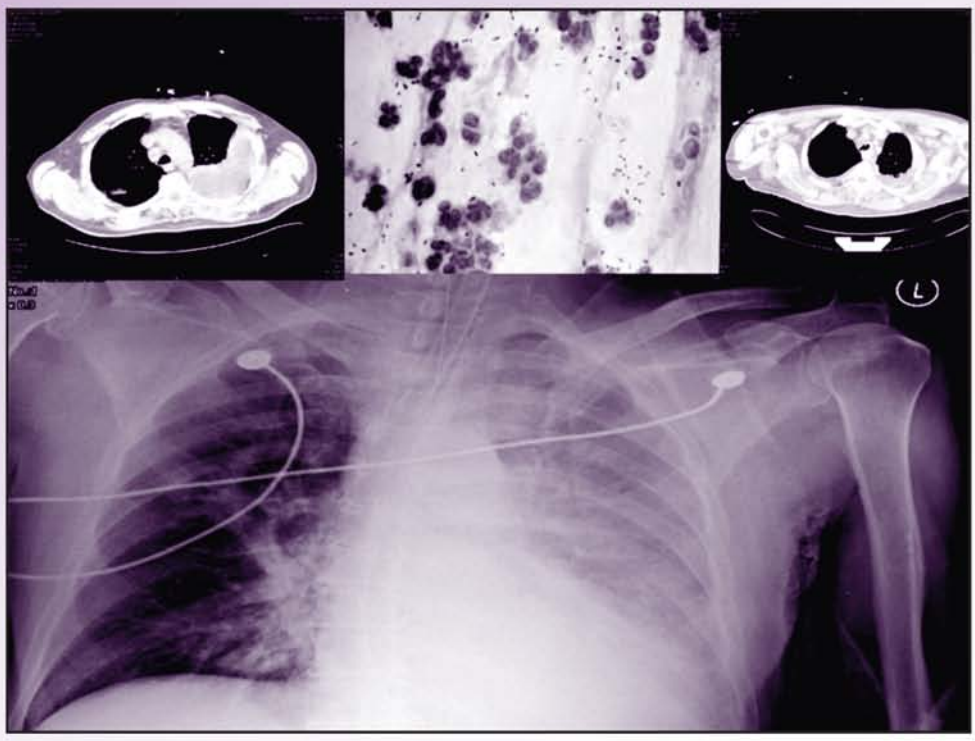
Lung Biology in Health and Disease Volume 206

Executive Editor: Claude Lenfant

Severe Pneumonia



edited by

Michael S. Niederman

SEVERE PNEUMONIA

LUNG BIOLOGY IN HEALTH AND DISEASE

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SEVERE PNEUMONIA

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Introduction

It has been reported that during the first century of the existence of the United States, infectious diseases were most prevalent as well as the leading cause of death. Among these diseases, influenza and pneumonia occurred in repeated epidemics.

In 1906, William Osler commented in a chapter "Medicine in the Nineteenth Century" from the book titled *Aequanimitas, with other Addresses to Medical Students, Nurses and Practitioners of Medicine* (1):

> "In the mortality bills, pneumonia is an easy second to tuberculosis; indeed, in many cities the death rate is now higher and it has become, to use the phrase de Bunyan, 'the Captain of the men of death.' (2)"

At the turn of the twentieth century, in 1902, the Rockefeller Institute for Medical Research was created. At that time, pneumonia had a mortality rate of about 40%. For this reason, the first research project initiated by the Rockefeller Institute Hospital after opening in 1910 was on *Pneumococcus* pneumonia. Later, in 1918 a Pneumonia Commission was created to assure a coordinated attack against this disease.

Today, pneumonia remains a major public health problem in the United States. From 2000 to 2003, slightly more than 2.4 million deaths occurred each year. The number of deaths due to pneumonia oscillated between 61,000 and 65,000 per year, or about 2.7% of all deaths, most of them in the over 65 years old population. This population experienced about 1.8 million deaths a year during this period; 3.25% of these deaths were due to pneumonia.

Pneumonia exerts a toll in all countries, and is even more of a burden in developing countries. Furthermore, it is now well recognized that pneumonia and influenza are significant risk factors for exacerbation and aggravation of

chronic pulmonary diseases such as asthma and chronic obstructive pulmonary disease. Undoubtedly, pneumonia is a complicated disease due to multiple causes, some occurring in health care settings. Its treatment is complex and requires diligence as well as specialized knowledge.

This volume, *Severe Pneumonia*, edited by Dr. Michael S. Niederman, provides a comprehensive description and analysis of pneumonia, its causes, and therapeutic approaches. Pneumonia knows no frontier and thus concerns about this disease in the United States are also the concerns of experts in many other countries. Dr. Niederman has capitalized on the knowledge and experience of international experts by inviting them to share their knowledge with the readership of the Lung Biology in Health and Disease Series.

As Executive Editor, I am grateful and thankful to Dr. Niederman and all his contributors for developing this monograph which undoubtedly will set a new standard in the treatment of patients with pneumonia.

Claude Lenfant, MD
Gaithersburg, Maryland

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Preface

Pneumonia is the number one cause of death from infectious diseases in the United States and can arise both in the hospital as well as in the community. When patients enter the intensive care unit with pneumonia, they have the most severe form of the illness, and the factors that lead to development of severe pneumonia, the optimal management of this disease, and the efforts that can be made to control and improve outcomes in this disease are of great importance to the practicing physician. The aim of this book is to outline the problems associated with the pathogenesis of severe pneumonia and to use these basic principles to guide effective management.

At the current time when patients develop pneumonia, it is sometimes uncertain when they cross the line into severe illness and will benefit from admission to the intensive care unit. This book explores the prospective clinical definition of severe pneumonia, including patients with community-acquired pneumonia, nosocomial pneumonia, and ventilator-associated pneumonia. The bacteriology of severe pneumonia is not, in many instances, very different from that of less severe forms of pneumonia and, therefore, the host inflammatory response to infection is a key determinant of whether or not patients develop severe illness. The cytokine response to infection is discussed along with the reasons why patients with pneumonia progress to severe illness. When patients develop pneumonia during mechanical ventilation, there are a number of pathogenic factors including their underlying chronic illness as well as the mechanical ventilator itself. The role of the ventilator in pneumonia pathogenesis is becoming clear, particularly since noninvasive mechanical ventilation can prevent pneumonia. Therefore, we explore the role of mechanical ventilation in the pathogenesis of this illness.

In an effort to better understand how to optimally manage patients with severe community-acquired pneumonia, it is necessary to look at prognostic scoring systems that identify risk factors for death as well as specific

patient features associated with a higher risk of severe illness. These factors are explored and the practical utility of scoring systems for patient managements is discussed. Ultimately, however, to improve the outcome in severe community-acquired pneumonia, it is necessary to anticipate the likely bacteriology and to craft an empiric therapy regimen that covers all likely etiologic pathogens. Both the bacteriology and regimens for empiric therapy are evaluated and examined.

When pneumonia arises during mechanical ventilation, patients are at great risk for mortality, and, in fact, ventilator-associated pneumonia is the leading cause of death from nosocomial infection in the intensive care unit. In this book we examine the risk factors and frequency of ventilator-associated pneumonia as well as the mortality implications of this disease and the factors associated with attributable mortality from ventilator-associated pneumonia. Although it is possible to define the clinical consequences of pneumonia, there remains great controversy about how to diagnose pneumonia and whether it could be diagnosed by clinical means alone or if specific invasive methods with microbiologic cultures should be used. The answers to these questions remain elusive and both sides of this controversy are presented.

To deal effectively with patients who have ventilator-associated pneumonia, it is necessary to choose appropriate antibiotic therapy. Effective choice is limited to some extent by the increasing frequency of antibiotic resistance in the intensive care unit. Therefore, we examine the mechanisms of antibiotic resistance in the intensive care unit and ask how knowledge of antibiotic resistance can be used to achieve optimal and adequate antibiotic therapy. This involves not only knowledge of microbiology and choices of therapy, but also an understanding of the role of microbiologic surveillance. Also, when choosing antibiotic therapy, it is not always enough to choose the right antibiotic, but it is also necessary to choose the appropriate dose and dosing regimen. The science of pharmacokinetics and pharmacodynamics is evolving and the principles associated with this discipline can be used to help with antibiotic choices in the intensive care unit. Specifically, an understanding of pharmacokinetics and pharmacodynamics can help explain the controversies surrounding the use of mono versus combination therapy for the management of ventilator-associated pneumonia.

