. If a primary renal defect in natriuresis does exist in hypertension, then, to avert disaster due to persistent positive sodium balance with inexorable fluid accumulation, compensatory mechanisms must be invoked that restore sodium balance. These compensatory processes restore sodium balance and normal extracellular fluid volume but, in the process, cause systemic hypertension.

Guyton's hypothesis states that the most important and fundamental mechanism determining the long-term control of blood pressure is the renal fluid-volume feedback mechanism. In simple terms, this is the basic mechanism through which the kidneys regulate arterial pressure by altering renal excretion of sodium and water, thereby controlling circulatory volume and cardiac output. Changes in blood pressure, in turn, directly influence renal excretion of sodium and water, providing a negative feedback mechanism for control of extracellular fluid volume, cardiac output, and blood pressure. The hypothesis is that derangements in this renal fluid-volume pressure control mechanism are the fundamental cause of virtually all hypertensive states (Fig. 14-2). In every hypertensive state, an underlying abnormality exists in the intrinsic natriuretic capacity of the kidney, so that the daily salt intake cannot be excreted normally, and the development of hypertension is necessary to induce a pressure natriuresis that allows the kidney to excrete the daily salt intake. Normal sodium balance and extracellular fluid volume are maintained, but at the expense of systemic hypertension. The underlying cause for the abnormality in the natriuretic capacity depends on the etiology of hypertension. In essential hypertension, some underlying abnormality increases renal avidity for sodium. In patients with obesity and insulin resistance, hyperinsulinemia increases proximal tubular sodium reabsorption. Increased angiotensin II levels and sympathetic nervous system activity also enhance sodium reabsorption. Mineralocorticoids enhance distal tubular sodium reabsorption. Renal parencal disease causes nephron loss resulting in a natriuretic defect. Abnormalities in renal endothelin or nitric oxide levels may also impair natriuresis. To date, each of the genetic causes of hypertension that have been elucidated has been shown to relate to an abnormality of renal sodium handling. For example, Liddle's syndrome results from enhanced distal tubular sodium reabsorption due to an abnormality in sodium channels in the distal nephron. Cross-transplant experiments in hypertensive and normotensive rat stains validate the importance of the kidney in the pathogenesis of hypertension, because the presence or absence of hypertension is dependent on the donor source of the kidney. Guyton's hypothesis states that this decreased natriuretic capacity of the kidney initially leads to renal salt and water retention, extracellular fluid volume expansion, and increased cardiac output with hypertension. This phase of volume expansion and high cardiac output is short lived. In the setting of high cardiac output, autoregulatory vasoconstriction of each vascular bed matches the blood flow to the metabolic requirements of the tissues. This phenomenon of circulatory autoregulation leads to an increase in systemic vascular resistance (SVR). Thus, hypertension that was initially caused by high cardiac output becomes high-SVR hypertension.

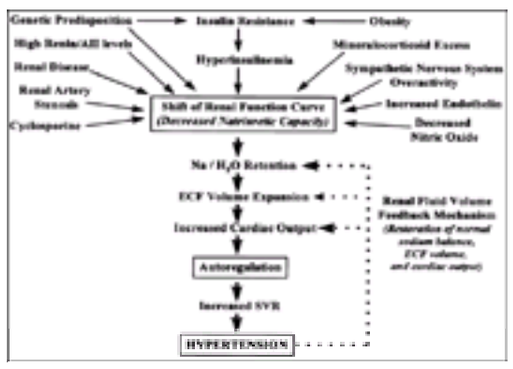

Figure 14-2. The Guyton hypothesis. In the setting of essential hypertension, primary renal disease, mineralocorticoid excess, or insulin resistance with hyperinsulinemia, a defect in the intrinsic natriuretic capacity of the kidney is present that prevents sodium balance from being maintained at a normal level of blood pressure. Initially, this impairment in natriuresis leads to increases in extracellular fluid (ECF) volume and cardiac output. This hemodynamic state is short lived, however. Circulatory auto-regulation occurs to maintain normal perfusion of the tissues, resulting in an increase in the systemic vascular resistance (SVR). The increase in SVR leads to systemic hypertension. With pressure-induced natriuresis, the renal fluid–volume feedback mechanism returns sodium balance, ECF volume, and cardiac output to normal. Systemic hypertension can be conceptualized as an essentially protective mechanism that prevents life-threatening fluid overload in the setting of reduced renal natriuretic capacity. Normal salt balance and fluid volume are maintained, but at the expense of systemic hypertension. (AII, angiotensin II.) (From Nolan CR, Schrier RW. The kidney in hypertension. In: Schrier RW, ed. *Renal and electrolyte disorders*, 5th ed. Philadelphia: Lippincott–Raven, 1997. Adapted with permission.)

The development of hypertension is a protective mechanism; it induces the kidney to undergo a pressure natriuresis and diuresis, thereby restoring normal salt balance and returning extracellular fluid volume to normal. This mechanism explains why an underlying problem with sodium excretion, as in salt-sensitive hypertension, is manifest as high-SVR hypertension without evidence of fluid overload. Support for this hypothesis is found in animal models of mineralocorticoid-induced hypertension. To substantiate the role of direct pressure–induced natriuresis in the regulation of sodium balance in mineralocorticoid hypertension, Hall and colleagues compared the systemic blood pressure and natriuretic effect of aldosterone infusion in a dog model in which the renal perfusion

pressure was either allowed to increase or mechanically servocontrolled to maintain renal artery pressure at normal levels. In the intact animal, continuous aldosterone infusion caused a transient period of sodium and water retention with a mild increase in blood pressure. However, the sodium retention lasted only a few days and was followed by an escape from the sodium-retaining effects of aldosterone and restoration of normal sodium balance. In contrast, when the renal perfusion pressure was servocontrolled during aldosterone infusion, no escape from aldosterone occurred, and there was a relentless increase in sodium and water retention accompanied by severe hypertension, edema, ascites, and CHF. When the servocontrol device was removed and the renal perfusion pressure was allowed to rise to the systemic level, a prompt natriuresis and diuresis ensued, with restoration of sodium balance and a fall in blood pressure. These observations highlight the pivotal role of blood pressure in the regulation of renal sodium and water excretion.

IV. Clinical features of hypertension

A. **Signs and symptoms.** Hypertension has been appropriately called the *silent killer*, because it is usually entirely asymptomatic for decades until cardiovascular, neurologic, or renal complications eventually develop. Thus, hypertension detection must begin with measurement of blood pressure at each health care encounter and in community-based screening programs. Headache is so common in the general population that the coexistence of hypertension and headache is usually fortuitous. In the rare patient with malignant hypertension, its onset may be signaled by a sudden change in visual acuity due to HNR or the sudden onset of polyuria and polydipsia due to a hypertension-induced spontaneous natriuresis and diuresis.

B. **Target organs.** The major target organs affected by hypertension are the heart, peripheral vasculature, central nervous system, the kidney, and the eye. Most of the consequences of hypertension are the result of progressive vascular injury. Hypertension accelerates atherosclerotic vascular disease and aggravates the deleterious effects of diabetes, smoking, and hyperlipidemia on the aorta and its major branches. Atherosclerotic disease results in significant morbidity from myocardial infarction, atherothrombotic cerebral infarction, peripheral vascular disease with claudication, and renal disease due to ischemia or cholesterol embolization. Hypertensive renal disease may result from hypertension-induced vasculitis in the setting of malignant hypertension or more insidious renal injury from long-standing essential hypertension with hypertensive nephrosclerosis. Hypertension is also an important cofactor in progression of other renal diseases, especially diabetic nephropathy. Hypertension may also cause cerebrovascular disease in the form of lacunar infarction or intracerebral hemorrhage. Left ventricular hypertrophy (LVH) and CHF, often due to isolated diastolic dysfunction, are the result of the heightened peripheral vascular resistance (afterload) imposed by systemic hypertension.

C. **Effect of hypertension on the incidence of cerebrovascular accidents.** The prospective study of 5,200 men and women conducted over three decades by Kannel and his coworkers in Framingham, Massachusetts, has provided valuable information regarding the relative risks of arterial hypertension. The risk of cerebrovascular accident correlates with increases in both SBP and DBP. Asymptomatic hypertension is associated with a fourfold increase in the risk of atherothrombotic brain infarcts compared to normotensive controls. Hypertension also increases the risk of the less common but more devastating types of stroke, such as intracerebral hemorrhage and subarachnoid hemorrhage.

D. **Effect of hypertension on the prevalence of CHF.** Framingham data also highlight the close relation between the prevalence of CHF and the presence of hypertension. CHF developed six times more frequently in hypertensive than in normotensive men and women. The risk of CHF correlated with both SBP and DBP. LVH was also directly related to blood pressure, and the prevalence of LVH increased ten- to 20-fold in hypertensive men and women aged 45 to 74 years.

E. **Effect of hypertension on coronary artery disease.** In the Framingham study, the age-adjusted annual incidence rates of coronary vascular disease, as manifested by angina pectoris, myocardial infarction, or sudden death, also increased progressively with increasing blood pressure. Diabetes, hyperlipidemia, and smoking are also well known to be very significant risk factors for cardiovascular disease. Consequently, the effect of antihypertensive therapy on cardiovascular mortality was less dramatic than its impact on stroke and CHF. Nonetheless, hypertension treatment trials such as the Systolic Hypertension in the Elderly Trial, the Medical Research Council Trial, and the Hypertension Detection and Follow-Up Program have confirmed the benefits of treatment of hypertension with regard to reduction of cardiovascular mortality.

F. **Effect of hypertension on renal function.** Malignant hypertension results in rapid decline in renal function with the development of end-stage renal disease within 1 year if adequate blood pressure control is not achieved. Renal injury in malignant nephrosclerosis results from hypertension-induced vascular injury with the development of fibrinoid necrosis and obliterative endarteropathy resulting in renal ischemia; malignant nephrosclerosis is preventable and potentially reversible if the hypertension is identified and adequately treated early in the course of the disease. Hypertension is clearly an important cofactor in the progression of other renal diseases, especially diabetes. In animal models of diabetes, with renovascular hypertension induced by a metallic clip applied to one renal artery, diabetic nephropathy develops only in the kidney exposed to systemic hypertension. The clipped kidney is protected from hypertension and fails to develop diabetic glomerulosclerosis. In patients, treatment of hypertension has been clearly shown to slow the progression of diabetic nephropathy. The frequency with which essential hypertension, in the absence of malignant hypertension, causes end-stage renal disease is the subject of considerable controversy. Among white patients, end-stage renal disease rarely results from essential hypertension with benign arteriolar nephrosclerosis. Indeed, in white patients with hypertension and renal insufficiency, the renal disease is more likely to be caused by underlying primary renal parenchymal disease, major renal artery atherosclerosis with ischemic nephropathy, or atheroembolic (cholesterol-embolic) renal disease. In contrast, evidence suggests that essential hypertension with benign arteriolar nephrosclerosis may be a common cause of end-stage renal disease among black patients. For unknown reasons, black hypertensive patients, especially men, have a sixfold increase in the risk of developing chronic renal failure due to hypertensive nephrosclerosis compared with their white counterparts. The reason for this racial disparity is unclear, but it cannot totally be explained by undiagnosed malignant hypertension or by lack of access to health care and inadequate blood pressure control. The availability of effective antihypertensive therapy over the past three decades has decreased the prevalence of stroke and CHF in blacks as well as whites, but it has failed to reduce the incidence of hypertensive end-stage renal disease.

V. Diagnostic evaluation of hypertension

Detection of hypertension begins with proper measurement of blood pressure at each health care encounter. Repeated blood pressure measurements are used to determine whether initial elevations persist and require prompt attention or have returned to normal values and require only periodic surveillance (Table 14-6). Blood pressure measurement should be standardized as follows: After at least 5 minutes of rest, the patient should be seated in a chair with the back supported and one arm bared and supported at heart level. The patient should refrain from smoking or ingesting caffeine for 30 minutes before the examination. For an appropriately sized cuff, the bladder should encircle at least 80% of the arm. Many patients require a large adult cuff. Measurements should ideally be taken with a mercury sphygmo-manometer. Alternatively, a recently calibrated aneroid manometer or a validated electronic device can be used. The first appearance of sound (phase 1) is used to define SBP. The disappearance of sound (phase 5) is used to define DBP. Measurement of blood pressure outside of the physician's office may provide some valuable information with regard to the diagnosis and treatment of hypertension. Self-measurement is useful in distinguishing sustained hypertension from white-coat hypertension, a condition in which the patient's blood pressure is consistently elevated in the clinician's office but normal at other times. Self-measurement may also be used to assess response to antihypertensive medications and as a tool to improve patient adherence to treatment. Ambulatory blood pressure monitoring is useful for the evaluation of suspected white-coat hypertension, patients with apparent drug resistance, hypotensive symptoms with antihypertensive medications, and episodic hypertension. However, ambulatory blood pressure measurement is not appropriate for the routine evaluation of patients with suspected hypertension. In elderly patients, the possibility of pseudohypertension should always be considered in the diagnostic evaluation of possible hypertension. Pseudo-hypertension is a condition in which indirect measurement of arterial pressure using a cuff sphygmomanometer is artificially high in comparison to direct intraarterial pressure measurement. Failure to recognize pseudo-hypertension can result in unwarranted and sometimes frankly dangerous treatment. Pseudohypertension can result from Monckeberg's medial calcification (a clinically benign form of arterial calcification) or advanced atherosclerosis with widespread calcification of intimal plaques. In these entities, stiffening of the arterial wall may prevent its collapse by externally applied pressure, resulting in artificially high indirect blood pressure readings affecting both systolic and diastolic measurements. The presence of a positive Osler's maneuver, in which the radial or brachial artery remains palpable despite being made pulseless by proximal inflation of a cuff above systolic pressure, is an important physical-examination finding that should suggest the diagnosis. Roentgenograms of the extremities frequently reveal calcified vessels. However, the diagnosis can only be made definitely by direct measurement of intraarterial pressure. Patients with pseudohypertension are often elderly and therefore may have critical limitation of blood flow to the brain or heart such that inappropriate blood pressure treatment may precipitate life-threatening ischemic events.

Blood pressure classification	Initial blood pressure (mm Hg)		Follow-up recommendation
	Systolic	Diastolic	
Normal	<130	<85	Recheck in 2 yr
High-normal	130–139	85–89	Recheck in 1 yr
Stage 1 hypertension	140–159	90–99	Confirm within 2 mo
Stage 2 hypertension	160–179	100–109	Evaluate or refer to source of care within 1 mo
Stage 3 hypertension	≥ 180	≥ 110	Evaluate or refer to source of care within 1 wk if hypertensive crisis is absent; refer to source of care immediately if hypertensive crisis is present

From Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. The sixth report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC VI). Arch Intern Med 1997;157:2413–2446. Adapted with permission.

Table 14-6. Recommendations for follow-up based on initial blood pressure measurements

A. **History and physical examination.** The initial evaluation of patients with documented hypertension should be designed to identify other cardiovascular risk factors and evidence of TOD or cardiovascular disease that affect the overall risks of hypertension and influence treatment decisions (see Table 14-3). Although the vast majority of hypertensive patients have essential (primary) hypertension without a clearly definable etiology, the initial evaluation is also designed to screen for the relatively rare secondary causes of hypertension that may be amenable to surgical intervention. A medical history should include information about prior blood pressure measurements to assess the duration of hypertension, and details about adverse effects from any prior antihypertensive therapy. History or symptoms of coronary heart disease, CHF, cerebrovascular disease, peripheral vascular disease, or renal disease should be carefully evaluated. Symptoms suggesting unusual secondary causes of hypertension should be queried, such as weakness (hyperaldosteronism) or episodic anxiety, headache, diaphoresis, and palpitations (pheochromocytoma). Information regarding other risk factors, such as diabetes, tobacco use, hyperlipidemia, physical activity, and any recent weight gain, should be obtained. Dietary assessment regarding the intake of salt, alcohol, and saturated fat is also important. Detailed information should be sought regarding all prescription and over-the-counter medication use, including herbal remedies and illicit drugs, some of which may raise blood pressure or interfere with the effectiveness of antihypertensive therapy. For example, nonsteroidal antiinflammatory drugs (NSAIDs) impair the response to virtually all antihypertensive agents and increase the risk of hyperkalemia or renal insufficiency with ACE inhibitor therapy. Cocaine, amphetamines, and anabolic steroids can raise blood pressure. A family history of hypertension, diabetes, premature cardiovascular disease, or renal disease should be sought. A psychosocial history is important to identify family situation, working conditions, employment status, educational level, and sexual dysfunction that may influence adherence to the antihypertensive treatment regimen.