The future in managing and preventing severe pneumonia is bright and a number of preventive strategies are being developed. These preventive strategies are examined along with new ideas for diagnosis and management that are still in the developmental stage.

I hope that through this book the reader will gain a better appreciation of the pathogenesis, bacteriology, and important clinical features associated with severe pneumonia. Only through an understanding of these complex features will more effective management and prevention become possible, which is our true hope for the future.

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1

Severe Pneumonia: Definition of Severity

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INTRODUCTION

The assessment of severity in patients with community-acquired pneumonia (CAP) has evolved as a key determinant in currently recommended guidelines of the management of this condition (1–9). The principal conceptual idea behind this is to build up risk-adapted algorithms. It definitely leaves behind traditional syndromatologic approaches based on the typical–atypical paradigm, which proved to be invalid for predictions of underlying microbial etiologies. Ideally, the assessment of severity serves as a framework that allows one to: (1) predict the risk of morbidity and mortality as well as the specific microbial and resistance patterns, and (2) derive decisions about the most adequate treatment setting, amount of microbiological workup, as well as initial empiric antimicrobial treatment.

In view of the crucial importance of the assessment of pneumonia severity, the definition of severe pneumonia has gained much interest in the recent literature. We review the evidence from the recent literature regarding prognostic factors, prognostic rules, and severity criteria and their implications for clinical decision making. At the same time, emphasis is given to explaining unresolved critical issues with regard to severity assessment.

ROLE OF SEVERITY ASSESSMENT OF CAP

The guidelines of the American Thoracic Society (ATS) (1,2), the Canadian Thoracic Society (3), the Infectious Disease Society of America (IDSA) (4,5), the British Thoracic Society (6), and the European Respiratory Society (7,8) all agree that severe CAP represents a pneumonia syndrome of its own that requires a distinct approach to diagnosis and treatment.

Usually, severe CAP is an entity described in the literature in reference to patients admitted to the intensive care unit (ICU). In fact, the first 16 reports until 1996 about severe CAP had simply ICU admission as the only criterion of patient inclusion (10). However, the decision to admit a patient with CAP to the ICU may depend on subjective clinical views and peculiarities of the local treatment setting. Therefore, the establishment of valid criteria for a definition of severe pneumonia would form a more reliable basis for any effort to improve patient risk assessment in daily practice as well as in diagnostic or therapeutic trials.

Pathophysiologic Clues to Predictors of Severity

Prior to consideration of the data available on predictors of severity, it seems worthwhile to have a brief look at the basic pathophysiologic mechanisms that determine the clinical severity of pneumonia. Such an approach provides important clues to the recognition of the truly independent predictors directly reflecting the severity of inflammation and its sequelae (11).

The most common route of inoculation of infectious pathogens into the terminal airways is the aspiration of bacteria-loaded secretions of the upper airway, especially during sleep. The inhalational route is less frequently encountered, except in the case of infection with viruses, atypical organisms (e.g., *Legionella* spp., *Mycoplasma pneumoniae*), mycobacteria and fungi (e.g., *Aspergillus* spp.). Other rare routes of bacterial invasion into the lung are hematogeneous emboli from distant infectious foci or spread from infections via direct contact (12).

When aspiration of bacteria-loaded secretions or inhalation of bacteria into the terminal airways occurs, the interactions between the invading pathogens and the pulmonary host defenses determine the outcome, i.e., clearance of bacterial challenge or infection.

With regard to the offending pathogens, a high bacterial load as well as the virulence of the microorganisms are factors that may overwhelm the host defense. The critical bacterial load capable to establish an infection has been assessed in several animal studies. For example, the alveolar macrophages have been shown to be capable to eliminate a challenge of up to 10^5 cfu/mL of *Staphylococcus aureus*, whereas particular virulent microorganisms such as *Pseudomonas aeruginosa* caused infection in much lower amounts (13). In the experimental setting, an inoculum in the order of 10^7 cfu/mL or more has been demonstrated to overwhelm even normal host

defenses (14). However, it is not known whether the bacterial load is a factor independently associated with pneumonia severity.

Pathogen-related factors of virulence are numerous. Each pathogen has a typical set of virulence factors that determine pathogen-specific patterns of injury. For example, *Streptococcus pneumoniae* is characterized by its antiphagocytic capsule serotypes, typically associated with bacteremia, *Haemophilus influenzae* exerts local damage to the tracheobronchial mucosa by IgA proteases and ciliotoxins, and *Legionella* spp. typically are resistant to phagosomes. Both *S.* aureus and *P. aeruginosa* have several adhesion factors and cytotoxins promoting the initiation of infection and exert a battery of additional enzymes for its propagation. In clinical studies, it has been demonstrated that severe CAP is more frequently associated with bacteremia and distinct microorganisms such as *S. pneumoniae, S. aureus*, *Legionella* spp., Gram-negative enteric bacilli (GNEB), particularly *Klebsiella pneumoniae*, and *P. aeruginosa* (15–20).

On the other hand, the integrity of the mucosal barrier and the first line cellular defense are the two host-related factors that may preclude a significant infectious injury. In case of a small bacterial load together with a limited virulence, the first line cellular defense (i.e., the alveolar macrophages) can sucessfully eliminate the pathogens without inducing an extensive local inflammatory response. Otherwise, the alveolar macrophages will recruit polymorphonuclear cells (PMNs) from the pulmonary microvasculature via cytokine expression, mainly including tumor necrosis factor (TNF), interleukin 1 (IL-1), interleukin 6 (IL-6), and interleukin 8 (IL-8) (12,21). By definition, this is the starting point of what we call pneumonia.

The clinical severity of pneumonia depends on three main factors:

1. Local extension
2. Pulmonary spread
3. Systemic spread of the inflammatory response

An inflammatory response confined to a limited area of the lung may remain clinically asymptomatic or cause only minor symptoms such as fever, cough, and mild leucocytosis without any vital sign abnormalities. If, however, the inflammation cannot be controlled within a small area due to pathogen or host factors or because of a multifocal process, a ventilation–perfusion mismatch significant enough to cause an oxygenation failure may result (22). Such an extension of inflammation is usually readily detectable on chest radiograph. The amount of clinical respiratory symptoms may range from mild dyspnea up to severe acute respiratory failure requiring mechanical ventilatory support. In the latter case, mismatching of ventilation and perfusion may include a shunt fraction of up to 20–25% and a dead space ventilation up to 45–50% may be present. Finally, pathogen-related as well as host factors will determine whether this can be cleared or severe sepsis or septic shock will develop. The development of severe

sepsis or septic shock may not strictly correlate with the amount of pulmonary infectious injury, although most often it is associated with acute respiratory failure as well as extensive, and frequently multilobar, infiltrates.

This basic sequence of events is modified by four factors:

1. Genetic susceptibility
2. Age
3. Underlying comorbidities including both pulmonary and extrapulmonary conditions
4. Antimicrobial treatment

Exciting insights into genetic factors determining the susceptibility to septic shock in severe pneumonia have been presented. In patients with CAP, the carriage of the AA (TNF-α-hypersecretor) genotype at either the TNF-β+250 or TNF-α-308 polymorphism sites was associated with a significantly increased risk of developing septic shock (18.8 vs. 7.2%) (23).

In the presence of severe COPD, not only may pneumonia more readily develop but also respiratory compromise may occur much earlier (24). In these patients, even limited infectious foci causing small increases of ventilation–perfusion inequalities may lead to severe acute respiratory failure. The same is true for patients with other underlying pulmonary comorbidities and severe congestive heart failure. Factors which may favor septic complications by impairing cellular host defenses include alcohol abuse, iatrogenic immunosuppression with corticosteroids, and other conditions associated with partial cellular or humoral immunodeficiencies such as diabetes mellitus, liver disease, or splenectomy (25,26).

A single dose of appropriate antimicrobial treatment reduces the load of most pathogens encountered in CAP within 12–24 hr, particularly *S. pneumoniae* and *H. influenzae*, thereby significantly modifying the natural history of the infectious inflammatory response. In fact, we have shown that ambulatory antimicrobial treatment is protective against the development of severe CAP (27). Accordingly, an adverse outcome of CAP in the elderly was demonstrated to be closely related to a delay in the administration of antimicrobial treatment (28). The effects of immediate administration of appropriate antimicrobial treatment are less evident in virulent pathogens such as *P. aeruginosa,* which are capable of effectively defending themselves against the antimicrobial challenge.

Finally, it is important to recognize that the inflammatory response is a dynamic event. Once the patient has become symptomatic, the further evolution will be decided within hours and days. Therefore, the timepoint of the initial clinical evaluation may not adequately reflect the true severity of the disease that is developing.

The following clinically recognizable factors will determine the severity of pneumonia at initial clinical evaluation:

1. Age and comorbidity
2. Acute respiratory failure and severe sepsis or septic shock
3. Radiographic extension of infiltrates

Excitingly, these are exactly the main factors that directly or indirectly have been identified as the main predictors of adverse outcomes and, consequently, as predictors of severity.

Prognostic Factors

Prognostic factors associated with death from pneumonia have been continuously studied in diverse patient populations, and, as outlined in detail in recent reviews covering this subject, there are more than 40 corresponding predictors in multivariate analyses (25,29). The adverse independent prognostic factors reported in the last decade are listed in Table 1 (15,18,30–42). A meta-analysis comprising 122 studies and dealing with the investigation of prognostic factors found 10 independent predictors of death, including male gender, diabetes mellitus, neoplastic disease, neurologic disease, tachypnea, hypotension, hypothermia, leukopenia, bacteremia, and multilobar infiltrates, with pleuritic chest pain as protective factor (43).

From a clinical point of view, it seems useful to arrange these variables, similar to the APACHE score, into factors reflecting acute pneumonia related-illness and those reflecting the underlying health state (25,29). The former can be further divided into clinical signs and symptoms and laboratory, radiographic, microbiological and oxygenation parameters; whereas the latter would include age, sex, referral (home or nursing-home), comorbidity, and steroid pretreatment. A third group of parameters would represent evolutionary parameters reflecting disease progression. These factors differ in that they are not available at the time of initial assessment but indicate prognosis during the course of disease. Again, these factors can be divided into clinical, radiographic, and treatment-associated parameters as well as other complications.

If we look at the variety of factors found to be associated with death, it appears that the main determinants of prognosis include age, male sex, comorbidity, acute respiratory failure, severe sepsis and septic shock, extension of radiographic infiltrates, bacteremia, and CAP caused by several different pathogens (*S. pneumoniae*, *S. aureus*, Gram-negative enteric bacilli (GNEB), and signs of disease progression within the first 48–72 hr.

Risk Score Assessment

Although published in 1997, Fine et al.'s study (44) is already a classic reference for the assessment of mortality by a risk score. Although the study was primarily used to determine which patients can be safely treated as

Table 1 Independent Prognostic Factors Associated with Death from CAP in Studies Originating from the Last Decade Including Both the General and the ICU Treated Populations

Population	Reference
General	
Respiratory rate $\geq$ or >30/min	32–34
Systolic blood pressure $\leq$80 mm Hg or $<$90 mm Hg	32–34, 36
Diastolic blood pressure $<$60 mm Hg	32–34
Blood urea nitrogen $>$7 mmol/L	32–34
Heart rate $\geq$90 bpm	36
Mental confusion	32–34
Low lymphocyte count	31
Low serum albumin	31
LDH $\geq$260 U/L	36
Bilateral pleural effusions	37
Elderly	
Temperature $\leq$37°C	38
Respiratory rate $\geq$30/min	38
Number of affected lobes $\geq$3	38
Bedridden state	38
ICU-treated: General	
Age	15, 56
Anticipated death within 4–5 years	15, 56
SAPS $>$12 or $>$13	15, 18
Bilateral infiltrates	15
Requirement for mechanical ventilation	15, 56
Septic shock	15, 18, 39, 40, 56
Involvement $>$1 lobe	56
Rapid radiographic spread	39
Inadequate or ineffective initial antimicrobial treatment	39, 40
Nonpneumonia related complications	40
Nonaspiration pneumonia	56
Bacteremia	40
Streptococcus pneumoniae	18
Gram-negative enteric bacilli (GNEB)	18
P. aeruginosa	15
ICU-treated: Elderly	
Septic shock	41
Acute renal failure	41
Rapid radiographic spread	41

outpatients, the score is now increasingly being used to discriminate between mild and moderate severe pneumonia.

In a study comprising a derivation and validation population of more than 50,000 patients from the Medisgroups and PORT cohorts, a two-step risk score was developed (44). Data necessary for the calculation of the rule were assessed within the first 24 hr (i.e., not necessarily at admission). In a first step, the patient with a very low mortality risk (risk class I) is identified by age <50 years, lack of comorbidity, and the absence of vital sign abnormalities. In a second step, risk classes II–V are calculated summing up points assigned to age, comorbid conditions, as well as vital sign abnormalities, and diverse epidemiological, laboratory, oxygenation, and radiographic features recorded within the first 48 hr after the primary clinical evaluation (Table 2). It is noteworthy that in this risk score, age determines the risk class assignment to the largest extent. Additional factors with exceptionally high impact on the risk score (30 points) include neoplastic disease and mild acidosis.

The first two risk classes were associated with a very low risk of mortality of $<1\%$, whereas risk classes III–V were associated with a 2.8, 8.2, and 29.2 and 1.2, 9.0, and 27.1% mortality in the derivation and validation cohorts, respectively. Thus, risk classes I–III are now frequently regarded as mild-to-moderate pneumonia with a risk of mortality no higher than 3%, whereas classes IV–V are addressed as severe pneumonia.

Fine et al.'s pneumonia severity index (PSI) proved to provide excellent predictions on risk class-associated mortality. For example, we recently validated this rule in an elderly population with CAP. Mortality rates for risk classes II–V (risk class I was absent by definition) were 0, 2.7, 7.5, and 30.3%, respectively (45).

The most useful implication for the practitioner is the fact that patients in lower risk classes I–III have low risk of mortality and, therefore, are candidates for ambulatory treatment. Nevertheless, several limitations of the PSI have been described when used as the guide for hospitalization decisions. These limitations mainly relate to the fact that: (1) pneumonia severity in younger patients may be underestimated due to the large impact of higher age in this score, and (2) pleural effusion may represent a typical reason for non-severity-related hospitalization (46). Finally, it is important to recognize that the use of the PSI means relying on the risk of mortality as the only determinant of hospitalization. This may be inappropriate since practical and social reasons for hospitalization should also be taken into account.

In this context, the most important question is how many patients require ICU admission despite having been classified as low risk patients (risk classes I–III). In a recent study, 8% of risk class II and 5% of risk class III required ICU admission. In view of the fact that these patients have been classified as low-risk patients who can be treated as outpatients, this lack in

Table 2 Criteria Used in the Severity Assessment Model for CAP (Risk Classes II – V)

Criterion	Points
Age	Age (years)
Female sex	−10
Nursing home residency	10
Comorbidity	
Neoplastia[a]	30
Liver	20
Congestive heart failure	10
Cerebrovascular disease	10
Renal disease	10
Vital sign abnormality	
Mental confusion	20
Respiratory rate ≥30/min	20
Systolic blood pressure <90 mm Hg	20
Temperature <35 or ≥40°C	15
Tachycardia ≥125 bpm	10
Laboratory abnormalities	
Blood urea nitrogen ≥11 mmol/L	20
Sodium <130 mmol/L	20
Glucose ≥250 mg/dL	10
Hematocrit <30%	10
Radiographic abnormalities	
Pleural effusion	10
Oxygenation parameters	
Arterial pH <7.35	30
PaO_2 <60 mm Hg	10
SaO_2 <90%	10

Point scoring system: risk class I, age <50, no comorbidity, no vital-sign abnormality; risk class II, ≤ 70 points; risk class III, 71–90 points; risk class IV, 91–130 points; and risk class V, >130 points.
[a]Criteria from Fine et al. (44).

sensitivity is a serious concern. The specificity of risk classes IV and V was also limited (53%). Thus, although the PSI provides excellent predictions of group-related risks of death, these data clearly demonstrate that the PSI is not an appropriate tool for the prediction of an individual patient with pneumonia requiring ICU admission (47). Having said this, it appears that the term ''severe pneumonia'' based on PSI scores should not be used in clinical studies. Instead, ''increased or high-risk group'' or similar labels appear more appropriate.