   Physical examination should include measurement of height, weight, and waist circumference. Funduscopic examination is important to identify striate hemorrhages, cotton-wool spots, and papilledema, the characteristic findings of HNR, which are indicative of the presence of malignant hypertension. Documentation of the presence of arteriosclerotic retinopathy (e.g., arteriolar narrowing, arteriovenous crossing changes, changes in light reflexes) is less important, given its lack of prognostic significance with regard to the potential long-term cardiovascular complications of hypertension. Examination of the neck for carotid bruits, distended neck veins, and thyromegaly is important. Cardiac examination should include investigation for abnormalities of rate or rhythm, murmurs, and third or fourth heart sounds. The lungs should be examined for rales and evidence of bronchospasm. Abdominal examination should include auscultation for bruits (an epigastric bruit present in both systole and diastole suggests renal artery stenosis), abdominal or flank masses (polycystic kidney disease), or increased aortic pulsation (abdominal aortic aneurysm). Peripheral pulses should be examined for quality and bruits. The lower extremities should be examined for edema. A screening neurologic examination is used to identify prior cerebrovascular events.

B. **Laboratory tests and other diagnostic procedures.** Routine laboratory tests are recommended before the initiation of antihypertensive therapy to identify other risk factors and screen for the presence of TOD. These routine tests include blood chemistry (sodium, potassium, creatinine, fasting glucose), lipid profile (total cholesterol, low-density lipoprotein and high-density lipoprotein cholesterol), and complete blood cell count. A urinalysis is used to identify proteinuria or hematuria that would suggest the presence of underlying primary renal disease. A 12-lead electrocardiogram is used to identify left atrial enlargement, LVH, or prior myocardial infarction. Optional tests, depending on the clinical situation, include creatinine clearance, 24-hour urine protein or urine protein to creatinine ratio, serum uric acid, glycosylated hemoglobin, and thyroid function tests. A limited echocardiogram to identify the presence of LVH may be useful in selected patients to determine the clinical significance of labile hypertension.

C. **Screening for secondary causes of hypertension.** The majority of patients with hypertension have primary (essential) hypertension in which no clearly definable underlying etiology is apparent. Essential hypertension is most likely due to a variety of underlying conditions that lead to abnormalities in the renal handling of sodium. A wide variety of uncommon conditions can lead to so-called secondary hypertension, some of which are potentially amenable to surgical correction. Secondary causes of hypertension include underlying primary renal disease, primary hyperaldosteronism, pheochromocytoma, renovascular hypertension due to fibromuscular dysplasia or atherosclerotic renal artery stenosis, coarctation of the aorta, and Cushing's syndrome. Secondary causes of hypertension amenable to surgical intervention are so unusual that extensive diagnostic testing is unwarranted. The initial history, physical examination, and routine laboratory tests are usually all that is required to evaluate for the possibility of secondary hypertension. A normal serum creatinine and urinalysis are usually sufficient to exclude underlying renal disease as a secondary cause of hypertension. Examination for abdominal or flank masses is used to screen for polycystic kidney disease, which can be confirmed by ultrasound examination. Because most patients with primary hyperaldosteronism have unprovoked hypokalemia while they are not on diuretic therapy, measurement of serum potassium is a suitable screening test, and routine measurement of aldosterone levels is not necessary. Assessment for any delay or diminution of pulses in the lower extremities, or a discrepancy between arm and leg blood pressures can be used to screen for coarctation of the aorta. Careful assessment for a history of episodic hypertension, associated with headache, palpitations, diaphoresis, and pallor, is all that is usually required to screen for pheochromocytoma. Routine measurement of serum or urine catecholamines is not warranted. Likewise, evaluation for truncal obesity and abdominal purple striae is all that is usually required to screen for Cushing's syndrome, and therefore routine measurement of serum cortisol or cortisol suppression testing is unnecessary. Several tests are notably absent from the recommended list of routine screening tests for secondary hypertension. Hypertensive intravenous pyelography, renal scanning, captopril renography, and arterial digital subtraction angiography all lack sufficient specificity to be of any value as routine screening tests for renovascular hypertension. In this regard, the prevalence of renovascular hypertension in the general hypertensive population is so low that the predictive value of a positive test from any of these procedures when used as a general screening tests is abysmal. Some authoristies have recommended the routine measurement of plasma renin activity profiled against dietary sodium intake in all patients with hypertension. However, selection of initial antihypertensive therapy on the basis of renin profiling is impractical and expensive. Moreover, there is broad overlap in the response to antihypertensive agents regardless of renin levels, and even patients with low plasma renin activity may respond favorably to ACE inhibitors or angiotensin-receptor blockers.

VI. Treatment of hypertension

A. **Lifestyle modifications for treatment of hypertension.** Lifestyle modifications have been shown to be effective in reducing blood pressure, and they also help to address other cardiovascular risk factors. Patients should be encouraged to adopt the lifestyle modifications outlined in Table 14-7, especially if they have additional cardiovascular risk factors such as hyperlipidemia or diabetes. Even if antihypertensive drug treatment is required, these lifestyle changes should be recommended.

Weight loss for overweight individuals
Moderation of ethanol intake—no more than 30 mL (1 oz) of ethanol [e.g., 720 mL (24 oz) of beer, 300 mL (10 oz) of wine, or 60 mL (2 oz) of 100-proof whiskey per day]; for women and lighter-weight people, limit ethanol to 15 mL (0.5 oz) per day
Increase aerobic physical activity (30–45 min several times per week)
Reduce sodium intake to less than 100 mEq/d (2.4 g of sodium or 6 g of sodium chloride)
Maintain adequate intake of dietary potassium (more than 90 mEq/d)
Maintain adequate intake of dietary calcium and magnesium for general health
Stop smoking to reduce cardiovascular risk
Reduce intake of dietary saturated fat and cholesterol to reduce cardiovascular risk

Table 14-7. Lifestyle modifications for the treatment of hypertension

1. **Weight.** A body mass index [weight (kg) divided by height (m^2)] of 27 or greater is closely associated with increased blood pressure. A waist circumference of more than 85 cm (34 in.) in women or 98 cm (39 in.) in men has been associated with increased risk of hypertension, hyperlipidemia, insulin resistance with diabetes, and cardiovascular mortality. Modest weight reduction of as little as 4 kg (10 lb) significantly reduces blood pressure. Anoretic agents should be avoided, because they can raise blood pressure.
2. **Dietary sodium intake** in the form of sodium chloride (table salt) has a strong epidemiologic link to hypertension, as discussed in section II. Metaanalysis of clinical trials indicated that limitation of dietary sodium intake to 75 to 100 mEq per day lowers blood pressure over a period of several weeks to a few years. Restriction of sodium intake has been shown to reduce the need for antihypertensive medication, reduce diuretic-induced renal potassium wasting, lead to regression of LVH, and prevent renal stones through reduction in renal calcium excretion. Average American dietary sodium intake is in excess of 150 mEq per day, most of which (75%) is derived from processed foods. Moderation of sodium intake to a level of less than 100 mEq per day (2.4 g of sodium or 6 g of sodium chloride) is recommended for nonpharmacologic treatment of hypertension.
3. **Excessive intake of ethanol** is an important risk factor for high blood pressure, and it can lead to resistant hypertension. Ethanol intake should be limited to not more than 30 mL (1 oz) per day in men and 15 mL (0.5 oz) per day in women and lighter-weight men. This type of moderate ethanol intake may be associated with a reduction in risk of coronary heart disease.

4. **Diet and exercise.** Regular aerobic exercise can enhance weight loss and reduce the risk for cardiovascular disease and all-cause mortality. Inadequate potassium intake may increase blood pressure, whereas high dietary potassium intake may improve blood pressure control in patients with hypertension. An intake of 90 mEq per day in the form of fresh fruits and vegetables should be recommended. An increase in dietary calcium may lower blood pressure in some patients with hypertension, but the effect is negligible. Nonetheless, adequate calcium intake is recommended for general health and osteoporosis prophylaxis. Smoking cessation and reductions in dietary fat and cholesterol are also recommended to reduce overall cardiovascular risk. Although caffeine may acutely raise blood pressure, tolerance to this effect develops quickly. Most epidemiologic studies have found no direct relationship between caffeine intake and blood pressure.

B. **Pharmacologic treatment of hypertension.** The decision to treat hypertension with medications after the failure of lifestyle modifications to adequately control blood pressure or initially, as an adjunct to lifestyle modifications, is based on the severity (stage) of hypertension and an assessment of the risk of cardiovascular morbidity, given the presence of other risk factors and preexisting TOD or cardiovascular disease (see Table 14-3).

1. **Efficacy of antihypertensive drug therapy.** Reducing blood pressure with drugs clearly decreases cardiovascular morbidity and mortality regardless of age, gender, race, stage of hypertension, or socioeconomic status. Benefit has been demonstrated for stroke, coronary events, heart failure, progression of primary renal disease, prevention of progression to malignant hypertension, and all-cause mortality. In the 1960s, the Veterans Administration Cooperative Studies assessed the value of antihypertensive therapy (hydrochlorothiazide, reserpine, hydralazine) in a prospective, double-blind, placebo-controlled trial in 143 male hypertensive patients with DBP between 115 and 129 mm Hg. Whereas the placebo group experienced 27 morbid or fatal events, the treated group had only 2 morbid events and no deaths. The study was then extended to a larger group of patients with less severe hypertension and DBPs between 90 and 114 mm Hg. The estimated risk of a morbid event developing over a 5-year period was 55% in the placebo group and 18% in the antihypertensive treatment group. In this study, the benefit was most apparent in patients with moderate hypertension and DBP exceeding 105 mm Hg, whereas the benefit of blood pressure reduction was not clear in those patients with mild hypertension and DBP between 90 and 104 mm Hg. However, numerous more recent studies have confirmed the benefits of treating mild hypertension (stage 1 hypertension). In the Hypertension Detection and Follow-Up Program Trial, of the 10,940 subjects enrolled, 70% had DBP between 90 and 104 mm Hg at entry. Total mortality was reduced by 20% in the group treated by the study investigators with a stepped-care approach using thiazide diuretics and beta blockers compared to control patients in the referred-care group, who were treated by their primary physician and had less rigorous blood pressure control with medications. In a subgroup of high-risk patients with end-organ damage present at enrollment, the stepped-care patients had a 30% reduction in mortality. Several more recent studies, including the Australian National Blood Pressure Study, the Medical Research Council Trial, the European Working Party on Hypertension in the Elderly Trial, and the Medical Research Council Trial, have confirmed the benefits of drug treatment of hypertension. The benefits of antihypertensive drug treatment have been extended to isolated systolic hypertension (DBP lower than 90 mm Hg with SBP higher than 160 mm Hg). The Systolic Hypertension in the Elderly Program Trial demonstrated a 36% reduction in total stroke and a 27% decrease in myocardial infarction in subjects in the treatment group (diuretics and beta blockers) compared with individuals randomized to the placebo group. Metaanalysis of all randomized, placebo-controlled trials in hypertension verify a significant risk reduction with regard to the development of stroke, coronary heart disease, CHF, cardiovascular mortality, and total mortality (Fig. 14-3).

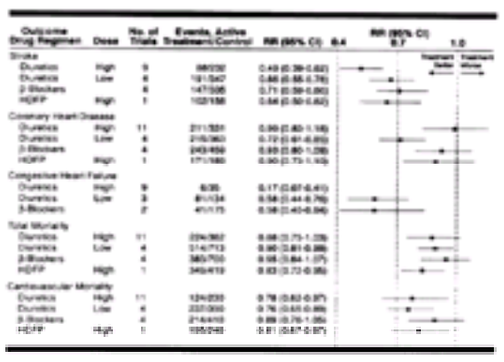

Figure 14-3. Metaanalysis of randomized, placebo-controlled clinical trials in hypertension. Studies are grouped according to first-line antihypertensive drug used and the outcome variable of interest. Number of trials indicates those studied with regard to a given endpoint. For these comparisons, the numbers of participants randomized to active treatment and placebo, respectively, were 7,768 and 12,075 for high-dose diuretic therapy, 4,305 and 5,116 for low-dose diuretic therapy, and 6,736 and 12,147 for beta-blocker therapy. Diuretics and beta blockers have been evaluated in 18 long-term randomized trials. Compared with placebo, beta-blocker therapy was effective in preventing stroke and congestive heart failure. The findings were similar for high-dose diuretic therapy with regard to stroke, congestive heart failure, and cardiovascular mortality. Low-dose diuretic prevented not only stroke and congestive heart failure, but also coronary disease and total mortality. The Hypertension Detection and Follow-Up Program (HDFP) was not a placebo-controlled trial. Patients (*n* = 10,940) were randomized to stepped-care treatment by the study investigators with high-dose diuretics and beta blockers or referred back to their primary care physician for administration of less intensive antihypertensive therapy. Stepped-care therapy was effective in preventing stroke, congestive heart failure, cardiovascular mortality, and total mortality. Similar outcome data for angiotensin-converting enzyme inhibitors or calcium channel blockers are not yet available. A relative risk (RR) less than 1 implies that active treatment was better than control. RR higher than 1 indicates that active treatment outcome was worse than control. If the 95% confidence interval (95% CI) does not overlap 1, the treatment effect is statistically significant. (From Psaty BM, Smith NL, Siscovick DS, et al. Health outcomes associated with antihypertensive therapies used as first-line agents. A systematic review and meta-analysis. *JAMA* 1997;277:739–745. Reprinted with permission.)

2. **Choice of initial antihypertensive agent.** Virtually all of the published trials demonstrating improved morbidity and mortality with antihypertensive drug therapy have used traditional first-line antihypertensive therapy with thiazide diuretics, beta blockers, or both. For this reason, the Sixth Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC VI) continues to recommend thiazide diuretics or beta blockers as first-line therapeutic agents for the treatment of essential hypertension. In certain comorbid conditions, an alternative agent may be recommended as first-line antihypertensive therapy, such as ACE inhibitors in patients with diabetic nephropathy. ACE inhibitors, calcium channel blockers, alpha $_1$-receptor blockers, and combined alpha-beta blockers decrease arterial blood pressure to a similar degree as diuretics and beta blockers do. Large-scale trials, designed to assess the efficacy of these newer agents with regard to reducing morbidity and mortality in comparison to traditional first-line therapy, are in progress but not yet complete. The Antihypertensive and Lipid Lowering Treatment to Prevent Heart Attack Trial (ALLHAT), a randomized, double-blind trial in 40,000 high-risk hypertensive patients, is designed to determine whether the combined incidence of fatal coronary heart disease and nonfatal myocardial infarction differs between patients randomized to diuretic (chlorthalidone) treatment and each of three alternative treatments; a calcium antagonist (amlodipine), an ACE inhibitor (lisinopril), and an alpha blocker (doxazosin). ALLHAT is designed to address the question of whether newer potential first-line antihypertensive agents are as good or better than diuretics in reducing coronary heart disease incidence and progression.
3. **Diuretics for the treatment of hypertension.** Thiazide and thiazidelike agents are the diuretics of choice for the treatment of hypertension. Diuretics are quite cost-effective; a 3-month supply of a generic drug should not cost the patient more than a few dollars. Low-dose therapy is recommended with drugs such as hydrochlorothiazide (12.5 to 50.0 mg per day) or chlorthalidone (12.5 to 50.0 mg per day). Related sulfonamide drugs such as chlorothiazide, quinethazone, and metolazone are equipotent and can be used interchangeably. Surprisingly, the more potent loop diuretics such as furosemide, bumetanide, torsemide, and ethacrynic acid are not as effective as thiazide diuretics for blood pressure control. Nonetheless, these more potent diuretics may be required in patients with renal impairment or refractory edema and in patients requiring treatment with the potent vasodilator minoxidil, which causes tremendous renal salt and water retention that cannot be effectively controlled with thiazide diuretics. In these circumstances, adequate diuresis often requires twice-daily or more frequent administration of the short-acting loop diuretics. The potassium-sparing diuretics, amiloride, triamterene, and spironolactone, should be used only in the minority of patients who develop significant hypokalemia (less than 3 mEq per L) due to thiazide-induced kaliuresis. The expected hypotensive effect of thiazide diuretics used as monotherapy should be in the range of 20 mm Hg systolic and 10 mm Hg diastolic. A sodium intake of more than 100 mEq per day reduces the efficacy of diuretic therapy. Diuretic therapy potentiates the antihypertensive effect of most other antihypertensive drugs. For this reason, the drug treatment algorithm outlined in JNC VI (Fig. 14-4) recommends addition of diuretic as a second-step agent if blood pressure is inadequately controlled with any other drug chosen as a first-line agent. The mechanism of action of thiazide diuretics is to block sodium reabsorption by inhibiting the thiazide-sensitive sodium chloride cotransporter in the distal tubule. However, the sustained antihypertensive effect of thiazides is mediated through a reduction in SVR rather than through volume depletion and a reduction of cardiac output, as one might predict. In fact, thiazides do not cause a large, sustained decrease in intravascular volume or sodium balance when used for the treatment of hypertension. Within a few days to weeks of the initiation of therapy with thiazide diuretics, salt balance returns toward normal, and total-body sodium and intravascular volume returns toward pretreatment levels. This seeming paradox can be understood in the context of Guyton's hypothesis regarding the pathogenesis of hypertension, whereby the development of systemic hypertension is conceptualized as an essential protective mechanism to maintain normal fluid volume in various disease states in which an underlying renal impairment exists with regard to excreting the daily sodium load at a normal blood pressure (see Fig. 14-2). In this context, diuretics lower blood pressure by addressing the primary renal defect in salt excretion, so that systemic hypertension (high SVR) is no longer a prerequisite for maintaining sodium balance.