BTS Severity Criteria and Risk Score Assessment

Since the report of the British Thoracic Society (BTS) on CAP, indicating that in-hospital mortality of the individual patient can accurately be predicted by prognostic rules including only a few simple clinical or laboratory parameters, there has been considerable interest in validating these rules (Table 3) (30,32–35,48,49). Several studies could confirm excellent operative characteristics of the original (32,33) or a slightly modified rule (34). The

Table 3 Prognostic Rules for the Individual Outcome in Patients with CAP and Their Performances

	Sensitivity	Specificity	PPV	NPV
Rule 1				
Derivation study (30)	88	79	19	99
Validation studies				
Farr et al. (32)	70	84	29	97
Karalus et al. (33)[a]	83	80	23	99
Neill et al. (34)	90	76	25	99
Lim et al. (35)	52	79	n.r.	n.r.
Ewig et al. (36)[b]	65	73	21	95
Conte et al. (48)[b]	50	70	n.r.	n.r.
Rule 2				
Derivation study (30)	39	94	36	97
Validation studies				
Farr et al. (32)	35	89	22	94
Neill et al. (34)	65	88	33	97
Ewig et al. (36)[b]	47	88	31	94
Rule 3				
Derivation study (34)	95	71	22	99
Validation study (35)	66	73	n.r.	n.r.
Rule 4				
Derivation study (36)	77	75	42	93
Validation study (45)[a]	47	80	21	93

Rule 1 (original BTS-rule 1)—at least two of the following: respiratory rate $\geq$30/min; diastolic blood pressure $\leq$60 mmHg; blood urea nitrogen $>$7 mmol/L.
Rule 2 (original BTS-rule 2)—at least two of the following: respiratory rate $\geq$30/min; diastolic blood pressure = 60 mmHg; mental confusion.
Rule 3 (modified BTS-rule)—at least two of the following: respiratory rate $\geq$30/min; diastolic blood pressure = 60 mmHg; blood urea nitrogen $>$7 mmol/L; mental confusion.
Rule 4 (Ewig et al.)—at least two of the following: systolic blood pressure = 80 mmHg; heart rate = 90 bpm; LDH $\geq$260 U/L.
[a]Using rule 1 or rule 2.
[b]Elderly population ($\geq$65 years).
PPV, positive predictive value; NPV, negative predictive value; n.r., not reported.

sensitivities ranged from 70% to 90%, and the specificities from 76% to 84% (Table 3). More recently, two studies have failed to confirm these favorable prediction results, one in a general (35) and another in an elderly population (48). We developed an alternative rule that displayed similar predictive potential (36).

Since the majority of sicker patients with CAP belong to the elderly population, we were particularly interested in the performance of the original BTS rules in these patients. We hypothesized that elevated blood urea nitrogen that is more frequently present, or at least can more readily develop in the elderly, would represent a confounding factor whereas mental confusion as a marker of severe sepsis would work particularly well in this frequently oligosymptomatic population. In fact, we found that blood urea nitrogen had only a very low specificity whereas the opposite was true for mental confusion. Accordingly, the second BTS rule had the best performance as evidenced by operative indices (sensitivity 47%, specificity 88%) as well as by risk assignment of prognostic rules according to risk classes as proposed by Fine et al. (45).

Looking at the performance of these rules, two issues should be pointed out. First, the predictive power of these simple rules is considerably high. This can best be explained if we consider that these rules include parameters mainly reflecting two of the most important prognostic factors, i.e., acute respiratory failure (respiratory rate $\geq$30/min) and severe sepsis or septic shock (blood urea nitrogen, mental confusion, hypotension, or tachycardia). Second, since specificity was consistently found to be high but sensitivity to be quite variable, the true strength of these rules is their negative predictive value, i.e., the identification of patients who are not at risk of death from pneumonia. This value was found to exceed 90% in all validation studies published so far (32–35,48).

In contrast, the BTS criteria were not found to be accurate for individual prediction of the need for ICU admission. In the study by Angus et al. (47), the BTS score in its original form (not including age and confusion) achieved a sensitivity of 40% and a specificity of 78%, resulting in a PPV of 20% and an NPV of 90%, very comparable to our results (34% and 89%, as well as 38% and 87% correspondingly). In our study, two modified BTS rules (including confusion instead of urea nitrogen, and including all four factors, predicting death in the presence of two of four) did not perform better than the original (50).

More recently, the original application of the BTS criteria was transformed from a rule for individual prediction of death from pneumonia to a risk assessment score according to the PSI. The score consists of the four BTS severity criteria based on information available at initial hospital assessment, resulting in the acronym of CURB (Confusion, Urea nitrogen $>$7 mmol/L, Respiratory rate $\geq$30/min, systolic or diastolic Blood pressure $<$90 and $\leq$60 mmHg). It is calculated assigning one point in the

presence of each criterion. It was further modified by adding the criterion of age >65, which resulted in the modified acronym "CURB65."

In fact, this rule provided impressive results. This five-point score enabled patients to be stratified according to increasing risk of mortality: score 0, 0.7%; score 1, 3.2%; score 2, 3%; score 3, 17%; score 4, 41.5%; and score 5, 57%. The validation cohort confirmed a similar pattern. The authors concluded that this simple score can be used to stratify patients with CAP into different management groups (51). In contrast to these results, in our recent validation study of different criteria for pneumonia severity, the CURB score was not superior to the CURB65 score. However, the CURB score provided the following predictions of mortality: CURB 0, 1%; CURB 1 or 2, 8%; and CURB 3 or 4, 34%. The corresponding predictions for ICU admission were 3%, 21%, and 56%, respectively (50). Thus, both studies confirm that lower CURB classes are associated with a very low mortality, whereas the highest classes are associated with a strong increase in mortality.

This score has several advantages that deserve special attention. First, it is a very simple score that can be calculated at the bedside even by nonspecialists. Second, it includes mainly clinical variables that can be assessed immediately without any sophisticated technical facilities. The only exception is the criterion of urea nitrogen, which requires laboratory testing and implies corresponding delay in score calculation. Third, it provides results very similar to the PSI, with risk scores 0–2 corresponding to PSI classes I–III, and risk scores 3–5 corresponding to PSI classes IV and V (and 0 corresponding to PSI classes I–III, risk scores 1–2 to PSI class IV, and 3–4 to PSI class V in our study). Finally, it is a true initial risk assessment score that does not suffer from the inconsistency of including potentially evolutionary criteria, which in fact does happen in the PSI criteria (by including true evolutionary criteria and by allowing assessment within the first 24 hr after admission, respectively).

However, the BTS score suffers from limitations similar to those of PSI; it provides risk estimates for groups and not for individuals. Therefore, it does not seem useful in the assessment of the need for ICU admission in the individual patient.

ATS Severity Criteria

The first definition of severe CAP in the individual patient was provided by the ATS guidelines of 1993 (1). Here, 10 criteria were listed, each of which defined the presence of severe CAP. The selection of these criteria was largely based on prognostic studies indicating that factors reflecting acute respiratory failure, severe sepsis, or septic shock, as well as extension and spread of infiltrates on chest radiograph, were the basic determinants of outcome. This means that the definition was built up around simple clinical and radiographic criteria reflecting the actual pneumonia-related morbidity, clearly focused on clinical applicability. Other relevant prognostic factors

identified in several studies and meta-analysis reflecting age, gender, amount, and types of comorbidity were not included in the definition. Accordingly, more sophisticated laboratory factors as well as pathogen-related risks were not included. A closer look reveals that the selected criteria include a first set of criteria, which must be assessed at admission, and a second one, which includes criteria that may be present at admission or during follow-up. This logical inconsistency represents a principal bias in this first definition because if we recognize the many reasons behind progressive pneumonia, it remains highly questionable whether patients meeting severity criteria at admission should be mixed with those developing severity criteria during follow-up. For example, progressive pneumonia may be caused by inadequate initial empiric antimicrobial treatment, primarily resistant pathogens, nosocomial pneumonia, or ARDS (52).