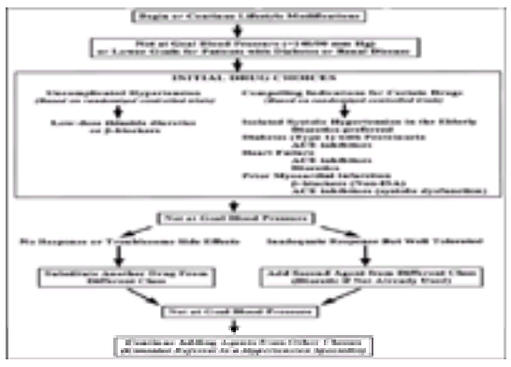

Figure 14-4. Algorithm for treatment of hypertension. (ACE, angiotensin-converting enzyme; ISA, intrinsic sympathomimetic activity.) (From Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. The sixth report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC VI). *Arch Intern Med* 1997;157:2413–2446. Adapted with permission.)

The potential adverse effects of diuretic therapy have been significantly overstated, in part due to promotion of the use of the newer, more expensive generations of antihypertensive agents. At the higher doses used in the early antihypertensive trials (Veterans Administration Cooperative trials, Hypertension Detection and Follow-Up Program), thiazide diuretics caused a modest short-term (less than 1 year) increase in the levels of total cholesterol, triglycerides, and low-density lipoprotein cholesterol. However, the use of low-dose thiazide diuretics for the treatment of hypertension as currently recommended does not result in dyslipidemia. Although dyslipidemia is commonly present in hypertensive patients before the initiation of drug treatment, it is not a contraindication to the use of low-dose diuretic therapy. An additional concern has been expressed that thiazide treatment of essential hypertension may increase the risk of diabetes. However, a study using the New Jersey Medicaid Registry that compared the incidence of new-onset diabetes (new prescription of insulin or oral hypoglycemic agent) with the use of various antihypertensive agents used as monotherapy has demonstrated the converse. Indeed, thiazide diuretic use was no more likely to be associated with new onset diabetes than was the use of ACE inhibitor, calcium channel blocker, or selective alpha-blocker monotherapy. Moreover, low-dose diuretic use is not contraindicated in patients with diabetes. Indeed, in the Systolic Hypertension in the Elderly Trial, patients with diabetes who were treated with diuretics and beta blockers experienced a greater reduction in coronary heart disease and total cardiovascular events than patients with systolic hypertension without diabetes. Another erroneous assertion made about thiazide diuretic use for the treatment of hypertension is that LVH persists despite control of blood pressure because chronic volume depletion leads to activation of the renin-angiotensin and sympathetic nervous systems, which provides trophic stimuli to the heart and prevents regression of LVH. In reality, the Treatment of Mild Hypertension Study, which compared diuretic and various newer antihypertensive drugs as monotherapy, demonstrated that all antihypertensive drugs, including diuretics, led to a regression of LVH (assessed by echocardiography) when compared with placebo. Asymptomatic mild diuretic-induced hypokalemia (3.0 to 3.5 mEq per L) usually does not require treatment unless the patient is receiving treatment with digitalis or has serious underlying cardiovascular disease. In uncomplicated hypertension, if the serum potassium decreases to below 3 mEq per L, potassium-sparing diuretics or potassium supplements should be used, and consideration should be given to evaluating the patient for primary hyperaldosteronism. In patients with underlying coronary artery disease, the serum potassium should be maintained above 3.5 mEq per L. Asymptomatic hyperuricemia may develop in patients treated with diuretics. No specific treatment is required for hyperuricemia unless crystal-proven gout develops.

4. **Beta blockers for the treatment of hypertension.** Beta-adrenergic receptor blockers are effective as monotherapy for hypertension in 60% to 70% of patients with stage 1 or stage 2 hypertension. The mechanism of their antihypertensive effect is primarily in the central nervous system and secondarily by a decrease in cardiac output and plasma renin activity. Beta blockers are also useful in combination therapy with direct-acting arteriolar vasodilators such as hydralazine and minoxidil, in that they mitigate the reflex increase in heart rate induced by vasodilatation. The major side effects of beta blockers include fatigue, bronchospasm, cold extremities, disturbing dreams, depression, and sexual dysfunction. In general, beta blockers are contraindicated in asthma, obstructive lung disease, heart block, and labile diabetes. Metoprolol, atenolol, and acebutolol in low doses may be safer for use in patients with bronchospasm, because they have a relative specificity for the cardiac and central nervous system beta $_1$-receptors. In the past, severe heart failure was listed as a strict contraindication to the use of beta-blocker therapy; however, more recently, beta blockers have become accepted therapy in selected patients with heart failure. Even though beta blockers may mask hypoglycemic symptoms and prolong hypoglycemia, they have been shown to decrease cardiovascular mortality in hypertensive patients with diabetes. Although beta blockers may increase levels of plasma triglycerides and reduce levels of high-density lipoprotein cholesterol, they nonetheless have been shown to reduce the rate of sudden death, overall mortality, and recurrent myocardial infarction in patients with previous myocardial infarction.
5. **ACE inhibitors in the treatment of hypertension.** ACE inhibitors selectively block the conversion of angiotensin I to angiotensin II. Inhibition of the formation of the potent vasoconstrictor angiotensin II decreases SVR. However, ACE inhibitors are also effective in patients with low-renin forms of hypertension. The antihypertensive effect of ACE inhibitors may be mediated in part by their beneficial effects on renal sodium handling. Angiotensin II directly stimulates sodium reabsorption in the proximal tubule. Glomerular and peritubular hemodynamic changes induced by angiotensin II also favor sodium reabsorption. Angiotensin II–induced increases in aldosterone mediate distal tubular sodium reabsorption. Thus, ACE inhibitors have a modest diuretic effect that may explain some of their antihypertensive action. Nonetheless, addition of a diuretic improves the antihypertensive response to ACE inhibition.

   ACE inhibitors have been shown to provide beneficial effects in patients with heart failure from systolic dysfunction. They may also be useful after myocardial infarction, especially in patients with left ventricular systolic dysfunction, to prevent subsequent heart failure and mortality. The Appropriate Blood Pressure Control in Diabetes Trial compared an ACE inhibitor (enalapril) with a long-acting calcium channel blocker (nisoldipine) as first-line antihypertensive therapy in terms of prevention and slowing the progression of the complications of type II diabetes. Among 470 hypertensive patients, the incidence of fatal and nonfatal myocardial infarction was significantly higher in the group treated with nisoldipine (*n* = 25) than among those treated with enalapril (*n* = 5). Comparison with morbidity and mortality data from prior studies suggests that the observed difference may have resulted from a beneficial effect of the ACE inhibitor rather than a deleterious effect of the calcium channel blocker. LVH is a well-recognized complication of hypertension, and it is a powerful independent risk factor for cardiovascular disease. Metaanalyses suggest that ACE inhibitors may be more efficacious than other first-line antihypertensives in reducing left ventricular mass.

   ACE inhibitors have also been shown to have a beneficial effect in slowing the progression of diabetic nephropathy as well as nondiabetic renal disease. In the setting of adequate blood pressure control, ACE inhibitors seem to have a beneficial effect on slowing progression of renal disease that is independent of their antihypertensive effect. This may be due to a reduction in glomerular capillary hypertension mediated by a decrease in efferent arteriolar tone or by mitigation of the adverse effects of angiotensin II on mesangial hypertrophy and glomerulosclerosis. Thus, patients with hypertension who have renal insufficiency should receive, unless it is contraindicated, an ACE inhibitor.

   The beneficial effects of ACE inhibitors are demonstrated in the setting of adequate blood pressure control; in this regard, ACE inhibitors alone may not be adequate to control blood pressure, and in most cases other agents, such as a diuretic, must be added to obtain ideal blood pressure control and slow the progression of renal disease. In patients with significant renal insufficiency (creatinine higher than 3 mg per dL) or diabetes with underlying hyporenin-hypoaldosteronism, ACE inhibitors should be used with caution because of the risk of life-threatening hyperkalemia due to inhibition of aldosterone production. In patients treated with ACE inhibitors who are euvolemic, a sustained rise in creatinine of more than 1 mg per dL over baseline should raise clinical suspicion for the presence of bilateral renal artery stenosis with ischemic nephropathy, because decreased angiotensin II effect interferes with autoregulation of glomerular filtration in conditions associated with decreased renal perfusion. In this setting, ACE inhibitors or angiotensin receptor blockers should be discontinued, because they can markedly decrease renal perfusion and exacerbate renal injury in patients with bilateral renal artery stenosis or renal artery stenosis affecting a solitary kidney.

   The most common adverse effect of ACE inhibitors is the development of a troublesome, dry, hacking cough, which may occur in up to 20% of patients and generally subsides dramatically within 4 days after discontinuation of therapy. The recently introduced angiotensin II receptor blockers produce hemodynamic effects similar to those of ACE inhibitors while avoiding the adverse effect of cough. However, in the absence of data documenting long-term cardiac and renal protection in hypertensive patients, angiotensin II receptor blocker should be reserved primarily for patients in whom ACE inhibitors are indicated, but who are unable to tolerate them because of cough.
6. **Treatment of hypertension with calcium channel blockers.** Calcium channel blockers selectively inhibit calcium entry into vascular smooth muscle cells

and therefore reduce SVR and blood pressure. These agents are effective antihypertensive drugs when used either as monotherapy or in combination treatment. They are particularly effective in older patients and black patients. Common adverse effects include headache, flushing, and lower extremity edema for dihydropyridines (nifedipine, amlodipine, felodipine, isradipine, nisoldipine, nicardipine, nitrendipine), and constipation, bradycardia, and heart block for nondihydropyridines (verapamil and diltiazem). Gingival hypertrophy can occur with all calcium channel blockers. In the Systolic Hypertension in Europe Study, nitrendipine treatment, with the addition of ACE inhibitor (enalapril) and hydrochlorothiazide if needed, significantly reduced the incidence of stroke, cardiovascular endpoints, and cardiovascular mortality in comparison with placebo. All-cause mortality was not significantly different. A provocative case-control study of the risk of myocardial infarction associated with antihypertensive drug therapies has ignited a firestorm of controversy regarding the long-term safety of short-acting calcium channel blockers for the treatment of hypertension. Compared with patients treated with diuretics alone, the adjusted relative risk for myocardial infarction was increased by approximately 60% among patients treated with calcium channel blockers with or without diuretics (relative risk, 1.62; 95% confidence interval, 1.21 to 2.04). Moreover, the use of calcium channel blockers compared with beta blockers was associated with a 60% increase in the adjusted risk of myocardial infarction (relative risk, 1.57; 95% confidence interval, 1.21 to 2.04). A dose-response metaanalysis of 16 randomized secondary prevention trials of nifedipine suggest that use of nifedipine was associated with a significant adverse effect on total mortality (relative risk, 1.16; 95% confidence interval, 1.1. to 1.33). A significant effect of the daily dose of nifedipine on mortality was apparent; for daily doses of 30 to 50, 60, and 80 mg, the relative risks were 1.06 (95% confidence interval, 0.089 to 1.270); 1.18 (95% confidence interval, 0.93 to 1.50); and 2.83 (95% confidence interval, 1.35 to 5.93), respectively. Initially, these alarming results were thought to be restricted to treatment with short-acting calcium channel blockers such as capsular nifedipine, rather than the sustained-release nifedipine and other longer-acting calcium channel blocker preparations. However, trials in the late 1990s suggest that the excess cardiovascular risk seen in hypertensive patients treated with calcium channel blockers may not be restricted to the short-acting class of calcium channel blockers. Studies in hypertensive patients with type II diabetes have raised concerns about the longer-acting calcium channel blockers as well. In the Fosinopril Amlodipine Cardiovascular Events Trial, 380 patients with hypertension and type II diabetes were randomized to fosinopril (ACE inhibitor) or amlodipine (long-acting calcium channel blocker). The patients randomized to fosinopril were significantly less likely to experience adverse cardiovascular outcomes, including acute myocardial infarction, hospitalized angina, or stroke, than those randomized to amlodipine (relative risk, 0.49; 95% confidence interval, 0.26 to 0.95). In the Appropriate Blood Pressure Control in Diabetes Trial, of 470 patients with hypertension and type II diabetes, the group randomized to long-acting nisoldipine (calcium channel blocker) had an adjusted sevenfold increased risk for acute myocardial infarction compared with those randomized to enalapril (ACE inhibitor) (relative risk, 7; 95% confidence interval, 2.3 to 21.4). In the multicenter Isradipine Diuretic Atherosclerosis Study, patients with hypertension and abnormal hemoglobin A_1C who were randomized to isradipine (calcium channel blocker) had a threefold increased risk for major cardiovascular events compared with those randomized to hydrochlorothiazide (relative risk, 2.81; 95% confidence interval, 1.09 to 7.26). Therefore, evidence is emerging that ACE inhibitors and low-dose diuretics may be more effective than calcium channel blockers for prevention of cardiovascular events among hypertensive patients with diabetes or impaired glucose control. Ongoing large-scale clinical trials such as ALLHAT are under way to assess the effect of various antihypertensive therapies, including long-acting calcium channel blockers, on several important cardiovascular endpoints. Until the results of these trials become available, diuretics and beta blockers should remain the first-line drug therapy for the vast majority of patients with hypertension. Calcium channel blockers may be indicated as second- or third-step agents in patients whose blood pressure is difficult to control. In the setting of true hypertensive crises, discussed in section **I.C**, use of sublingual or oral nifedipine is not recommended because of its unpredictable response and the potential for sustained overshoot hypotension. Moreover, nifedipine should not be used for the treatment of severe uncomplicated hypertension in the acute care setting.

7. **Treatment of hypertension with postsynaptic alpha$_1$-adrenergic receptor blockers.** Alpha$_1$-receptor blockers such as prazosin, doxbazosin, and terazosin lower blood pressure by dilatating arteriolar resistance vessels. The major adverse effect of this class of drugs is orthostatic hypotension, which can be problematic in the treatment of elderly individuals who are at risk for falls and of diabetic patients with underlying autonomic neuropathy. These drugs have gained widespread acceptance for medical management of prostatic hypertrophy to improve bladder emptying. With regard to the treatment of hypertension, much has been made of the potential benefits of the drugs on lipid profiles, because they tend to reduce total cholesterol and increase high-density lipoprotein cholesterol, and thereby decrease the total cholesterol to high-density lipoprotein ratio. However, to date no trials are available to verify that these drugs have the same beneficial effect on morbidity and mortality that is observed with use of diuretics and beta blockers for first-line therapy of hypertension.
8. **Treatment of hypertension with centrally-acting alpha$_2$-adrenergic receptor agonists.** Clonidine, guanabenz, guanfacine, and methyldopa exert their antihypertensive effects primarily by stimulating central alpha $_2$-receptors, resulting in a reduction in central sympathetic tone with a consequent decrease in peripheral resistance and heart rate. These drugs are generally not used as first-line therapy for hypertension because of their tendency to cause pseudotolerance due to renal salt and water retention. Adverse effects of this class of drugs include somnolence, dry mouth, dizziness, constipation, and fatigue. Methyldopa can also cause hepatic toxicity and a Coombs'-positive hemolytic anemia. In some patients, especially those with renal insufficiency or those treated with concomitant beta-blocker therapy, abrupt discontinuation of these drugs can lead to a withdrawal syndrome with rebound sympathetic overactivity manifest by headache, tachycardia, diaphoresis, tremor, restlessness, and sometimes profound hypertension. Consequently, these drugs should be used with caution in patients with a history of noncompliance with drug treatment. These drugs have no role in the treatment of true hypertensive crises; the hypotensive response is unpredictable, and the sedation they produce interferes with assessment of the patient's mental status. Moreover, oral clonidine loading is no longer recommended for the treatment of severe uncomplicated hypertension in the acute care setting.
9. **Treatment of hypertension with direct-acting arteriolar vasodilators.** Hydralazine and minoxidil are potent direct-acting peripheral vasodilators that lower blood pressure by reducing SVR. In the treatment of hypertension, these drugs must always be used as part of a triple-drug regimen that includes a beta blocker to prevent reflex tachycardia and a diuretic to prevent the reflex renal salt and water retention that occurs in response to vasodilation. Failure to adequately control tachycardia and fluid retention often lead to development of pseudotolerance to the hypotensive effect of these drugs. Hydralazine should always be tried before minoxidil is used. Concomitant diuretic therapy with low-dose thiazide diuretics is usually adequate in hydralazine-treated patients unless significant renal insufficiency is present. Hydralazine should be used on a twice-daily dosing schedule, starting at a dose of 50 mg per day and increasing to a maximum of 200 mg per day. Doses above this range are associated with increased risk of drug-induced lupus syndrome. Other potential adverse effects include headache, palpitations, and tachycardia, especially if beta blockade is inadequate. Parenteral hydralazine has no role in treatment of hypertensive crisis, given its unpredictable effect and the risk of overshoot hypotension. Moreover, reflex tachycardia may induce myocardial ischemia. Parenteral hydralazine is absolutely contraindicated in patients with aortic dissection, because the increased inotropic effect results in propagation of the dissection, but it is still a useful drug for the treatment of hypertensive crises in pregnancy. Minoxidil is a much more potent peripheral vasodilator that is useful for treatment of severe or resistant hypertension. It must always be used as part of a triple-therapy regimen in conjunction with beta blockers and potent loop diuretics. Thiazide diuretics cannot control the impressive renal salt and water retention induced by minoxidil. The most common side effect of minoxidil is tremendous fluid retention, which is a frequent occurrence if salt restriction and diuretic therapy are inadequate. After initial control of blood pressure, minoxidil-treated patients often present days to weeks later with anasarca, ascites, pleural effusions, pericardial effusions, and sometimes frank CHF. Thus, after initiation of minoxidil therapy, frequent (once- or twice-weekly) outpatient follow-up is required until the dose of loop diuretic required to prevent fluid retention can be defined. The use of minoxidil in patients with nephrotic syndrome due to diabetic nephropathy or other primary renal diseases is difficult, because diuretic resistance becomes even more problematic and difficult to manage.

C. **Hypertension treatment goals.** The goal of treatment of hypertension is to reduce morbidity and mortality by achieving and maintaining SBP below 140 mm Hg and DBP below 90 mm Hg, while controlling other treatable risk factors for cardiovascular disease such as hyperlipidemia, diabetes, and tobacco use. The goal of treatment in older patients should be the same as in younger patients, to reduce blood pressure below 140/90 mm Hg if at all possible, although an interim goal of an SBP lower than 160 mm Hg may be necessary in patients with marked systolic hypertension. In older individuals, any reduction in blood pressure appears to confer benefit; however, the closer the blood pressure is to normal, the greater the benefit. In patients with hypertension and diabetes, the goal blood pressure should be 130/85 mm Hg. Some but not all studies have suggested that lowering DBP too much in patients with coronary artery disease may increase the risk for coronary events by lowering diastolic perfusion pressure in the coronary circulation, the so-called J-curve hypothesis. A logistic regression model suggested that, compared with a treated DBP of 85 mm Hg, a pressure of 80 mm Hg was associated with a small increase in cardiac risk (relative risk, 1.2; 95% confidence interval, 1.2 to 2.1), whereas DBP treated to 70 mm Hg was associated with a more than twofold increase in the risk of primary cardiac arrest (relative risk, 2.3; 95% confidence interval, 1.4 to 3.8). These data form the basis for recommending a DBP treatment goal of 85 mm Hg. In patients with renal disease and hypertension, a blood pressure goal of 130/85 mm Hg has been recommended. In patients with proteinuria exceeding 1 g per 24 hours, an even more aggressive goal of 125/75 mm Hg has been suggested, based on the results of the Modification of Diet in Renal Disease Study. With regard to slowing the progression of underlying renal disease in hypertensive patients, the most important factor is reduction of the blood pressure to the goal level. All classes of antihypertensive drugs are effective in slowing disease progression. In fact, in most patients with renal insufficiency, multiple antihypertensive drugs in combination are required to obtain adequate control. As discussed in section **VI.B.5**, the inclusion of an ACE inhibitor in the antihypertensive regimen may provide Ladditional benefits with regard to slowing progressive renal deterioration.

D. **Algorithm for treatment of hypertension.** When the decision has been made to begin antihypertensive therapy, initial drug therapy should begin with a diuretic or beta blocker, given that numerous randomized controlled trials have demonstrated a reduction in cardiovascular morbidity and mortality with these agents (see Fig. 14-4). In the setting of certain comorbid conditions, compelling reasons for choosing a certain first-line agent may exist based on the results of randomized controlled trials. Thus, low-dose thiazide diuretics are the preferred treatment for isolated systolic hypertension in the elderly. In hypertensive patients with type 1 diabetes and proteinuria (diabetic nephropathy), treatment with ACE inhibitors is indicated to slow progressive renal dysfunction. In patients with heart failure (systolic dysfunction), ACE inhibitor or diuretic therapy is indicated. In hypertensive patients with a history of myocardial infarction, beta-blocker therapy is advantageous. ACE inhibitors may be indicated after myocardial infarction if concomitant heart failure due to systolic dysfunction is present. In

nondiabetic patients with renal insufficiency, an ACE inhibitor may be useful for first-line antihypertensive therapy, although other agents, especially diuretics, are often required to adequately control blood pressure.

Therapy for most patients (uncomplicated hypertension, stages 1 and 2) should begin with the lowest possible dose of the selected drug to prevent adverse effects from too great or too abrupt a reduction in blood pressure. If blood pressure remains uncontrolled after 1 to 2 months, the next dosage level should be prescribed. It may take many months to control hypertension adequately while avoiding adverse effects of therapy. Most antihypertensive medications can be given on a once-daily basis, and this should be the goal, to improve patient adherence. Home or office blood pressure measurements can be obtained in the early morning before patients have taken their daily dose of medication, to ensure adequate modulation of the surge in blood pressure after arising. Measurements in the late afternoon or evening can be used to monitor adequate control across the day. The blood pressure treatment goals for out-of-office measurements should be lower than those based on office measurements; readings of 130/85 mm Hg or higher should be considered to be elevated.

If the response to the initial drug choice is inadequate after reaching the full dose, two options for subsequent therapy should be considered (see Fig. 14-4). If the patient is tolerating the first choice well, a second drug from another class may be added. On the other hand, if the patient is experiencing significant adverse effects or no response, an agent from another class should be substituted. In either case, if a diuretic was not chosen as the first drug, it is usually indicated as a second-step agent, because its addition enhances the effects of agents from other classes. If addition of a second agent leads to adequate control of blood pressure, an attempt to withdraw the first agent should be considered. If hypertension persists despite treatment with two antihypertensive agents, a third drug of another class may be added.

In older persons, drugs that exaggerate postural blood pressure changes (peripheral alpha-adrenergic blockers and high-dose diuretics) or drugs that can cause cognitive dysfunction (central alpha$_2$-agonists) should be avoided. Therapeutic options for patients with hypertension that is difficult to control include classical triple therapy (diuretic plus beta blocker plus hydralazine); diuretic plus ACE inhibitor plus calcium channel blocker; diuretic plus beta blocker plus alpha$_1$-receptor blocker; or diuretic plus beta blocker plus dihydropyridine calcium channel blocker. Before proceeding to each successive step, clinicians should consider possible reasons for lack of responsiveness to therapy. Failure to include a thiazide diuretic in the regimen is a common reason for lack of adequate blood pressure control. Poor adherence to antihypertensive therapy remains a major therapeutic challenge contributing to the lack of adequate control in more than two-thirds of patients with hypertension. Other causes of resistant hypertension are discussed in section **VII**.If blood pressure control remains inadequate after these treatment measures have been implemented, referral to a hypertension specialist should be considered. Use of minoxidil as part of a triple-drug regimen in conjunction with a loop diuretic and a beta blocker should only be undertaken by hypertension specialists.

The treatment approach to high-risk patients, those with stage 3 hypertension or those in risk group C, should follow the same algorithm (see Fig. 14-4). However, some modification may be required. Drug treatment should begin with minimal delay without an initial trial of nonpharmacologic therapy. Although some patients respond to monotherapy, adding a second or third drug after a much shorter interval is often necessary if control is not achieved. In patients with very severe hypertension, it may be necessary to initiate treatment with more than one agent simultaneously. The treatment of hypertensive crises is discussed in detail in section IX.

VII. Resistant hypertension is diagnosed when the blood pressure cannot be reduced below the target of 140/90 mm Hg in response to an adequate triple-drug regimen that includes a diuretic, with all three drugs prescribed in near-maximum doses. For older patients with isolated systolic hypertension, resistance is defined as failure of this type of regimen to reduce SBP to less than 160 mm Hg. The various causes of resistant hypertension are outlined in Table 14-8.

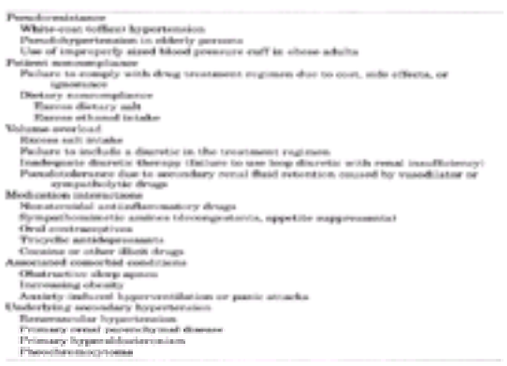

Table 14-8. Causes of resistant hypertension

White-coat (office) hypertension should be considered when patients are thought to be adherent to a well-designed antihypertensive regimen but still do not appear to have adequate control of blood pressure. In these patients, office readings are substantially above those obtained on home blood pressure measurements. Pseudohypertension due to noncompressible arteries should be considered in elderly patients and confirmed with Osler's maneuver. Use of a regular cuff on a very large obese arm may also produce falsely elevated blood pressure readings.

The most common cause of true resistant hypertension is patient noncompliance, which can be minimized by prescribing a drug treatment regimen that minimizes side effects and expense and emphasizes patient education. Lack of instruction about or lack of adherence to a low sodium diet (80 to 90 mEq per day) is a very common cause of resistant hypertension. Ethanol intake of more than 1 oz (30 ml) day can elevate blood pressure and lead to resistant hypertension. Obstructive sleep apnea can also cause resistant hypertension, and this diagnosis should be considered in obese patients with daytime hypersomnolence and headache. A sleep study can be used to confirm the diagnosis, and appropriate therapy can lead to weight loss and improvement in blood pressure control.

In compliant patients, one of the most common reasons for inadequate control of blood pressure is volume overload due to inadequate diuretic therapy, resulting in the development of pseudotolerance to the effect of other antihypertensive agents. Pseudotolerance is most commonly seen with the use of direct-acting vasodilators or sympatholytic agents and is unusual with beta blockers and ACE inhibitors. This is why resistant hypertension cannot be diagnosed until a diuretic has been included in the drug treatment regimen. Other causes of so-called physician-related resistant hypertension include use of drug combinations at less than optimal dosage, use of illogical drug combinations, or use of thiazide diuretics instead of loop diuretics in patients with moderate to severe renal impairment. Adverse drug interactions are often the cause of resistant hypertension. In this regard, NSAIDs are frequent offenders, especially given their over-the-counter availability and widespread use. Although NSAIDs have no effect on blood pressure in normotensive persons or untreated hypertensive patients, their administration blunts the depressor response to virtually all antihypertensive drugs. The increment in blood pressure caused by NSAIDs in treated hypertensive patients is variable but can be as large as 25 to 30 mm Hg. Oral contraceptives, sympathomimetic amines, and tricyclic antidepressants can also interfere with the response to antihypertensive agents. Another infrequent but commonly considered cause of resistant hypertension is the presence of an occult underlying secondary cause of hypertension, such as renal artery stenosis with renovascular hypertension.

VIII. Evaluation of suspected renovascular hypertension The principal cause of renal artery stenosis is atheromatous narrowing of one or both main renal arteries. Atheromatous renal artery stenosis occurs in older individuals, with a peak incidence in the sixth decade. Men are affected twice as often as women. It is most often found in association with diffuse atherosclerotic disease of the aorta, coronary arteries, cerebral arteries, and peripheral vasculature. A second type of arterial lesion, of obscure etiology, that affects the main renal artery is fibromuscular dysplasia (hyperplasia). The lesion appears as a multifocal “string-of-beads,” beginning in the middle of the renal artery and often extending into peripheral branches. This variant is typically seen in young to middle-aged females. The risk of progression to total arterial occlusion is small. Although renovascular hypertension due to renal artery stenosis is the most common cause of potentially remediable secondary hypertension, available estimates suggest that less than 0.5% of the hypertensive population has renovascular hypertension. Thus, an aggressive approach to screening for this disorder is often not warranted, and sound clinical judgment is essential in the selection of patients in whom an aggressive evaluation for renovascular hypertension is indicated.

Certain clinical clues suggest the possibility of underlying renovascular hypertension. The onset of hypertension before the age of 30 years should suggest secondary hypertension. A truly abrupt onset of hypertension at any age suggests renal vascular disease. However, more often than not, this finding represents newly diagnosed

essential hypertension rather than recently developed secondary hypertension. A definite worsening of previously well-controlled hypertension should suggest renovascular hypertension. Clues on physical examination include the finding on funduscopy of striate hemorrhages, cotton-wool spots or papilledema (malignant hypertension), or a continuous systolic and diastolic epigastric bruit. Even in the presence of diffuse atherosclerotic disease, aggressive evaluation for renovascular hypertension is only indicated if the blood pressure is truly resistant (higher than 150/100 mm Hg) to a rational triple-drug regimen that includes a diuretic. Unexplained deterioration of renal function despite adequate blood pressure control suggests the possibility of ischemic nephropathy and should prompt a search for bilateral renal artery stenosis with ischemic nephropathy. Deterioration of renal function on the addition of an ACE inhibitor suggests the possibility of bilateral renal artery stenosis or stenosis of a solitary kidney. This phenomenon probably reflects maintenance of glomerular filtration rate in the ischemic kidneys by angiotensin II–mediated vasoconstriction of the efferent arteriole to increase filtration fraction.

In the patient in whom the probability of renovascular hypertension is high, the conventional screening tests are of little value, because the predictive value of a negative test is low. In this setting, many clinicians proceed immediately to renal angiography, which allows for a definitive diagnosis of renal artery stenosis. It is important to note that selective renal angiography carries definite risks, including contrast media–associated nephrotoxicity and renal atheroembolic disease. Furthermore, anatomic renal artery stenosis does not always imply functional renovascular hypertension. Incidental renal artery stenosis can clearly occur in essential hypertension. Selective renal vein renin determinations have been used to predict the functional significance of anatomic lesions. A renal vein renin ratio greater than 2 to 1 (involved to uninvolved) is highly predictive of a beneficial response to intervention. However, a significant number of patients with nonlateralizing ratios ultimately prove to benefit from intervention. Preliminary data suggest that a change in the technetium-99m (^{99m}Tc)-labeled DTPA or MAG_3 renogram after treatment with captopril may help to define the functional significance of a renal artery lesion prior to intervention with surgery or angioplasty.

IX. Treatment of hypertensive crises

A. **Malignant hypertension** must be treated expeditiously to prevent complications such as hypertensive encephalopathy, acute hypertensive heart failure, and renal failure. The traditional approach to patients with malignant hypertension has been the initiation of potent parenteral agents. In general, parenteral therapy should be used in patients with evidence of acute end-organ dysfunction (hypertensive encephalopathy or pulmonary edema) or those unable to tolerate oral medications. Nitroprusside is the treatment of choice for patients requiring parenteral therapy. Diazoxide, employed in mini-bolus fashion to avoid sustained overshoot hypotension, may be advantageous in patients for whom monitoring in an intensive care unit is not feasible. In general, reducing the mean arterial pressure by 20% or to a level of 160–170/100–110 mm Hg is safe. The use of a short-acting agent such as nitroprusside has obvious advantages, because blood pressure can quickly be stabilized at a higher level if complications develop during rapid blood pressure reduction. If no evidence of vital organ hypoperfusion is apparent during the initial reduction, the DBP can gradually be lowered to 90 mm Hg over a period of 12 to 36 hours. Oral antihypertensive agents should be initiated as soon as possible to minimize the duration of parenteral therapy. The nitroprusside infusion can be weaned as the oral agents become effective.

   The cornerstone of initial oral therapy should be arteriolar vasodilators such as hydralazine or minoxidil. Beta blockers are required to control reflex tachycardia, and a diuretic must be initiated within a few days to prevent salt and water retention in response to vasodilatator therapy when the patient's dietary salt intake increases. Diuretics may not be necessary as a part of initial parenteral therapy, because patients with malignant hypertension often present with volume depletion due to pressure-induced natriuresis. Although many patients with malignant hypertension definitely require initial parenteral therapy, some patients may not yet have evidence of cerebral or cardiac dysfunction or rapidly deteriorating renal function and therefore do not require instantaneous control of blood pressure. These patients can often be managed with an intensive oral regimen, often with a beta blocker and minoxidil, designed to bring the blood pressure under control within 12 to 24 hours.

   After the immediate crisis has resolved and the blood pressure has been controlled with initial parenteral therapy, oral therapy, or both, lifelong surveillance of blood pressure is mandatory. If blood pressure control lapses, malignant hypertension can recur even after years of successful antihypertensive therapy. Triple therapy with a diuretic, a beta blocker, and a vasodilator is often required to maintain satisfactory long-term blood pressure control.
B. **Other hypertensive crises.** Sodium nitroprusside is the drug of choice for management of virtually all hypertensive crises outlined in Table 14-5, including malignant hypertension, hypertensive encephalopathy, acute hypertensive heart failure, intracerebral hemorrhage, perioperative hypertension, catecholamine-related hypertensive crises, and acute aortic dissection (in combination with beta blockers). Intravenous nitroglycerin may also be useful in patients with concomitant myocardial ischemia, because it dilatates intracoronary collaterals.