The validation of the ATS pneumonia severity criteria revealed that it was associated with high sensitivity but low specificity. Whereas 98% of patients admitted to a respiratory ICU of a tertiary care university hospital in Barcelona met at least one criterion, *no less* than 68% of patients with at least one severity criterion were not admitted. To develop a more balanced predictive rule of pneumonia severity, we rearranged the ATS severity criteria according to those available after initial clinical examination (baseline parameters) and those that are assessed either at admission or during clinical course and clearly imply more severe illness (major criteria) (Table 4). Within both groups of parameters, those independently associated with severity were assessed by multivariate analysis, and these

Table 4 Criteria for Severe Community-Acquired Pneumonia According to the ATS Guidelines (1), Rearranged According to Baseline ("minor") and Major Criteria

Baseline ("minor") criteria assessed at admission
1. Respiratory rate >30/min
2. Severe respiratory failure (PaO_2/F_IO_2 <250)
3. Bilateral involvement in chest radiograph
4. Involvement of >2 lobes in chest radiograph (multilobar involvement)
5. Systolic blood pressure <90 mmHg
6. Diastolic blood pressure ≤ 60 mmHg
Major criteria assessed at admission or during clinical course
1. Requirement for mechanical ventilation
2. Increase in the size of infiltrates by $\geq 50\%$ in the presence of clinical nonresponse to treatment or deterioration (progressive infiltrates)
3. Requirement of vasopressors >4 hr (septic shock)
4. Serum-creatinine ≥ 2 mg/dL or increase of ≥ 2 mg/dL in a patient with previous renal disease or acute renal failure requiring dialysis (acute renal failure)

parameters were tested for their ability to predict pneumonia severity (Table 4). The presence of two of three baseline criteria had a sensitivity of 33% and a specificity of 94%. However, if severe CAP was defined as the presence of two of three baseline or one of two major criteria, the performance was more balanced, with a sensitivity of 75%, a specificity of 94%, a positive predictive value of 74%, and a negative predictive value of 95%. The addition of the major criterion acute renal failure did not improve the predictive potential of this rule (53).

Only recently, another study had validated both the original and the modified ATS rule. The population studied was comprised of in-patients of the pneumonia PORT cohort study at three U.S. sites and one Canadian site. It appeared that the original ATS criteria had a sensitivity of 82% and a specificity of 43%, whereas the corresponding indices for the modified ATS criteria were 71% and 72%, respectively. Although the modified ATS criteria had the best overall discrimination, as measured by ROC curves, the positive predictive values remained low (22% at best, measured for the modified ATS criteria) (47).

Nevertheless, these figures are difficult to understand. The fact that 18% of ICU patients did not meet at least one ATS severity criterion raises the question as to why these patients were admitted at all. It is hard to imagine a clinical picture of severe pneumonia requiring ICU admission that which does not meet any criterion of acute respiratory failure, severe sepsis or septic shock, or radiographic extension, and spread of infiltrates. Alternatively, it is difficult to assume a syndrome of acute respiratory failure, severe sepsis or shock that is not reflected by at least one ATS criterion. Unfortunately, the authors did not describe the characteristics of these ''false-negatives.'' Therefore, it remains impossible to decide whether the limited sensitivity reflects a truly limited predictive potential of these criteria, an overuse of ICU resources because of inappropriate clinical decision-making, or other factors.

Likewise, whereas the sensitivity of the modified ATS criteria was similar to that described in the first validation study (71% as compared to 74%), the specificity of 72% was surprisingly different (95% in the first validation study). Again, it is difficult to imagine why 28% of patients met the severity criteria but were not admitted to the ICU. Clearly, a large number of the 28% represent patients with ''minor'' baseline criteria because all patients requiring mechanical ventilation were admitted to the ICU and met the ''major'' criteria. Nevertheless, specificity for the second major criterion of septic shock was 97% only—implying that 3% were not admitted. Because patients meeting ''minor'' criteria, in fact, do meet two of three criteria reflecting acute respiratory failure, severe sepsis, or shock, or extension of radiographic infiltrates, these patients would have been candidates for ICU admission. Hence, were some patients subject to treatment limitations because of end-stage disease? Could there have been intermediate care facilities allowing observation of critical patients without admitting them

to the ICU? The authors do not provide information about this and, therefore, the meaning of these data remains elusive.

Nevertheless, the detailed discussion of the problems in interpretation of this study provides many clues for the understanding of the limitations of any definition of what severe pneumonia really is. First, the emergence of intermediate care facilities, and in line with this, of noninvasive ventilation, fundamentally changes the basis for the definition of severe pneumonia and, as a result, of the calculation of operative indices. It shifts the meaning of ICU admission toward a synonym for the need for invasive mechanical ventilation. In fact, the revised ATS criteria proved to be an excellent predictor of the need for invasive mechanical ventilation (specificity 100%, PPV 100%, and NPV 88%). However, the low sensitivity of 7% hints at many other factors that might determine pneumonia severity. Therefore, if these are to be reflected appropriately by a predictive rule for severe pneumonia, the reference used must specify exactly how patients at apparently increased risk are managed in the corresponding treatment center. In other words, a setting providing both intermediate and intensive care units cannot apply the traditional predictive rules for ICU admission for severe CAP. In these settings, the need for admission to either intermediate or intensive care units should probably be used as a reference for clinical predictions. Alternatively, definitions of severity must be modified into criteria for ''moderately severe'' and ''severe'' pneumonia. Such definitions would be most valuable if we are enabled to recognize the patient at risk of early deterioration after hospitalization, an important and exciting tool further discussed later. Second, it remains extremely important to provide information as to whether patients who are subject to treatment limitations are included in the study or not, and to specify the criteria for such treatment limitations.

Recently, we had completed a study validating our proposed modified ATS severity criteria. In this research, we found these criteria to be the best predictors of the need for ICU admission, with a sensitivity of 69% and a specificity of 98%, a PPV and an NPV of 87% and 94% (50). Importantly, it turned out that in contrast to the PORT population, the rate of ICU admissions was twice as high in our population, ranging in the upper limit of the reported rates of 10–18% in the literature. This difference is most probably because of different medical attitudes with regard to the treatment of patients with severity criteria but not requiring mechanical ventilation and/or vasopressors. In our study, these patients were regarded as those at higher risk of adverse outcomes and were defined as severe CAP. This view might be supported by the observation that our mortality rates were lower than those predicted by PSI, which may mean that ICU was used expectantly and to the benefit of the patients.

Our recent data demonstrate that the modified ATS criteria are the best currently available criteria for the definition of severe pneumonia, at

least in settings with comparable strategies of utilization of ICU resources (Table 5). These data, therefore, support the inclusion of the modified ATS criteria in the ATS guidelines update of 2001 (2).

Having stated this, it is also obvious that the best available criteria for severe pneumonia are not perfect and can only serve as an aid to the clinical decision-making of the attending physician. However, this does not devalue the role of these criteria, as suggested by a recent critical review (54). First, these criteria are supported by strong evidence in the literature. Second, objective criteria of severity should reflect a formally validated extract of our clinical experience. When such an approach is used in conjunction with sound clinical judgment, it can help to guide clinical decisions more safely without challenging what may be called the medical art of optimal patient care.

Future Issues in the Assessment of Pneumonia Severity

Acute pneumonia is a highly dynamic process, particularly at the onset of disease and after the initiation of antimicrobial treatment. Therefore, the assessment of severity may include three different approaches:

1. Initial investigations on admission
2. Repeated investigations within a short time period (ranging from minutes to the first 24 hr) and

Table 5 Predictive Potential of Severity Rules for Admission at the ICU (50)

	Sensitivity	Specificity	Positive predictive value	Negative predictive value	Overall accuracy
Modified ATS rule	80/116	568/580	80/92	568/604	648/696
	69%	98%	87%	94%	93%
Original derivation cohort (3)	47/60	268/284	47/63	268/281	47/344
	78%	94%	75%	95%	92%
Alternative ATS rule	99/114	476/578	99/201	476/491	575/692
	87%	82%	49%	97%	83%
BTS I	37/108	488/549	37/98	488/559	525/657
	34%	89%	38%	87%	80%
BTS II	51/115	496/578	51/133	496/560	547/693
	56%	86%	38%	89%	79%
Modified BTS rule	47/98	409/494	47/132	409/460	456/592
	48%	83%	36%	96%	77%

3. Reinvestigations during the course of the disease (beyond the first 24 hr)

Initial investigations on admission include basic factors reflecting the underlying health state [age, sex, referral (home or nursing home), comorbidity, and steroid pretreatment], as well as baseline factors reflecting acute pneumonia-related illness (clinical signs and symptoms, and laboratory, radiographic, microbiological, and oxygenation parameters) (25). This initial investigation, however, may not adequately reflect the severity of disease because of biases arising from the prehospitalization period (estimation of severity oversensitive) and also of the failure to recognize a rapidly deteriorating clinical course (estimation of severity undersensitive).