Sodium nitroprusside is a potent intravenous hypotensive agent with an immediate onset and brief duration of action. The site of action is the vascular smooth muscle. It has no direct action on the myocardium, although it may indirectly affect cardiac performance through alterations in systemic hemodynamics. Nitroprusside is an iron-coordination complex with five cyanide moieties and a nitroso group. The nitroso group combines with cysteine to form nitrosocysteine, a potent activator of guanylate cyclase that causes cyclic guanosine monophosphate (cGMP) accumulation and relaxation of vascular smooth muscle. Nitroprusside causes vasodilation of both arteriolar resistance vessels and venous capacitance vessels. Its hypotensive action is a result of a decrease in SVR. The combined decrease in preload and afterload reduces myocardial wall tension and myocardial oxygen demand.

The net effect of nitroprusside on cardiac output and heart rate depends on the intrinsic state of the myocardium. In patients with left ventricular systolic dysfunction and elevated left ventricular end-diastolic pressure, it causes an increase in stroke volume and cardiac output as a result of afterload reduction, and heart rate may actually decrease in response to improved cardiac performance. In contrast, in the absence of left ventricular dysfunction, venodilation and preload reduction can result in a reflex increase in sympathetic tone and heart rate. For this reason, nitroprusside must be used in conjunction with a beta blocker in acute aortic dissection.

The hypotensive action of nitroprusside appears within seconds and is immediately reversible when the infusion is stopped. The cGMP in vascular smooth muscle is rapidly degraded by cGMP-specific phosphodiesterases. Nitroprusside is rapidly metabolized with a half-life of 3 to 4 minutes. Cyanide is formed, as a short-lived intermediate product, by direct combination with sulfhydryl groups in red blood cells and tissues. The cyanide groups are rapidly converted to thiocyanate by the liver in a reaction in which thiosulfate acts as a sulfur donor. Thiocyanate is excreted by the kidney with a half-life of 1 week in patients with normal renal function. Thiocyanate accumulation and toxicity can occur when a high-dose or prolonged infusion is required, especially in patients with renal insufficiency. When these risk factors are present, thiocyanate levels should be monitored and the infusion stopped if the level is over 10 mg per dL. Thiocyanate toxicity is rare in patients with normal renal function requiring less than 3 µg per kg per minute for less than 72 hours. Cyanide poisoning is a very rare complication, unless hepatic clearance of cyanide is impaired by severe liver disease, or massive doses of nitroprusside (more than 10 µg per kg per minute) are used to induce deliberate hypotension during surgery.

Once the hypertensive crisis has resolved and the blood pressure is adequately controlled, oral antihypertensive therapy should be initiated. The nitroprusside infusion is weaned as the oral antihypertensive agents become effective.

X. Management of severe uncomplicated hypertension in the acute care setting

The benefits of acute reduction in blood pressure in the setting of true hypertensive crisis are obvious. Fortunately, true hypertensive crises are relatively rare events that never affect the vast majority of hypertensive patients. Much more common than true hypertensive crisis is the patient who presents with stage 3 hypertension (blood pressure higher than 180/100 mm Hg) in the absence of HNR or acute end-organ damage that would signify a true crisis. This entity, which is known as *severe uncomplicated hypertension*, is very common in the emergency department or other acute care settings. Sixty percent of patients with severe uncomplicated hypertension are entirely asymptomatic and present for prescription refills or routine blood pressure checks, or are found to have elevated pressure during routine physical examinations. The other 40% present with nonspecific findings such as headache, dizziness, or weakness in the absence ,of evidence of acute end-organ dysfunction.

In the past, this entity was referred to as *urgent hypertension*, reflecting the erroneous notion that acute reduction of blood pressure over a few hours before discharge from the acute care facility was essential to minimize the risk of short-term complications from severe hypertension. Commonly used treatment regimens included oral clonidine loading or sublingual nifedipine. However, more recently, the practice of acute blood pressure reduction in severe uncomplicated hypertension has been questioned. The Veterans Administration Cooperative Study of patients with severe hypertension included 70 placebo-treated patients who had an average DBP of 121 mm Hg at entry. Among these untreated patients, 27 experienced morbid events at a mean of 11 (plus or minus 2) months of follow-up. However, the earliest morbid event occurred after only 2 months. These data suggest that in patients with severe uncomplicated hypertension in which severe hypertension is not accompanied by evidence of malignant hypertension or acute end-organ dysfunction, eventual complications due to stroke, myocardial infarction, or CHF tend to occur over a time frame of months to years rather than hours to days. Although long-term control of blood pressure can clearly prevent these eventual complications, a hypertensive crisis cannot be diagnosed, because no evidence indicates that acute reduction of blood pressure results in an improvement in short-term or long-term

prognosis.

Although acute reduction of blood pressure in patients with severe uncomplicated hypertension with sublingual nifedipine or oral clonidine loading was once the de facto standard of care, this practice was often an emotional response on the part of the treating physician to the dramatic elevation of blood pressure, or it was motivated by the fear of medicolegal repercussions in the unlikely event of a hypertensive complication occurring within hours to days. Observing and documenting the dramatic fall in blood pressure is a satisfying therapeutic maneuver, but no scientific basis for this approach exists. No literature supports the notion that some goal level of blood pressure reduction must be achieved before the patient with severe uncomplicated hypertension leaves the acute care setting. In fact, acute reduction of blood pressure is often counterproductive, because it can produce untoward side effects that render the patient less likely to comply with long-term drug therapy.

Instead, the therapeutic intervention should focus on tailoring an effective, well-tolerated maintenance antihypertensive regimen with patient education regarding the chronic nature of the disease process and the importance of long-term compliance and medical follow-up (Fig. 14-5). If the patient has simply run out of medicines, reinstitution of the previously effective drug regimen should suffice. If the patient is thought to be compliant with an existing drug regimen, a sensible change in the regimen, such as an increase in a suboptimal dosage of an existing drug or the addition of a drug of another class, is appropriate. In this regard, addition of a low-dose of a thiazide diuretic as a second-step agent to existing monotherapy with ACE inhibitor, angiotensin II receptor blocker, calcium channel blocker, beta blocker, or central alpha$_2$-agonist is often remarkably effective. Another essential goal of the acute intervention should be to arrange suitable outpatient follow-up within a few days. Gradual reduction of blood pressure to normotensive levels over a few days to a week should be accomplished in conjunction with frequent outpatient visits to modify the drug regimen and reinforce the importance of lifelong compliance with therapy. Though less dramatic than acute reduction of blood pressure in the acute care setting, this type of approach to the treatment of chronic hypertension is more likely to prevent long-term hypertensive complications and recurrent episodes of severe uncomplicated hypertension.

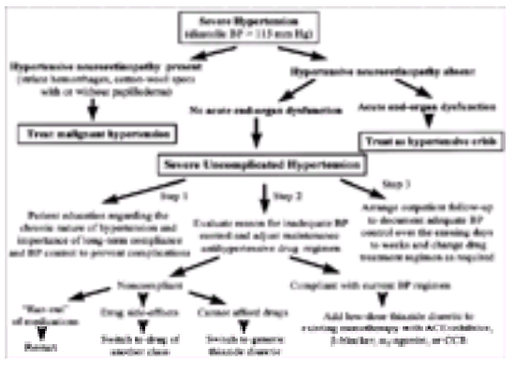

Figure 14-5. Algorithm for treatment of severe uncomplicated hypertension. (ACE, angiotensin-converting enzyme; BP, blood pressure; CCB, calcium channel blocker.) (From Nolan CR. Hypertensive crisis. In: Schrier RW, ed. *Atlas of diseases of the kidney,* vol. 3. Philadelphia: Current Medicine, 1999. Adapted with permission.)

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Chapter 15 Use of Radiologic Techniques in the Patient with Renal Problems

Ronald R. Townsend and Robert A. Older

Urographic procedures providing information about the urinary tract
Ultrasound in evaluation of renal disease
CT in evaluation of renal disease
MRI in evaluation of renal disease
Radionuclide evaluation of renal disease
Renal angiography
Percutaneous renal techniques
Problem-oriented approach to radiologic evaluation of the urinary tract

Diagnostic imaging of the urinary tract is undergoing rapid expansion. This provides a wider choice of examinations for any individual problem, but it also necessitates an understanding of each available study and a knowledge of its indications.

I. Urographic procedures providing information about the urinary tract

A. The routine **abdominal film** provides considerable information about disease processes involving the urinary tract. These can be considered in four main categories:
   1. **Bone.** Changes of renal osteodystrophy and either lytic or blastic metastases can be demonstrated.
   2. **Soft tissue changes.** Obliteration of the psoas outline, the renal outline, or both may be a clue to local inflammation, hemorrhage, tumor, or urinoma.
   3. **Abnormalities of "air."** Dilated small or large bowel is evident in cases of ileus or obstruction. Areas in which abdominal gas is decreased may indicate displacement by a mass.

      Air outside of the normal intestinal tract usually indicates a serious underlying pathologic condition. Intraperitoneal air is best visualized just under the diaphragm on an upright chest film. Free intraperitoneal air is usually related to bowel perforation, trauma, recent abdominal surgery, or a severe infectious process such as abscess. In most cases, gas collections within an abscess remain locally confined. Retroperitoneal air outside the intestinal tract also occurs; this can be visualized in several areas, including in and around the kidneys or bladder (Fig. 15-1) and along lateral abdominal walls. Air within or adjacent to the kidneys or within the bladder wall or lumen may be due to severe infection, particularly in diabetic patients. When emphysematous infection is clinically suspected, or a radiograph raises the question of retroperitoneal gas, computed tomography (CT) is both more sensitive in gas detection and more specific in its localization. Trauma with perforation of the retroperitoneal portions of the intestines can also produce retroperitoneal air, as can the postoperative setting.

Figure 15-1. Abnormal air outlines the bladder in a diabetic patient with emphysematous cystitis.

   4. **Calcifications**
      a. **Kidney**
         1. Within the **collecting system**
            a. Renal calculi (nephrolithiasis)
            b. Encrusted or calcified neoplasm
            c. Calcified sloughed papilla
         2. Within the **renal parenchyma** (nephrocalcinosis)
            a. **Medullary nephrocalcinosis (Fig. 15-2):** hypercalcemic states including hyperparathyroidism, renal tubular acidosis type I, medullary sponge kidney, or papillary necrosis

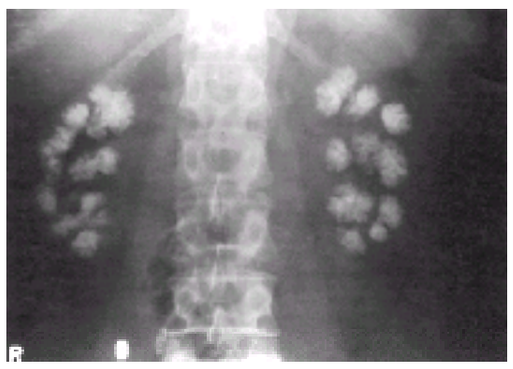

Figure 15-2. Medullary calcification typical of renal tubular acidosis or hyperparathyroidism.

            b. **Diffuse or cortical nephrocalcinosis:** chronic glomerulonephritis, cortical necrosis, or hypercalcemic states, or hereditary nephritis
            c. **Focal nephrocalcinosis:** neoplasm, cyst wall, tuberculosis, posttraumatic or postinfectious dystrophic calcification
         3. **Ureter:** calculus
         4. **Bladder**
            a. **Lumen:** bladder calculus, encrusted tumor, or foreign body
            b. **Wall:** tuberculosis, schistosomiasis, diabetes mellitus, Cyclophosphamide cystitis, or postradiation therapy

B. **Renal tomograms without contrast media.** Renal tomography may reveal renal calcification not observed on the plain film, especially when the renal shadows are obscured by bowel gas or stool.

C. **Excretory urography** [intravenous pyelography (IVP)] is the radiographic study of the urinary tract after intravenous administration of a radiographic contrast agent. The diagnostic information obtained is directly related to the quality of the study performed.
   1. **Factors determining quality of excretory urography.** Factors that influence the quality and therefore the diagnostic accuracy of the excretory urogram include

a. **Amount of contrast used:** 50 to 100 mL of 50% to 60% contrast media for an average adult
b. **Technical factors,** such as proper coning and the use of low-kilovolt technique
c. **Tomography** (especially if much stool is present in the colon)
d. **Abdominal compression**
e. **Radiographs** tailored for each patient. Excretory urography is an accurate diagnostic procedure when properly performed and individualized for each patient. The use of tomography within 30 seconds after the injection of a bolus of contrast produces maximum visualization of the renal parenchyma, both normal and abnormal (Fig. 15-3). Films obtained at 5 and 10 minutes after the injection of contrast are used for evaluation of the collecting structures, ureters, and bladder. Abdominal compression is used to produce greater distention of the calyceal system and to allow better visualization of the entire ureter after compression is released (Fig. 15-4).

Figure 15-3. Tomogram obtained immediately after the bolus injection of contrast media. The entire renal parenchyma and outlines are well visualized. The intensity of the nephrogram allows detection of a small hypovascular mass (*arrows*).

Figure 15-4. Normal collecting system using compression.

2. **Relative contraindications for excretory urography.** Excretory urography is useful as a screening modality for most forms of renal pathology. Certain relative contraindications, however, should be mentioned.

The safety of excretory urography is enhanced by careful patient selection and judicious use of appropriate iodinated contrast material. Preprocedure patient evaluation allows identification of risk factors for the procedure, including risks associated with intravenous iodinated contrast administration. A lower frequency of complications from urography (including current estimates of risk of death from contrast of less than 1 in 100,000) than has occurred in the past is attributed to patient selection, availability of nonionic contrast, and widespread training of imagers in early diagnosis and treatment of contrast reactions. If significant contraindications to excretory urography are identified, alternative imaging strategies to address the specific clinical problem at hand can be considered.

Two classes of iodinated contrast material for intravascular use are appropriate for excretory urography or contrast-enhanced CT. These include ionic agents (the only form available until the 1980s) and nonionic, low osmolar agents. The nonionic, low osmolar agents have fewer minor and major adverse reactions, but are more expensive, than the ionic agents. No difference in risk of death between the two classes of contrast agent has been demonstrated, and one is not likely to be, because death is extremely rare with any agent. Although some institutions use exclusively one type of contrast, many imagers select the contrast agent to be used for an individual patient based on the individual patient's circumstances, including the risk factors below.

a. **Previous allergic reaction to contrast media.** Although this is only a relative contraindication, the need for urography and the possibility of using other imaging technologies not requiring contrast (e.g., ultrasound) should be carefully considered. Patients with a history of previous reaction may benefit from premedication with steroids and antihistamines and/or use of nonionic contrast agents. Patients with asthma or history of previous serious allergic reaction to materials other than contrast are also at higher risk for contrast reaction and use of nonionic agent should be considered to decrease the risk of allergic reaction in these patients.
b. **Decreased renal function.** Iodinated contrast agents are potentially nephrotoxic, but a significant effect is extremely rare in patients with normal renal function or even mildly decreased renal function alone. Patients with diabetes mellitus and decreased renal function are at a much higher risk of nephrotoxicity, although nonionic agents appear much safer in this patient population. Other risk factors include multiple myeloma and dehydration. In chronic renal failure patients on dialysis, use of low osmolality nonionic contrast agents generally obviates problems related to intravascular fluid overload, which can be seen with use of high osmolar ionic agents.
c. **Cardiac disease.** Patients with known significant cardiac disease, including severe arrhythmias, congestive heart failure, unstable angina pectoris, recent myocardial infarction, and pulmonary hypertension may be at increased risk for intravascular contrast administration.
d. **Pregnancy.** Due to potential risks associated with radiation exposure to the fetus, urography should be performed during pregnancy only when absolutely necessary. Imaging strategies not using ionizing radiation (especially ultrasound) should be considered.
e. **Other/complex medical problems.** Any question regarding the safety of contrast administration, such as with urography, should prompt close communication between clinician and imager to ensure optimal safe evaluation of the patient and the patient's medical problem.

D. **Retrograde pyelography** is performed under cystoscopic control with the placement of a catheter in the ureteral orifice or through passage of a catheter up the ureter. Contrast media injected through the catheter demonstrates the ureter, renal pelvis, and calyces, but not the parenchyma. Since the advent of high-resolution excretory urography, the use of retrograde studies has declined.

Uses of retrograde pyelography include

1. Additional evaluation of possible filling defects not definite on excretory urography
2. Selective cytologic studies and cultures
3. Additional delineation of an obstructing lesion, especially the length of the obstruction and ureter distal to the obstruction
4. To exclude obstruction if all noninvasive studies are inconclusive and suspicion is still high on clinical grounds
5. Cases of ureteral trauma (Fig. 15-5)

Figure 15-5. Right retrograde pyelogram demonstrates extravasation of contrast (*arrows*) from a partially transected right ureter. Both the exact point of injury and the degree of extravasation are apparent.