Accordingly, one of the most striking findings in our validation study was the low predictive power of baseline clinical (minor) parameters reflecting acute respiratory failure. However, both the respiratory rate and the oxygenation index may be more accurate after the application of a defined amount of supplemental oxygen for a defined short period (e.g., 30 min). A corresponding effort to more accurately assess the initial degree of acute lung injury, taking into account fluctuations in oxygenation when pneumonia is in evolution and antibiotics are taking effect, was developed in a recent study evaluating patients with CAP requiring mechanical ventilation. This population is known to be at a particularly high risk of death. In this study, a hypoxemia index was defined as follows: 1—lowest (PaO_2/PAO_2) × (minimum F_IO_2 to maintain PaO_2 at >60 mmHg) × 100, to be calculated after the first 24 hr of mechanical ventilation, where PaO_2 is the alveolar partial pressure of oxygen. This hypoxemia index proved to be independently predictive of death. However, other (conventional) measures of lung injury proved to perform similarly well, suggesting that the specific predictive contribution of this hypoxemia index in mechanically ventilated patients remains limited (55).

Conversely, an important minority of patients who do not meet severity criteria on admission may nevertheless be at high risk of developing severe CAP in the following 72 hr but not receive intensive care and corresponding appropriate antimicrobial treatment. For example, in our study, only 47% of patients requiring mechanical ventilation were intubated within the first four hours of initial management, and septic shock as well as renal failure occurred in only 71% and 68% within this time limit, respectively. Overall, major criteria as defined in our study in fact were evolutionary, implying clinical deterioration during hospital stay in 40% of cases (53). Therefore, predictors of a high risk for early clinical deterioration requiring ICU treatment would be desirable to allow appropriate assessment of severity of pneumonia in these patients.

Reinvestigations during the course of disease (e.g., beyond the first 24 hr of hospital admission) not only serve as a basis for further risk-adopted

diagnostic and therapeutic decisions, but also provide prognostic information that may be useful for decisions to limit interventions. Evolutionary parameters reflecting disease progression can be divided into clinical, radiographic, and treatment-associated parameters, as well as other complications.

A recent study has contributed important insights into the role of the evolution of pneumonia for prognostic predictions (42). In this study of 472 eligible patients with severe CAP, the following six variables available at initial evaluation were independently associated with death: (1) age $\geq$40 years, (2) anticipated death within 5 years, (3) nonaspiration pneumonia, (4) chest radiograph involvement $>$1 lobe, (5) acute respiratory failure requiring mechanical ventilation, and (6) septic shock. Based on these factors, each factor was assigned a point value, and all factors had a point value of 1 except septic shock, which had a point value of 3. The resulting risk score included three classes of increasing mortality. The main clue from this study was that, whereas low-risk (point score 0–2) and high-risk (point score 6–8) patients could be confidently identified, the outcome of intermediate-risk patients was not predictable unless adjusted for evolutionary factors independently associated with death in an additional analysis accounting only for these factors. The impact of three factors (hospital-acquired lower respiratory tract superinfections, nonspecific CAP-related complications, and sepsis-related complications) on the outcome prediction was dramatic, indicating that it is largely determined by (initially hardly predictable) complications that occur after ICU admission.

In the study mentioned above evaluating patients with CAP who required mechanical ventilation, the following parameters collected over the first 24 hr of ventilatory support were predictive of death: the extent of lung injury assessed by the hypoxemia index (see definition above), number of nonpulmonary organ failures, immunosuppression, age $>$80 years, and medical comorbidity with a prognosis $<$5 years. The prediction model correctly classified outcome in 88% of cases (55). In these patients at least, prolonged intensive care may not be of benefit.

Thus, future directions of research in this field should be directed at three clinically important aims to improve the management of patients with CAP:

1. To establish a simple and easy way to handle baseline criteria (to be determined on admission or, less ideal but maybe more practical, within the first 24 hr after hospitalization), which allows identification of the patient with severe pneumonia on admission, i.e., the individual patient with a substantially increased risk of death from pneumonia
2. To establish a corresponding additional set of baseline criteria that predict the patient with an increased risk of early deterioration toward severe pneumonia after the first 24 hr of hospitalization

3. To provide criteria for a stratification of severity within the population with severe pneumonia

Whereas patients meeting the criteria of severe pneumonia would directly be admitted to the ICU, those with an increased risk of severe pneumonia would be admitted to an intermediate care unit or at least receive increased attention for potential deterioration in the general ward. Stratification of pneumonia severity holds the promise of identifying those patients who might benefit most from intensive care, i.e., those at intermediate risk according to the suggestion of Leroy et al. (42).

Finally, a new field of investigation is opened by the recognition of the importance of genetic host factors for the inflammatory response. Preliminary data suggest that TNF polymorphisms may independently contribute to the outcome of pneumonia. If so, genetic markers may also well contribute to future definitions of severe pneumonia.

NOSOCOMIAL PNEUMONIA

The subject of pneumonia severity has not yet been systematically assessed for nosocomial pneumonia (NP). The severity of NP forms of the algorithm presented in the guidelines of the ATS and essentially adapts the criteria developed for CAP. The only criterion introduced additionally and specific for NP defines any pneumonia requiring admission at the ICU as severe (9). However, whether this classification is appropriate has not yet been confirmed prospectively. There is, however, indirect evidence from studies on the outcome of those factors that might be most predictive of severe NP.

In fact, a principal prognostic factor seems to be ICU admission. In a case–control study, admission to ICU was associated with a 12-fold increase of the fatality rate as compared to a regular surgical ward (56). However, it seems that the risk behind ICU admission may basically be represented by the risk inherent to intubation (as well as length of intubation and broad-spectrum antimicrobial treatment), septic shock, and comorbidity.

Respiratory failure was found to be an independent adverse prognostic factor, as was worsening of acute respiratory failure caused by pneumonia and bilateral chest radiograph involvement (56,57). However, the issue remains whether respiratory failure alone or the complications associated with respiratory failure are the main causes behind the high mortality rate. The adverse effect of intubation on the risk of nosocomial infections could be demonstrated in studies comparing invasive vs. noninvasive ventilation. For example, in a matched case–control study, 50 corresponding patients who were treated with noninvasive ventilation for at least 2 hr and 50 mechanically ventilated controls were compared for the rate of nosocomial infections and other outcome variables. The rates of nosocomial infections and nosocomial pneumonia were significantly lower in patients who received

noninvasive ventilation. Antibiotic use, duration of ventilation, length of stay, and even crude mortality were all lower among patients who received noninvasive ventilation (Table 6) (58). One reason behind these differences is the risk of aspiration of large microbial inocula inherent to intubation. Thus, a first rationale of severity assessment seems to be the differentiation of NP with and without intubation and mechanical ventilation (i.e., ventilator-associated pneumonia).

Once intubation is performed, the risk of death associated with intubation seems largely related to the rate of nosocomial infections and the type of micro-organisms involved. In fact, several studies support an excess mortality for late onset pneumonia, a type of pneumonia typically associated with difficult-to-treat nosocomial micro-organisms (sometimes addressed as ''high-risk'' micro-organisms). In line with these observations, an excess mortality rate has been demonstrated for *MRSA, P. aeruginosa, Acinetobacter baumanii*, and *Aspergillus* spp. (56,57,59,61).