E. **Cystography and voiding cystourethrography.** Cystography is performed by obtaining radiographs after filling the urinary bladder with iodinated contrast material via a urethral catheter. If images of the urethra are also obtained during voiding, the study is termed a voiding cystourethrogram (VCUG) (Fig. 15-6). When the examination is performed because of a clinical question of vesicoureteral reflux (common in children, rare in adults), images of the bladder and ureters must be obtained during voiding, because reflux may occur only with the increased intraluminal bladder pressure associated with voiding. Postvoid bladder residual can also be estimated from appropriate images. Some information can be gained from voiding images at the time of excretory urography, but the generally low concentration of contrast in the urine limits that evaluation.

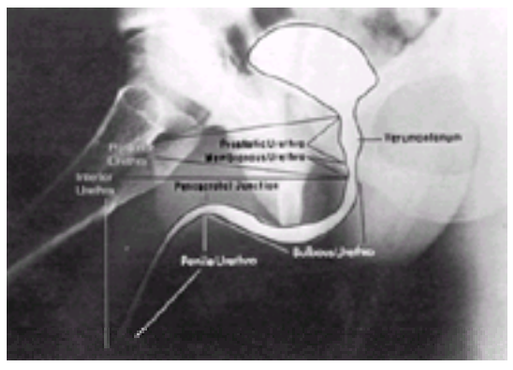

Figure 15-6. Normal male voiding cystourethrogram.

1. **Indications for cystography**
   a. **Pelvic trauma** (after normal retrograde urethrography in cases of possible urethral injury).
   b. **Anatomic delineation of bladder in patient with reduced renal function.** The retrograde cystogram provides somewhat better anatomic delineation of the bladder than the excretory urogram, especially in instances in which renal function is reduced. An example of this is the evaluation of the bladder of a potential transplant recipient before surgery.
   c. **Possible vesicovaginal or vesicoenteric fistulae**
   d. **Postoperative evaluation** (especially with suspicion of leak).
   e. **Neoplasms of the bladder.** Retrograde cystography *is not* a satisfactory screening study for evaluating possible neoplasms of the bladder. Cystoscopy is required.
2. **Indications for VCUG**
   a. **Vesicoureteral reflux.** The presence or absence of reflux, especially in children with recurrent episodes of pyelonephritis, is the most frequent indication for this examination. Damage to the kidneys as a result of reflux is not evaluated with this examination and is commonly defined with ultrasound, excretory urography, or radionuclide study.
   b. **Posterior urethral valves** in the male child
   c. **Strictures** of either the posterior or anterior urethra in both children and adults
   d. **Evaluation of incontinence.** Bladder and urethra imaging is usually only part of an evaluation, which also includes pressure/flow measurements (urodynamics). Dynamic magnetic resonance imaging (MRI) is also used in some centers.
   e. **Evaluation of the posterior urethra** (which is not well delineated by retrograde urethrography).

F. **Retrograde urethrography** is a limited, but useful, examination. Indications are
   1. Evaluation of **strictures** of the anterior urethra
   2. **Pelvic trauma.** This is an important study in patients with pelvic trauma who may have sustained urethral injury. Retrograde urethrography should be performed before attempted catheterization of the bladder, because catheterization could result in complete rupture of a urethra that was previously partially transected.

G. **Nuclear cystography** provides an alternative method for evaluation of vesicoureteral reflux in infants and children. Technetium-99m (^{99m}Tc) pertechnetate is instilled directly into the bladder via catheterization. Continuous imaging allows detection of reflux. A major advantage of this technique is a considerable reduction in radiation dose to the child, a factor that is of particular concern when multiple follow-up studies are necessary. It does not, however, provide clear anatomic evaluation of the bladder or urethra.

II. Ultrasound in evaluation of renal disease Because of its simplicity, noninvasiveness, low risk (no radiation), and relatively low cost, ultrasound has found considerable use in the urinary tract. Results depend on operator expertise and experience, but high-quality images are obtainable in most patients. Use of pulsed or color Doppler ultrasound allows evaluation of the renal arteries and veins and may help characterize other pathology. Obesity degrades ultrasound images. Ultrasound may be valuable in the following clinical circumstances:

A. **Renal mass.** Ultrasound may be useful to evaluate for the presence of a renal mass or to further characterize a mass identified by another imaging study, especially excretory urography. All renal masses thought to be cysts at urography should be evaluated by ultrasound to distinguish simple cysts, which generally can be dismissed as clinically insignificant, from complex cysts or solid lesions. Solid masses identified by ultrasound (Fig. 15-7) require further evaluation with contrast-enhanced CT to confirm the nature of the mass and to plan treatment (a soft-tissue density mass must be assumed to represent malignancy until proven otherwise). Ultrasound is relatively insensitive to the presence of transitional cell carcinoma, especially if the carcinoma is nonobstructive, a significant limitation of ultrasound in the evaluation of older adults with hematuria.

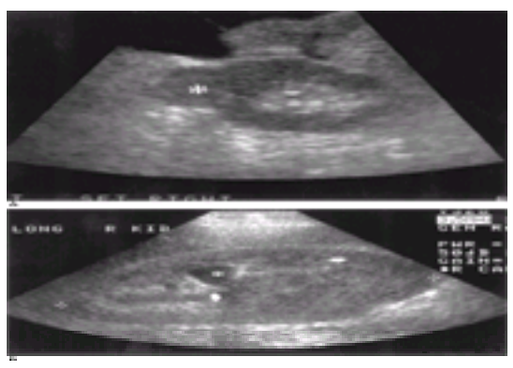

Figure 15-7. A: Transverse sonogram of right kidney demonstrates solid renal mass (*asterisk*) due to metastasis. **B:** Longitudinal sonogram of right kidney in a

different patient demonstrates 8-cm diameter solid mass (*arrows* at margins) due to renal cell carcinoma. A dilated calyx (*asterisk*) is due to obstruction by the carcinoma.

B. **Renal failure.** Ultrasound can distinguish between high-grade obstruction and parenchymal disease as a cause of renal failure. Hydronephrosis, readily detectable by ultrasound, is present in the vast majority of patients with obstruction of sufficient chronicity and severity to cause decreased renal function (Fig. 15-8). The cause of obstruction is frequently evident by imaging the dilated urinary collecting system to the point of a mass or stone. Additional imaging is frequently required, however. Ultrasound also delineates renal size. Small renal size is usually Hassociated with chronic renal failure (Fig. 15-9). Normal renal size is often associated with acute renal failure, but with diabetes, amyloid, polycystic kidney disease, and scleroderma, the kidney may remain large in association with chronic renal disease. When renal size is normal or increased and clinical and imaging findings are nonspecific, ultrasound-guided renal parenchymal biopsy may be useful to determine the cause and guide treatment of acute renal failure.

Figure 15-8. Longitudinal sonogram of right kidney demonstrates moderate hydronephrosis.

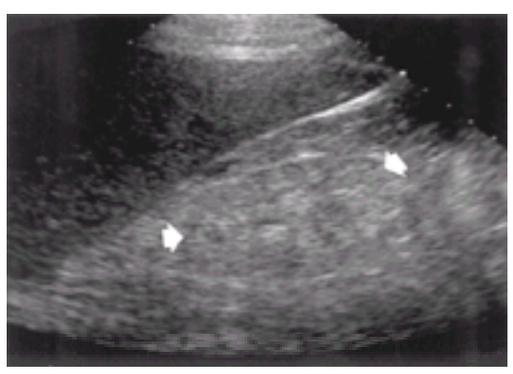

Figure 15-9. Longitudinal sonogram of right kidney. Kidney is small (7 cm in length) with echogenic cortex due to chronic glomerulonephritis (*arrows* at upper and lower poles of kidney).

C. **Stone disease/acute obstruction.** Ultrasound can detect renal and ureteral calculi and the hydronephrosis accompanying obstruction by a calculus. However, with very acute obstruction by a calculus, false negative sonograms are common. Some find Doppler ultrasound useful in this setting, but most practices prefer spiral (also known as *helical*) CT or excretory urography to evaluate for acute obstruction by stone. In a pregnant patient, ultrasound remains the most reasonable initial imaging study.
D. **Perirenal and pararenal spaces.** The perirenal and pararenal spaces can be well evaluated with ultrasound, specifically for the presence of abnormal fluid such as urinoma, hematoma, or abscess. Ultrasound also can be used to guide aspiration of these perinephric processes for both diagnosis and therapy. Because CT is more sensitive in detection of small retroperitoneal fluid collections and evaluates the full extent of any collection more completely than ultrasound, many prefer CT. CT is recommended to search for acute hematoma, because hematoma may be composed completely of clotted blood, which is indistinguishable from retroperitoneal tissues by ultrasound.
E. **Transplant dysfunction.** Transplant failure due to obstruction (hydronephrosis), venous thrombosis or arterial occlusion can be readily detected by ultrasound with Doppler. Sonographic findings may suggest rejection, but lack specificity in making that diagnosis. Doppler sonographic identification of a high resistance to arterial flow (which may be quantitated as a high resistive index) also suggests rejection, but it can also be seen with acute tubular necrosis and other pathologies. Ultrasound-guided biopsy is frequently necessary to distinguish rejection from immunosuppressant drug toxicity. A fluid collection around the transplanted kidney, such as a lymphocele, urinoma, or possibly hematoma, can be detected and followed with ultrasound or aspirated using ultrasound guidance.
F. **Renal infection.** Sonographic identification of hydronephrosis with or without debris in the dilated collecting system in the clinical setting of pyelonephritis suggests pyonephrosis and the need for immediate nephrostomy or ureteral stent placement. Focal bacterial nephritis and renal abscess may be detected with ultrasound.
G. **Renal cystic disease.** Ultrasound is an effective screening study for autosomal dominant or autosomal recessive polycystic kidney disease in relatives of affected patients who are at risk for either disease, or in patients whose symptoms and signs lead to suspicion of either of these diseases (Fig. 15-10).

Figure 15-10. Longitudinal sonogram of upper pole of right kidney. Multiple cysts replace the renal parenchyma in this patient with autosomal dominant polycystic kidney disease.

H. **Prostate disease.** Prostate carcinoma or benign prostatic hypertrophy may come to clinical attention because of urinary obstruction. The prostate is effectively imaged and biopsy guided with transrectal ultrasound.
I. **Dialysis fistula and graft.** Duplex Doppler/color Doppler ultrasound is useful to identify thrombosis or stenosis that may affect flow through a fistula or graft.

III. CT in evaluation of renal disease Technical advances in CT have increased its applications in the urinary tract and improved its accuracy in traditional applications. Advantages relative to ultrasound include increased sensitivity to many pathologies and less operator dependence. Disadvantages include higher cost, patient radiation exposure, and need to use intravenous iodinated contrast for many examinations. Many newer scanners incorporate spiral technology, which allows the entire abdomen to be scanned in a single breath hold. Advantages of this technique include improved evaluation of renal masses due to elimination of artifacts

related to breathing during the examination (e.g., misregistration) and the ability to accurately diagnose Lurinary stone disease and obstruction. With use of contrast and appropriate image processing, detailed vascular images can be constructed, so-called CT angiography.

A. **Renal mass.** A major use of CT is in the evaluation of suspected solid mass, suspicious for malignant neoplasm (Fig. 15-11). This is facilitated by imaging through the kidneys before and after rapid bolus injection of intravenous contrast material. Depending on the characteristics of the mass, additional delayed postcontrast images may be helpful. Definite identification of contrast enhancement (which can be confirmed with measurements of density before and after contrast administration) differentiates a neoplasm from hematoma and other pathology. Although a renal cell carcinoma may be isodense with renal cortex before contrast administration, and therefore easily missed, carcinomas are usually readily evident after intravenous contrast administration, because the masses are less dense than enhanced renal cortex. Staging information, critical to treatment planning, that can be obtained from a contrast-enhanced CT scan includes mass size, local extrarenal extension, renal vein and inferior vena cava extension, retroperitoneal adenopathy, and distant metastasis. Based on imaging characteristics of the renal mass alone, renal cell carcinomas cannot reliably be distinguished from other soft-tissue masses, such as lymphoma or metastatic disease. Other clinical and imaging findings may help in making an accurate diagnosis in these cases. A mass of predominantly fat density can be confirmed to be a benign angiomyolipoma by CT (Fig. 15-12).

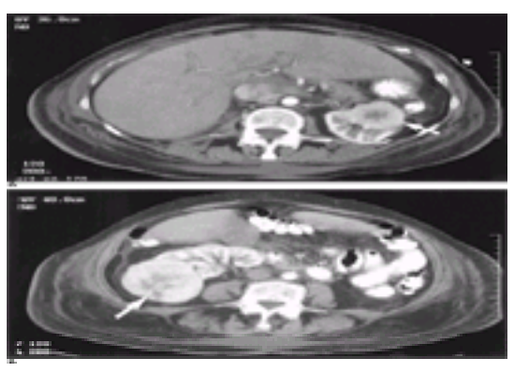

Figure 15-11. Computed tomographic scan of bilateral renal cell carcinoma in patient with von Hippel–Lindau disease. **A:** Solid mass (*arrow*) with central necrosis replaces the anterior cortex of the left kidney. **B:** Large solid mass at the lower pole of a malrotated right kidney (*arrow*).

Figure 15-12. Computed tomographic scan shows fat density mass at lower pole of left kidney, diagnostic of angiomyolipoma (*arrow*).

B. **Acute flank pain.** The presence or absence of an acutely obstructing renal or ureteral calculus can be accurately determined using spiral CT. Although plain radiographs do not detect urate calculi, they are dense enough that they appear just like calcified stones using standard display of CT images. The dilated intrarenal collecting system and ureter can be traced down to the obstructing calculus. Some find reconstructed coronal images useful for this purpose.
C. **Infection.** Patients with a clinical suspicion of a complication of acute pyelonephritis can be evaluated well with CT. With use of intravenous contrast, focal pyelonephritis, renal abscess, subcapsular abscess, perinephric abscess, and direct extension of abscess into surrounding structures can be readily visualized. Using CT guidance, suspicious fluid collections can be aspirated and percutaneous drainage catheters placed.
D. **Trauma.** CT provides the most information concerning the traumatized kidney and in most cases of suspected renal trauma is the imaging method of choice (Fig. 15-13). Nonexcretion, contusion, fracture, shattered kidney, and perirenal hematoma or urinoma are readily detected. CT provides additional information concerning other intraabdominal organs, especially the spleen and liver. In the setting of significant abdominal trauma, excretory urography is rarely indicated and represents an additional risk of contrast exposure. Excretory urography may be of value in those few patients with minimal trauma but with persistent microscopical hematuria. Even in this setting, CT may be preferable.

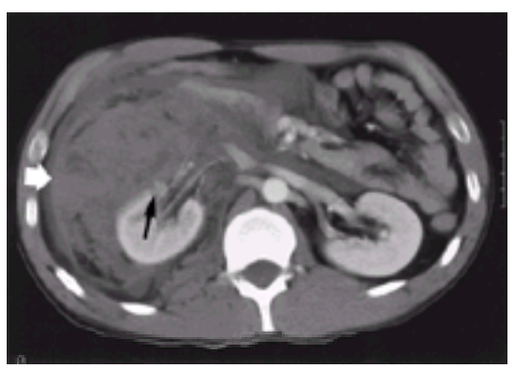

Figure 15-13. Computed tomographic scan obtained after a motor-vehicle accident in a patient with hematuria. A large hematoma (*white arrow*) is a result of a renal laceration (*black arrow*).

E. **Evaluation of the retroperitoneum.** CT and MRI are the most efficacious imaging modalities for visualizing retroperitoneal structures including the adrenal gland. The retroperitoneum has been very difficult to study with conventional radiography, and before the advent of CT, evaluation of the adrenal gland often required expensive and invasive arteriographic and venographic studies. The normal adrenal glands can be imaged routinely, and even very small lesions, such as aldosteronomas, can be visualized with CT. Optimal imaging of the adrenal glands requires thin-section images (usually approximately 3 mm). Density measurements of adrenal masses obtained on noncontrast CT are most useful in distinguishing benign nonhyperfunctioning adrenal adenoma from malignant adrenal mass (especially metastasis) (Fig. 15-14). Retroperitoneal processes such as lymph node enlargement, neoplasm, hematoma, and urinoma are well evaluated with CT.

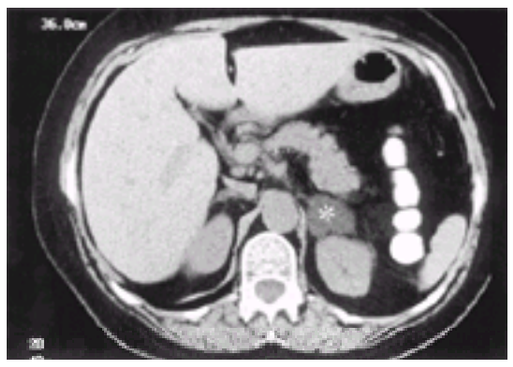

Figure 15-14. The low-density adrenal mass appearing on this non–contrastenhanced computed tomographic scan is a nonhyperfunctioning adenoma (*asterisk*).

Probably one of the most important uses of CT with respect to the retroperitoneum is to establish that no disease process is present. CT has been particularly helpful in excluding the presence of disease when somewhat unusual positions of the kidney or changes in the renal axes have suggested a retroperitoneal mass.

F. **Obstruction with renal failure.** CT is helpful in the obstructed patient even when renal function is reduced or absent on the involved side. Information regarding renal size and shape and the presence of obstruction can be obtained. The principal use of CT in obstructed patients is to evaluate for a possible obstructive mass. In some instances, CT-guided biopsies can be performed. The ability to obtain information even without the use of contrast media makes CT scanning and ultrasound alternative methods to excretory urography in a patient with known severe allergy to contrast media or one considered at high risk for contrast toxicity.
G. **Uses for CT within the pelvis** include
   1. Staging of transitional cell carcinoma of the bladder
   2. Evaluation of pelvic mass (tumor, abscess, hematoma, lipomatosis)
   3. Posttransplant evaluation

IV. MRI in evaluation of renal disease Advances in magnetic resonance hardware and software, increasing availability, and increasing experience have expanded the clinical usefulness of this technique. It remains more expensive and less available than CT, however.

A. **Renal mass.** MRI without and with intravascular contrast (gadolinium) can be used analogous to CT without and with contrast to characterize renal masses. This is especially useful in patients with allergy to iodinated contrast or with mild to moderate renal dysfunction, because gadolinium remains safe in these patients. MRI is used instead of CT in some practices to stage presumed renal cell carcinoma, because of its increased accuracy in detecting renal vein and inferior vena cava tumors. It is useful as an adjunct to CT to pursue questionable venous disease on contrast-enhanced CT scan.
B. **Adrenal and retroperitoneum.** MRI is highly sensitive for adrenal pathology and useful in characterizing many adrenal masses (Fig. 15-15). It is more sensitive than CT in detection of extraadrenal pheochromocytoma. It can be used, like CT, in evaluation of other retroperitoneal structures.

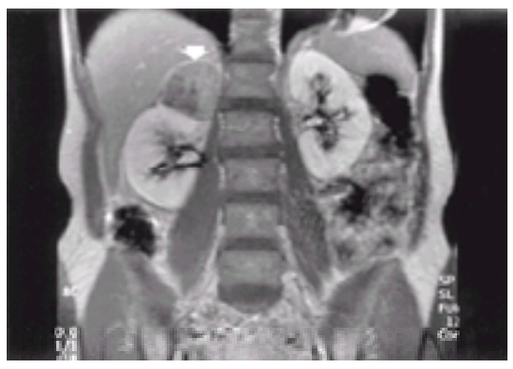

Figure 15-15. Coronal magnetic resonance image demonstrates right adrenal pheochromocytoma (*arrow*).

C. **Magnetic resonance angiography.** Special techniques allow evaluation of the renal arteries and veins with generated images showing the vessels free of overlying tissues, mimicking contrast arteriograms. This may be useful to evaluate for renal artery stenosis or to define renal arterial anatomy in planning resection of a mass.
D. **Pelvic pathology.** MRI staging of pelvic malignancies, including prostate cancer, transitional cell carcinoma of the bladder, cervical cancer, and others, may be more accurate than other imaging-based staging.

V. Radionuclide evaluation of renal diseas can provide unique functional information that compliments the higher-resolution anatomic information from other imaging studies. The agents most commonly used to image the kidneys include ^{99m}Tc-labeled mercaptylacetyl triglycine (MAG3) and ^{99m}Tc–labeled diethylenetriamine pentaacetic acid (DTPA). DTPA is cleared from the bloodstream by glomerular filtration, whereas MAG3 has more complex excretory mechanisms. Both are used for general purpose scanning—evaluating renal perfusion and excretion. MAG3 has somewhat better imaging characteristics, but it is also more expensive. A variety of additional agents are available for specific, less common, applications. Radionuclide studies may be useful to:

A. **Evaluate renal perfusion.** Analysis of the kinetics of early isotope accumulation within the kidneys allows evaluation of arterial inflow. This is used to evaluate renal transplants (arterial anastomosis/rejection evaluation) and, less commonly, native kidneys.
B. **Evaluate renal "function."** Global "function" can be evaluated in a gross sense. Relative "function" of the two native kidneys can be a useful parameter in planning treatment of a renal mass. In a patient with borderline renal function, impact of nephrectomy or partial nephrectomy on renal function can be determined.
C. **Evaluate renal "excretion."** One application is differentiation between obstructive and nonobstructive distention of the renal collecting system furosemide (Lasix) renogram]. In obstruction, the excretory phase of the renogram characteristically shows activity that is initially low but gradually increases over time. A nonobstructed but dilated collecting system may result in a renogram similar to that found in obstruction. Differentiation is possible based on the response to Lasix administration. Normally, and in cases of nonobstructive distention, intravenous administration of Lasix results in prompt decrease ("washout") of activity reflecting the diuresis, whereas in obstruction, washout of activity is limited by the obstruction.
D. **Parenchymal imaging.** Anatomic detail of the kidneys is generally better defined by CT with contrast than by radionuclide images. However, defects on a renogram, usually performed with ^{99m}Tc dimercaptosuccinic acid, may be useful in diagnosing acute pyelonephritis, especially in children.
E. **Renovascular hypertension.** The accuracy of renography performed with and without angiotensin-converting enzyme inhibitor administration is excellent, in some people's hands, in the diagnosis of clinically significant renal artery stenosis. Sensitivity as high as 96% and specificity as high as 95% have been reported, but in most institutions, statistics are not this good.
F. **Vesicoureteral reflux.** SeeVCUG under radiographic studies (see section **I.E**).

VI. Renal angiography The use of diagnostic renal angiography has diminished with greater use of ultrasound, CT, and MRI; however, in several areas, angiography still plays a major role.

A. **Evaluation of renovascular hypertension** (see section **VIII.H**).
B. **Interventional angiography.** Interventional uses of angiography are increasing. These include the use of special catheters and embolization techniques to control hemorrhage (Fig. 15-16) or to occlude arteriovenous fistulae, either congenital or traumatic. Embolization techniques are also used to infarct renal cell

carcinomas before surgery and, occasionally, as the only therapy. Interventional angiographic techniques of balloon angioplasty are used in the management of renovascular hypertension as an accepted alternative to surgery (Fig. 15-17). Success in treatment of renovascular hypertension due to fibromuscular dysplasia exceeds 90%, and angioplasty is now considered the treatment of choice in the management of this condition. Angioplasty is also effective in most instances of renal artery stenosis due to atherosclerosis. Clinical improvement in the severity of the patient's hypertension is seen in about 70% of cases; in unsuccessful cases, surgical correction can then be undertaken. Hypertension in transplant recipients caused by excess renin production from the patient's native kidneys can be treated by percutaneous ablation procedures.

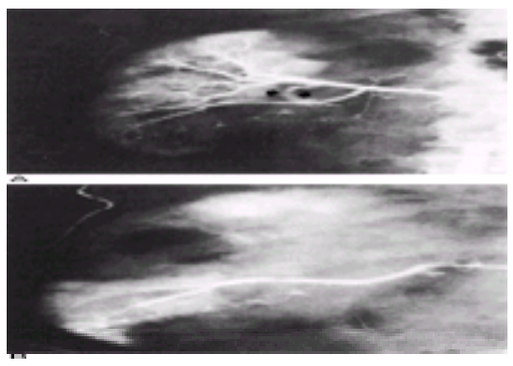

Figure 15-16. A: Selected right renal arteriography demonstrates posttraumatic extravasation of contrast in a branch of the renal artery (*arrows*). **B:** After injection of clotting material to embolize the renal artery, the bleeding has stopped.

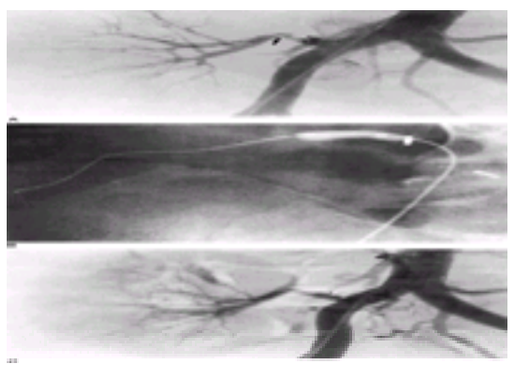

Figure 15-17. Renal artery angioplasty in a renal transplant patient. The patient was a 15-year-old boy with progressive hypertension 6 months after renal allograft transplant. **A:** Aortogram reveals 80% stenosis of transplant renal artery (*arrow*). Pressure gradient was 30 mm Hg. **B:** Angioplasty balloon inflated in region of stenosis. **C:** Postdilation arteriogram with improved blood flow to kidney. Pressure gradient across stenosis is decreased to zero.

C. **Renal transplant evaluation.** Renal arteriography can be used for preoperative evaluation of the donor kidney, but it is being increasingly replaced by noninvasive CT or magnetic resonance angiography. If noninvasive diagnostic studies (Doppler ultrasound, radionuclide study, CT or magnetic resonance angiography) suggest transplant renal arterial stenosis, renal arteriography may be performed to confirm diagnosis and guide treatment.
D. **Traumatized kidney without excretion.** Changes in therapeutic approach to a more conservative method of handling blunt renal trauma have reduced the need for renal arteriography. In traumatized kidneys that show no contrast excretion, angiography will outline specific renovascular abnormalities.
E. **Renal vein thrombosis.** Both renal arteriography and renal venography can establish the diagnosis of renal vein thrombosis. These techniques should be used when less invasive techniques (ultrasound, CT, and MRI) are equivocal.
F. **Dialysis access graft evaluation.** Noninvasive evaluation with Doppler ultrasound is frequently used to evaluate dialysis-access graft or fistula for thrombosis or stenosis. Direct contrast injections can be used to confirm diagnosis and plan percutaneous or surgical management.

VII. Percutaneous renal techniques

A. **Percutaneous nephrostomy for drainage.** This procedure, which consists of nonoperative placement of a catheter into the renal pelvis under imaging control, has largely replaced surgical nephrostomy for drainage of an obstructed kidney. It can be used for both short- and long-term drainage, and small or large catheters can be used depending on the consistency of the material to be drained. Material for diagnostic culture can be obtained.
B. **Antegrade pyelography.** This study, only rarely used in many practices, Finvolves placement of a thin needle or percutaneous catheter into the renal collecting system, with subsequent opacification with iodinated contrast media; it can be performed under ultrasound guidance or with fluoroscopy. It is indicated when evaluation of the anatomy of the upper urinary tract is necessary and when this cannot be done with excretory urography or retrograde pyelography. In addition to diagnosing a site of obstruction, antegrade pyelography can be used in conjunction with pressure measurements (Whitaker test) to help differentiate between true obstruction and persistent hydronephrosis without obstruction.
C. **Percutaneous stone extraction or lithotripsy.** Through larger catheters than are used for simple urinary drainage via nephrostomy, instruments for a stone extraction or contact lithotripsy can be inserted percutane ously to manage stone disease. Such procedures are frequently undertaken with radiologists and urologists working together through a combination of antegrade and retrograde approaches.

VIII. Problem-oriented approach to radiologic evaluation of the urinary tract

A. **Factors determining choice of procedure.** In general, the simplest noninvasive studies are performed first; but, if the diagnostic yield from these simpler studies is sufficiently low, more expensive and invasive procedures may be warranted. Although a number of studies may be listed for a given problem, this does not necessarily imply that any imaging studies are required. Which studies are warranted must be a clinical decision. The use of diagnostic imaging studies in any given situation depends to a large extent on the following four factors:
   1. Need for information to determine patient management
   2. Accuracy and reliability of a given study
   3. Invasiveness of the study (risks) and analysis of specific risk factors for the individual patient (e.g., contrast risk)
   4. Cost of the study
B. **Evaluation of the renal mass.** The imaging approach to a known or questionable renal mass depends on how the mass is initially identified and the specific circumstances of the patient. A palpable mass thought likely to be renal in origin can be imaged initially with ultrasound (Fig. 15-18) or CT. If ultrasound confirms a simple renal cyst, no further imaging is necessary. A solid mass (likely renal cell carcinoma) can be confirmed and staged with contrast-enhanced CT or MRI.

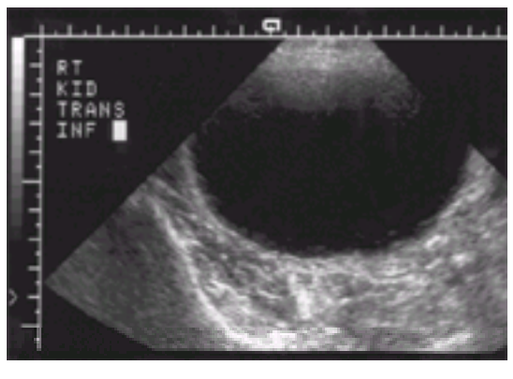

Figure 15-18. Transverse sonogram at lower pole of right kidney, performed to evaluate the cause of a palpable mass. The mass is confirmed to be a simple cyst.

A low-density renal mass initially identified at excretory urography should be evaluated with ultrasound to confirm that the mass is a simple cyst. If the mass appears solid on urography, proceeding directly to CT or MRI is advisable.

C. **Evaluation of patients with renal failure.** In patients with renal failure, imaging techniques are used primarily to define the size and shape of the kidney and to exclude obstruction as the cause. In patients at risk for arterial or venous thrombus as a cause of renal failure, the vessels should be evaluated. In most cases, defining the renal size allows differentiation from the chronic states, which usually produce bilaterally small kidneys. This differentiation and the exclusion of obstruction can provide the basic information necessary to determine additional management. Because of risks of contrast-induced exacerbation of renal failure, urography is generally not used in this patient population.
   1. **Ultrasonography** allows the exclusion of obstruction and determination of the renal size and shape. The presence of unsuspected conditions causing renal failure, such as autosomal dominant polycystic kidney disease, can be determined. Doppler evaluation allows confirmation of renal artery or renal vein patency or thrombosis (more common as the causes renal failure in transplants than in native kidneys). If hydronephrosis is identified, the dilated collecting system(s) should be followed to attempt to define the point of obstruction.
   2. **Retrograde pyelography** although used less frequently today than in the past, remains useful to define the cause/location of obstruction. When obstruction requiring stent placement is clinically likely, this examination can help guide that placement. It can also define presence of papillary necrosis and calyceal abnormalities which may not be evident with ultrasound.
   3. **CT.** A noncontrast examination can be useful in defining a mass (especially pelvic malignancy) as cause of bilateral obstruction. When ultrasound is inconclusive regarding the size or location of the kidneys, CT may be helpful to evaluate their presence, size, and position.
   4. Although not commonly used in this situation, **MR**I can demonstrate renal size and position and can evaluate for hydronephrosis. Fast imaging sequences allow a “magnetic resonance urogram” to be Bobtained. Magnetic resonance angiography may be useful to confirm vascular patency.
   5. Poor anatomic definition limits use of **radionuclide studies**, but blood flow, filtration, and excretion can be evaluated.

D. **Evaluation of urinary tract obstruction in the absence of renal failure.** Usually this becomes a clinical question because of acute flank pain, with obstructing stone the primary concern. Evaluation in the setting of infection is addressed separately below.
   1. **Abdominal film.** A radiograph may be obtained as an independent examination, or as the first image of an excretory urogram or spiral CT (digital preliminary radiograph). Possible stones or soft-tissue masses causing obstruction can be demonstrated on the preliminary film.
   2. **Excretory urography** has a long record of successful use in this situation, and it remains an excellent primary examination. However, it has been replaced by spiral CT in many centers (see VIII.D.3). In cases of obstruction, the renal density (nephrogram) increases with time after contrast until calyceal opacification occurs. Visualization of the collecting system may be delayed for minutes or hours. In acute obstruction, eventual visualization of the collecting system is to be expected. In a chronically obstructed kidney, contrast excretion may be absent. Direct signs of obstruction include abrupt termination of the contrast-filled pelvis or ureter and dilation of the collecting system proximally. The degree of dilation may be mild in cases of acute partial obstruction. Indirect signs include the negative pyelogram effect, which represents visualization of the dilated collecting system seen as a branching lucency against the background of density of the nephrogram. A second indirect sign is the full-column ureter sign. Normally, the ureteral column of contrast is interrupted by peristalsis. With partial obstruction, the ureter is often outlined in its entire length on multiple films.
   3. **Spiral CT** has replaced urography at many institutions for evaluation of patients with suspected acute obstruction by stone. The spiral technique allows the entire course of the urinary tract to be imaged in a single breathhold in most patients. This eliminates problems with respiratory misregistration, common with conventional CT. The technique allows detection of calculi (including urate stones) anywhere along the course of the urinary tract (Fig. 15-19) with a higher sensitivity than excretory urography or plain radiography. A collecting system dilated to the point at which the calculus is defined helps to confirm the calculus as the cause of the patient's obstruction and symptoms. The patient can be managed based on the size and location of the calculus. A disadvantage to CT in comparison to excretory urography is lack of functional information regarding obstruction, such as delay in excretion of contrast, that helps define the severity of obstruction. However, major advantages of the CT technique include the rapidity with which it can be performed—time in the examination room is usually only approximately 10 minutes. The charge for the examination is similar to urography at many institutions. Attempts can be made at a similar examination with conventional CT scanners, but little published information comparing the two techniques exists.