Finally, the risk of the acquisition of high-risk pathogens is particularly high in patients receiving prolonged mechanical ventilation and broad-spectrum antimicrobial treatment (62). In a paradigmatic study, Rello et al. (63) showed that antimicrobial pretreatment was the only adverse prognostic factor in a multivariate model. However, if pneumonia because of high-risk etiologies (including *P. aeruginosa, A. calcoaceticus,*

Table 6 Impact of Noninvasive Ventilation on Rates of Nosocomial Infections, Pneumonia, and Defined Outcome Variables in Patients with Acute Exacerbations of COPD and Hypercapnic Cardigenic Edema Suitable for Noninvasive Ventilation (58)

Variable	Noninvasive ventilation	Intubation and mechanical ventilation	*p*
Nosocomial infections (%)	18	60	< 0.001
Nosocomial pneumonia (%)	8	22	0.04
Proportion of patients receiving antibiotics for nosocomial infection (%)	8	26	0.01
Mean duration of ventilatory support (days)	6	12	0.01
Mean length of ICU stay (days)	9	15	0.02
Crude mortality (%)	4	26	0.002

S. marcescens, P. mirabilis, and fungi) was included in the model, the latter remained the only independent predictor, and antimicrobial pretreatment entirely dropped out. Thus, antimicrobial pretreatment exhibits a considerable microbial selection pressure and is associated with excess mortality because of pneumonia through potentially drug-resistant micro-organisms. Whereas all kinds of antimicrobial treatment may cause harm in this perspective, the adverse prognostic factor of ''inappropriate antimicrobial treatment'' identified by several studies (56,57) hints at a potential of prevention by a judicious use of antimicrobial treatment. Another principal risk factor is the development of septic shock. In numerous studies, septic shock has been identified as a strong risk factor of death from pneumonia (56,57,63).

In addition to these principal risk factors of death, several other predictors were reported, including age >60 years and factors reflecting comorbidity (such as ultimately or rapidly fatal underlying conditions according to McCabe's score) (56,57), and the impact of acute pneumonia in the presence of comorbidity (such as severity of illness when pneumonia is diagnosed) (61). The relative importance of these factors in relation to the principal ones discussed above remains unsettled.

In view of these prognostic data, it seems reasonable to hypothesize that the presence of acute respiratory failure and the type of respiratory support required, as well as the presence of septic shock, are the main predictors of severity. Compatible with the ATS guidelines on severity assessment approach, NP without the need for respiratory support other than continuous supplementation or requiring noninvasive ventilation could be tentatively addressed as mild to moderate, NP during mechanical ventilation or NP requiring intubation, both with or without septic shock, as severe. This concept, however, as well as the relative role of additional risk factors for adverse outcomes await further investigations. Moreover, clinically applicable prediction rules to aid the physician in clinical triaging decisions regarding patients with NP remain to be elaborated.

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2

Why Do Some Patients Get Severe Pneumonia?

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INTRODUCTION

Most patients with community-acquired pneumonia (CAP) will ask their physician at some point how and why they acquired it. When the pneumonia is severe or fatal, physicians are often left wondering "why" as well, particularly when the patient is young or has no obvious underlying chronic medical conditions.

The widespread introduction of penicillin in the 1940s led to a substantial reduction in mortality from infectious diseases, including CAP. However, despite significant advances in medical science, only a small improvement has occurred since, particularly in patients with bacteremic pneumococcal pneumonia. There is even some evidence that pneumonia mortality may be increasing (1), especially in the elderly (2).

In the 1960s, Austrian and Gold (3) found that survival in patients who received antibiotics for pneumococcal pneumonia was no better over the first two to four days compared to historical controls from the pre-antibiotic era (4). Only when deaths occurring in the first four days were excluded was a clear advantage of antibiotic therapy over placebo found.

A recent study of deaths from CAP in young adults in England and Wales reached a similar conclusion that no therapy could be identified, which was likely to reduce existing mortality rates (5).

If no existing therapy is likely to have any large impact, new ones need to be developed. The key to developing new methods is a greater understanding of the biological mechanisms explaining why some patients get severe pneumonia while others do not. This chapter focuses on what we currently know about why some patients develop severe pneumonia. As nosocomial pneumonia introduces even more variables, we will principally concentrate on CAP.

PATHOGEN VIRULENCE

Differences in the virulence of several pathogens or different strains of the same pathogen are one potential explanation for variations in the severity of pneumonia. In cohort studies of severe pneumonia, pathogens such as *Streptococcus pneumoniae*, *Legionella* spp., *Staphylococcus aureus* and Gram-negative bacilli such as *Klebsiella pneumoniae* and *Pseudomonas aeruginosa* are much more commonly identified (6–9) than in those of mild pneumonia where pathogens such as *Mycoplasma pneumoniae* and *Chlamydiae pneumoniae* are more frequent (10,11). Individual case series also suggest that CAP because of *P. aeruginosa* (12,13) and *Acinetobacter baumanii* (14) has a high mortality (15). Similarly, in ventilator-associated pneumonia, infection with *P. aeruginosa*, *A. baumanii*, or *methicillin-resistant S. aureus* is a risk factor for increased mortality (16).

Because certain pathogens are more commonly isolated in patients with more severe disease does not necessarily mean they are more virulent. A factor may be a common predisposition to both more severe disease and to infection with these organisms (e.g., alcohol and pneumococcal disease as discussed later). However, the weight of clinical and laboratory evidence suggests that some pathogens are much more virulent than others, and this may explain some of the clinical variability in severity of pneumonia. A recent example of a particularly virulent pathogen is the coronavirus responsible for the severe acute respiratory syndrome (17). Evidence of significant differences in pathogenic potential between different strains of the same pathogen also exists, including those of *S. pneumoniae* (18,19), the most common pathogen causing CAP.

However, differences in pathogen virulence do not explain why patients infected with identical strains of a pneumococci have markedly varying clinical presentations and outcomes (20–22). An impaired or abnormal host response is more likely than variability in pathogen virulence to be the major explanation for why some patients get severe pneumonia while others do not.

COMORBID ILLNESSES

Comorbid illnesses, in particular chronic organ failure, are obvious predisposing factors to more severe pneumonia. A meta-analysis of cohort studies of CAP by Fine et al. (23) identified the major risk factors for death to include chronic neurological disease [odds ratio (OR) 4.6], neoplastic disease (OR 2.8), and diabetes (OR 1.3). The pneumonia severity index, a severity scaling system developed specifically for CAP, also identifies congestive cardiac failure, chronic renal failure, chronic hepatic failure, and chronic neurological disease as significant factors increasing the risk of mortality (24).

In most cases, the link between comorbidities and reduced physiological ability to deal with infection is self-apparent, e.g., renal, hepatic, and cardiac failure. Poorly controlled diabetic patients have a variety of impaired-host defenses, especially of neutrophil function (25), as well as a greater risk of concomitant cardiac and renal disease.

A curious, but persistent, finding is that chronic obstructive pulmonary disease (COPD) is not associated with an increased risk of death from pneumonia (23,24). One explanation is that COPD does increase mortality but is accounted for in other severity measures such as heart rate, respiratory rate, and hypoxia. Patients with COPD often have chronic pulmonary infiltrates that may lead to simple bronchitis being labeled as CAP, again reducing the impact of COPD in studies of CAP. Finally, those with COPD may be more familiar with accessing health care and are more likely to be prescribed antibiotics earlier in their illness, potentially ameliorating its impact on severity.

Alcohol

An association between excess alcohol consumption and risk of pneumonia from both *S. pneumoniae* (26) and *K. pneumoniae* has long been recognized. Chronic alcohol abuse does not feature as a significant risk factor for mortality in either multivariate analysis or the pneumonia severity index mortality scoring system. This, however, may be because of difficulties in quantifying alcohol consumption in retrospective studies or, more likely, that the effects of alcohol are captured by other severity measures (such as white cell count, electrolyte disturbances, impaired hepatic function, hypotension, etc.).

Acutely, alcohol significantly impairs the recruitment, adhesion, and function of neutrophils (27–29). Inhibition of key chemokines and cytokines involved in neutrophil recruitment and activation is the probable mechanism (30). The association of alcohol and leukopenia with bacteremic pneumococcal pneumonia has been well documented (26). Chronic excess alcohol consumption is also clearly a risk factor for both developing and dying from pneumonia (31), although nutritional and comorbidity factors may be as or more important than specific alcohol-induced immunodeficiencies.