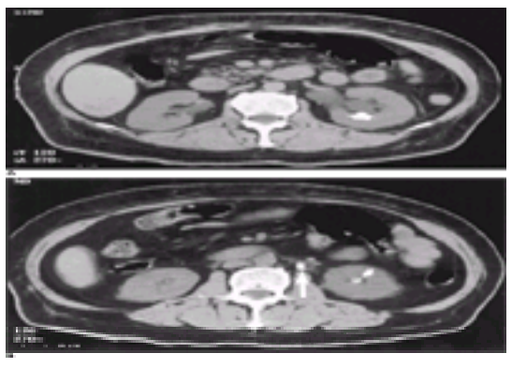

Figure 15-19. Noncontrast spiral computed tomographic scan for stone disease. **A:** Dilated left intrarenal collecting system (*arrow*) and renal pelvis are identified. **B:** A calculus is detected within the left ureter (*straight arrow*). An additional calculus is present in a lower pole calyx (*curved arrow*).

   4. **Ultrasound** can detect a dilated collecting system to the point of an obstructing stone or mass. However, when the obstruction is extremely acute (commonly the case with stone disease), collecting system dilation may not be sonographically detectable. Calculi in a nondilated collecting system may be missed. Although ultrasound has a high sensitivity in detecting intrarenal calculi and those at the ureterovesical junction, much of the course of the ureters may be obscured by bowel gas, limiting the evaluation. Because of this, ultrasound is not recommended routinely to evaluate these patients. In the pregnant patient, where fetal exposure to radiation must be minimized, ultrasound is certainly an appropriate initial examination. Some find Doppler useful in improving the ability of ultrasound to diagnose acute obstruction (increased resistance to arterial flow in the edematous obstructed kidney), but most practitioners do not find it definitive.
   5. **Retrograde pyelography** may allow better delineation of the exact point of obstruction, cause of obstruction, and ureter distal to the point of obstruction.
   6. **Antegrade studies.** Percutaneous antegrade pyelography may be used to delineate accurately the point of obstruction and also to provide drainage from above. Because of its invasive nature, this is not an appropriate initial diagnostic study, but it may be useful when percutaneous drainage is necessary. Pressure measurements (Whitaker test), although cumbersome, may be helpful in separating nonobstructive hydronephrosis from obstruction.

E. **Evaluation of hematuria**
   1. **Excretory urography** has long been the primary study for hematuria. An excretory urogram with tomography and compression may demonstrate
      a. **Parenchymal lesions:** neoplasm, arteriovenous malformation, nonneoplastic mass, and papillary necrosis.
      b. **Collecting systems** (intrarenal, ureters): tumor (especially transitional cell carcinoma), stones, leukoplakia.
   2. **Cystoscopy** is the procedure of choice for evaluation of suspected mass in the bladder. No imaging study suffices.
   3. **Ultrasound** may detect renal parenchymal masses, including carcinoma, missed by urography, especially if they are exophytic from the anterior or posterior aspect of the kidney. However, false-positive diagnoses of small parenchymal masses also occur with ultrasound. Use of color/power Doppler ultrasound facilitates identification of true renal masses and may allow detection of arteriovenous malformations. The inability to adequately image the ureters and the general lack of sensitivity for mucosal abnormalities (including transitional cell carcinoma) are significant limitations for ultrasound, especially in patient populations at risk for such pathology (positive urine cytology, elderly patients). Ultrasound is a reasonable approach in the setting of contraindication to intravenous contrast or during pregnancy.
   4. **CT.** With persistent hematuria and negative urography and cystoscopy, performing CT specifically for small tumors and stones is reasonable. CT with intravenous contrast is more sensitive than urography or ultrasound for small masses. Attention to detail (e.g., timing of imaging relative to contrast administration) is required to optimize the sensitivity and specificity of the CT examination.
   5. **MRI** can be used as an alternative to CT with contrast in patients with persistent hematuria of unknown cause. Few data are available regarding its use, however.
   6. **Renal biopsy.** If clinical evidence suggests acute glomerulonephritis or other glomerular problems (such as those associated with proteinuria and red cell

casts), renal biopsy may be more valuable than radiographic evaluation.

7. **Bilateral retrograde pyelography with cytologic study** provides information regarding small lesions when cytology is abnormal and no definite lesion is seen at urography.
8. **Selective renal arteriography.** Vascular lesions such as arteriovenous malformation and small renal cell carcinomas can produce hematuria and not be visible on any of the studies listed previously. These lesions may be clearly depicted by arteriography. However, if the other studies fail to delineate the cause of hematuria, the yield with angiographic studies will be very low.

F. **Evaluation of the renal transplant.** Some practitioners find that obtaining baseline radionuclide and ultrasound studies posttransplant provides a useful frame of reference for interpretation of subsequent examinations.

Although a particular study may be best for a specific transplant complication, using a combination of studies to separate the multiple variables is often clinically necessary.

1. **Radionuclide studies.** With decreased transplant function, especially early in the postoperative period, isotope studies may be useful in diagnosis of renal arterial or venous thrombosis. Vascular abnormalities can be differentiated from acute tubular necrosis, rejection, or immunosuppressive drug toxicity. There may be some overlapping findings with these pathologies, however, and correlation with Doppler ultrasound is frequently useful. As with native kidneys, evaluation of the excretory phase is useful in determining presence of obstruction. Extravasated radionuclide may be detected as evidence of leak of urine from the ureterovesical anastomosis or elsewhere.
2. **Ultrasound.** Duplex Doppler ultrasound is useful to confirm transplant arterial and venous patency. Ultrasonography is used additionally to assess any suspected fluid collection in the pelvis, such as lymphocele, hematoma, abscess, or urinoma. Ultrasound-guided aspiration of any fluid identified allows a specific diagnosis to be made. Obstruction can also be detected with ultrasound and differentiated from rejection and acute tubular necrosis. Although morphologic changes accompanying rejection (edema, loss of sinus fat, prominent medullary pyramids) are identifiable with ultrasound, accuracy of diagnosis of rejection with imaging is poor. Analysis of Doppler ultrasound tracings of arterial branches in the kidney can improve diagnosis of rejection (resistive index of more than 0.70 is correlated with rejection). There is significant overlap with other pathologies, however. Biopsy is commonly used to confirm rejection.
3. Ultrasound-guided **renal biopsy** is commonly required to confirm a diagnosis of rejection and is generally used when imaging studies show no other explanation for transplant dysfunction. Arteriovenous malformations, which can occur as a complication of biopsy, can be detected with color Doppler ultrasound.
4. **MRI/magnetic resonance angiography.** MRI can detect alterations in renal morphology accompanying rejection, but it is not commonly used clinically. Magnetic resonance angiography may develop a role in evaluating the transplant renal artery.
5. **CT** can evaluate the tissues surrounding the transplant, and it is sometimes useful in evaluating the extent of abscess or other fluid collection identified by ultrasound.
6. **Renal angiography.** If the noninvasive studies mentioned previously suggest significant arterial pathology, angiography may confirm the diagnosis. In the attempt to avoid contrast material administration in the setting of decreased renal function, this is not appropriate as an initial evaluation.

G. **Evaluation of renal and perirenal infection.** Pyelonephritis is generally diagnosed through a combination of clinical (flank pain or tenderness, fever) and laboratory (pyuria, positive urine cultures) findings. Imaging is generally not necessary in the setting of an uncomplicated infection that responds appropriately to antibiotic treatment. Imaging is useful in the setting of acute infection, when initial high suspicion of complicated infection (e.g., behind obstruction) exists, or when the patient does not respond rapidly to intravenous antibiotics, raising a question of abscess. In patients with chronic/recurrent infections, nonurgent imaging is useful to evaluate for structural abnormalities that may predispose to infection (e.g., obstruction, reflux).

1. **Acute infection/complicated infection.** The patient who presents with sepsis or does not rapidly respond to treatment for bacterial infection may suffer from pyonephrosis (infection behind an obstruction), acute focal bacterial nephritis, renal abscess, perinephric abscess, or, less commonly, emphysematous pyelonephritis or xanthogranulomatous pyelonephritis. Imaging strategies are aimed at identifying any of these processes and at guiding treatment, frequently with imaging-guided percutaneous drainage-catheter placement.
   a. **Abdominal film.** The abdominal radiograph may identify radiopaque calculus, raising suspicion of obstruction with pyonephrosis. However, further imaging to characterize the problem and plan treatment is required. Calcifications may also be identified accompanying xanthogranulomatous pyelonephritis. Gas related to the kidney, ureter, or bladder may be identified with emphysematous infection.
   b. **Excretory urography** may be useful to define the presence of calculus with or without obstruction. A mass may be seen with focal pyelonephritis or with abscess. Only secondary signs of large sub-capsular or perinephric collections are evident. Because of lack of sensitivity and specificity in diagnosing abscesses that require drainage, the usefulness of excretory urography is limited.
   c. **Ultrasound.** Identification of a dilated collecting system in the setting of infection raises the suspicion of pyonephrosis. Although internal echoes and shifting fluid debris levels may be evident with infected fluid, even anechoic fluid may be infected. Ultrasound-guided aspiration, nephrostomy catheter placement, or both may be useful to diagnose and treat pyonephrosis. A renal abscess is generally identified by ultrasound as a hypoechoic mass containing complex fluid centrally. Diagnostic aspiration and drainage can be performed with ultrasound guidance. Perinephric or subcapsular abscess may be identified with ultrasound and aspirated with ultrasound guidance. However, ultrasound frequently underestimates the extent of such fluid collections adjacent to the kidney, and CT scan is generally recommended to confirm the full extent of the abnormality in treatment planning.
   d. Contrast-enhanced **CT** may demonstrate a very heterogeneous or striated nephrogram in the setting of uncomplicated pyelonephritis. A focal mass-like area of poor enhancement is seen with focal pyelonephritis. When this mass becomes liquified, an abscess can be diagnosed. Presence of gas within such a fluid collection argues strongly for infection, but many abscesses lack gas. Differentiation from necrotic neoplasm can occasionally be difficult. CT-guided aspiration confirms the diagnosis, and a drainage catheter can be placed if clinically indicated. If the fluid collection is less than approximately 3 cm in greatest dimension, drainage catheter placement may not be necessary or possible. A large focal area of pyelonephritis may evolve into an abscess, so follow-up imaging may be useful with that finding, especially if the patient is not resolving clinical symptoms. Subcapsular or perinephric fluid collections are readily detected with CT (Fig. 15-20). Any extension into surrounding tissues, including the psoas muscle, can be well evaluated with this technique and percutaneous or surgical drainage planned. Gas within the collecting system, within the walls of the collecting structures, or within the substance of the kidney can be seen with emphysematous pyelonephritis, most commonly seen in diabetic patients. Extensive gas within the renal parenchyma is a poor prognostic sign, and nephrectomy may be necessary.

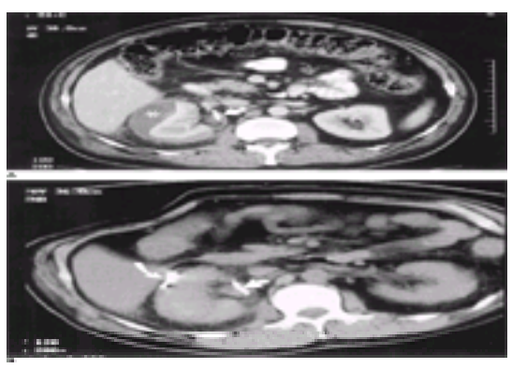

Figure 15-20. A: Subcapsular renal fluid collection (infected hematoma) identified with computed tomography (*asterisk*). A ureteral stent is in place (*arrow*). **B:** Fluid collection has resolved with percutaneous drainage catheter placement (*curved arrow*). Proximal end of a ureteral stent is seen in the renal pelvis (*straight arrow*).

   e. **Radionuclide scan.** Gallium 67 citrate or indium 111 leukocyte scans can be useful to localize inflammatory processes, including those in the kidney or surrounding tissues. Because of the high accuracy of the aforementioned imaging studies, radionuclide scans are seldom clinically necessary.
   f. **MRI** studies can demonstrate pyonephrosis, renal abscess, or perinephric abscess. Because of the difficulty of performing image-guided invasive procedures in a magnetic resonance scanner in comparison to a CT scanner, however, CT is generally preferred.

2. **Chronic and recurrent infection.** Repeated episodes of clinical pyelonephritis, especially in children, raise the question of reflux and related reflux nephropathy. Imaging strategies are aimed at identifying vesicoureteral reflux and associated damage to the kidneys and at identifying other structural abnormalities that may produce persistent or recurrent infection.
   a. **Abdominal film.** The abdominal radiograph is generally not useful in diagnosis of reflux, but it may identify calculi as a cause of recurrent or persistent infection.
   b. **Excretory urography** can demonstrate parenchymal scars overlying blunted and clubbed calyces, characteristic of reflux nephropathy. Urography cannot

define whether reflux is ongoing. Other structural abnormalities, including congenital ureteropelvic junction obstruction or duplicated collecting system with upper pole obstruction, can be defined with this technique.

c. **VCUG** evaluates for the presence of reflux and is generally most useful when done between episodes of pyelonephritis (see section **I.E**).

d. **Radionuclide studies.** Focal parenchymal defects related to reflux nephropathy can be well defined with radionuclide studies and are a routine part of this evaluation in some pediatric practices.

H. **Evaluation of renal hypertension.** Renal hypertension is defined as hypertension due to an anatomic renal abnormality. Hypertension may be associated with renal artery stenosis or renal parenchymal disease, and, much less commonly, with a renal mass, renin-secreting tumor, or other vascular abnormality. Evaluation of renal parenchymal disease and masses has been discussed above. The approach to the patient with the possibility of clinically significant renal artery stenosis (renal vascular hypertension) is the subject of ongoing controversy and research. The accuracy of any of the imaging studies discussed here in this condition depends highly on patient selection. Important factors in patient selection are discussed elsewhere in this manual. Published reports of the accuracy of these various noninvasive studies are extremely variable. No study can be universally recommended, and consultation with local imagers regarding their experiences is highly recommended.

1. **Radionuclide studies.** Renography performed with and without angiotensin-converting enzyme inhibitor administration is an effective screening test for renal artery stenosis. Although local experiences vary, this is the most widely used examination at present.
2. **Duplex Doppler ultrasound.** Evaluation of the main renal arteries with color/pulsed Doppler ultrasound and evaluation of the intrarenal arterial Doppler signals can be a highly effective screening examination. In high-volume laboratories, accuracy may be the same as or better than in radionuclide studies at the same institution. However, accuracy is considerably less among analysts with less experience.
3. **Magnetic resonance angiography** can be highly accurate in diagnosing renal artery stenosis (Fig. 15-21). As this technique becomes more widely available and experience increases, it may replace other noninvasive studies.

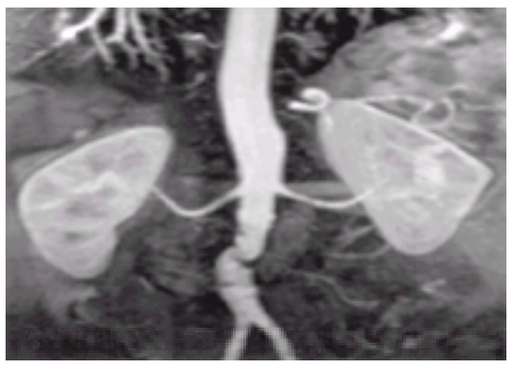

Figure 15-21. Renal magnetic resonance arteriogram. Normal examination.

4. **CT angiography.** Spiral CT scanners can be used to generate high resolution images of the renal arteries with contrast administration, mimicking conventional radiographic arteriography. Clinical experience is limited, however.
5. **Renal vein renin assay** can be useful in providing a measurement of the causal relation of renovascular lesions and hypertension. It is an invasive study, sampling the renal veins and the inferior vena cava below the renal veins. This may be useful at the time of arteriography to confirm the physiologic significance of an identified anatomic abnormality.
6. Selective **renal angiography** provides definitive diagnosis of renal arterial pathology, but it is not appropriate as a screening study because of its invasive nature. Atherosclerosis that involves the main renal artery at or near its origin is most common in old age. Fibromuscular dysplasia is the most common cause of renovascular hypertension in patients younger than 40 years of age. It occurs more peripherally in the main renal artery or within the extraparenchymal or intraparenchymal branches. Angioplasty to treat the stenosis can be considered at the time of the diagnostic angiogram.
7. **Excretory urography** is not sensitive or specific in the diagnosis of renal vascular hypertension and should not be performed for this purpose.

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