Age

Increasing age is consistently identified as a risk factor for death from CAP (10,32). This is not simply because of an increased frequency of comorbid illnesses because multivariate analysis shows age to be an independent risk factor for mortality (23,24). Poor nutrition has been identified as one important factor contributing to excess mortality in the elderly (33,34). Decreased mobility increasing the risk of secondary complications such as nosocomial pneumonia and thromboembolic disease may also play a role. Many studies have also noted a greater frequency of Gram-negative pathogens, already noted to be associated with a worse prognosis (35,36), possibly because of increased aspiration and oral colonization with these organisms.

The effect of aging on the immune response is much less clear. Defects of T cell and dendritic cell function have been described. Reduced in vitro and in vivo production of inflammatory cytokines in elderly people has been described (37). These findings are consistent with studies showing that the absence of fever and leukocytosis is an adverse prognostic indicator in the elderly (38,39). However, other studies have suggested the elderly have a more prolonged proinflammatory response (40), in keeping with the higher risk of the elderly developing septic shock (36). Much more research is required into both the mechanisms and prediction of immune dysfunction in the elderly.

Gender

As confirmed in the meta-analysis (23), a number of studies have identified male sex as a risk factor for mortality from CAP. Whether this is because of increased comorbid diseases inadequately accounted for the meta-analysis or gender differences in immune response that have been described (41,42) is uncertain.

Racial and Ethnic Differences

Racial and ethnic differences in mortality from infectious diseases have been known for centuries. Racial differences in death rates from pneumonia persist after accounting for socioeconomic factors. However, the type and degree of differences are not consistent. In some studies, African-Americans were found to have a higher mortality rate than Caucasian-Americans, while Asian-Americans had lower rates. However, recent data have demonstrated that for bacteremic pneumococcal pneumonia, mortality rates for Asian-Americans were significantly greater than those for African- and Caucasian-Americans (43). Other studies have demonstrated that the risk of death from pneumonia varied widely between different ethnic groups categorized as Hispanic-American or Asian-American. Several explanations may be offered for these contradictory observations. First, different genetic

backgrounds may be more important for bacteremic pneumococcal pneumonia than for pneumonia in general. Second, it is quite likely that several genetic subpopulations were sampled, and the statistical lumping of these ethnically diverse populations into broad "races" confuses the issue. Racial and ethnic differences not explained by socioeconomic factors support the possibility that genetic differences in the immune response to pneumonia pathogens play an important role.

GENETIC FACTORS

Although often underrecognized or underestimated, a strong inheritable risk for death from infection clearly exists (44). The explosion of interest in gene polymorphisms in the past decade has led to the identification of putative genetic markers of adverse prognosis in many infectious diseases. The large number of factors identified is not surprising because the genetic risk for severe infections is likely to be multifactorial, involve multiple genes, and have variable penetrance of the phenotypic expression of the gene. Even if an individual carries specific susceptibility markers, exposure to the infectious agent is still required. Many polymorphisms have now been described as being possible risk factors for severe sepsis (45,46) and are likely to be important in patients with CAP. While a discussion of all of these association studies is beyond the scope of this review, a number of gene polymorphisms have been identified specifically with respect to CAP. Polymorphisms in pro- and anti-inflammatory cytokines and antigen-recognition proteins are worthy of further discussion.

Antigen-Recognition Pathways

A key component of bacterial recognition is attachment of the immunoglobulin bound to bacterial antigens to their receptors on the surface of leukocytes. Several polymorphisms in immunoglobulin receptors lead to reduced binding affinity, the most well-studied being the CD32 (FcγRII) subclass. The histidine to arginine polymorphism at position 131 of the amino acid sequence (FcγRIIa-R131) is associated with decreased binding of the IgG2 subclass, important for encapsulated micro-organisms, as well as C-reactive protein.

Yee et al. (47) found that patients homozygous for the FcγRIIa-R131 allele were more common in those with bacteremic pneumococcal pneumonia compared to either nonbacteremic or control populations. In addition, all the early deaths from pneumonia occurred in patients homozygous for FcγRIIa-R131. Those with the FcγRIIa-R131 allele appear to be more susceptible to meningococcal meningitis, as well as to severe complications such as septic shock (48). Family studies confirm a predisposition to severe outcome (49).

Other low efficiency variants of the FcγRIII (CD16) receptors may increase the risk of meningitis (49). Complicating the association is the fact that the Fcγ receptor genes are located on chromosome 1 near other immunologically important genes such as interleukin-10 (IL-10). Van der Pol et al. (49) found that although the FcγRII receptor polymorphism was not in linkage disequilibrium with known IL-10 polymorphisms, the genotype combinations were not randomly distributed in first-degree relatives of patients with meningococcal disease.

Mannose-binding lectin (MBL) is a plasma opsonin, which activates the complement system and is therefore a key mediator of innate immunity. Several mutations in the gene can lead to little or no serum MBL. The incidence of homozygous variant alleles was twice as common in patients with invasive pneumococcal disease (50) and in children with meningitis (51). However, these findings were not confirmed in another study of adults with bacteremic pneumococcal pneumonia (52).

Surfactant Proteins

Surfactant proteins are known to be important in a number of pulmonary processes, including bacterial opsonization and modulation of pulmonary inflammation. A variety of polymorphisms are known within the SP-A, B, and D genes. In a case–control study, Lin et al. (53) found that carriage of the SP-B +1580 allele was associated with an increase in the odds of acute respiratory distress syndrome (ARDS), particularly in the setting of pneumonia.

Tumor Necrosis Factor-alpha (TNF)

A critical cytokine in the inflammatory response to infection is TNF. Accordingly, any genetic variability in the production of TNF after an infectious stimulus could have a significant impact on the degree of inflammatory response and therefore potentially influence the clinical outcome. The result is that TNF polymorphisms are the most extensively studied of the inflammatory molecule polymorphisms.

A significant amount of evidence exists to support the biological importance of polymorphisms within the TNF promoter region. A guanine (G) to adenine (A) transition at TNF-308 (54) is perhaps the best-studied cytokine polymorphism and the one for which the best evidence of functional significance exists. Stimulation studies in healthy volunteers suggest that carriage of the TNF-308 A allele is associated with significantly greater TNF production (55). Additional polymorphisms within the TNF promoter may also influence the rate of transcription of TNF, including TNF-238 (56), TNF-376 (57), and TNF-1031 (58).

Carriage of the A allele of TNF-308 has been associated with an increased risk of many diseases, including septic shock (59) and death from

meningococcal sepsis (60). Other investigators have not found a significant association between the TNF-308 A allele and death from or risk of sepsis (61).

Complicating assessment of TNF polymorphisms is the high degree of linkage disequilibrium between TNF promoter polymorphisms and between other polymorphisms within other nearby genes, many of which have significant inflammatory roles. In addition to the HLA loci (62), nearby genes with major inflammatory roles include lymphotoxin alpha (LTA), lymphotoxin beta, the heat shock protein-70 complex (HSPA1A, HSPA1B, and HSPA1L) (63), complement genes, and HLA B associated transcript 1 (BAT-1).

Lymphotoxin Alpha (LTA)

LTA+250 can have a G to A transition in the first intron of LTA and has been identified as a potentially influential locus in many inflammatory conditions. This polymorphism is part of a complex haplotype, including the nonsynonymous mutation LTA+250 Asp26Thr. Complicating assessment further is that the LTA+250 A allele is in linkage disequilibirium with the TNF-308G allele (64). Carriage of the A allele of LTA+250 has been associated with increased TNF production both in vitro (65) and in vivo (66–68), providing a biologically plausible effect. The actual mechanism of how this mutation impacts TNF production is unknown.

Stuber (66) demonstrated that carriage of the LTA+250 AA genotype was associated with a substantially greater risk of death in a group of patients with septic shock from diverse etiologies. We subsequently showed that LTA+250 AA genotype was a risk factor for developing septic shock in patients with community-acquired pneumonia (64). Interestingly, respiratory failure in the absence of shock strongly correlated with LTA+250 GG genotype, suggesting that polymorphisms may be ''good'' or ''bad,'' depending on the immune pathogenesis of the clinical outcome of interest.

Heat Shock Protein (HSP) 70

The recognition that LTA+250 is unlikely to be the ''real'' function site led us to examine polymorphisms known to be in linkage disequilibrium with this site. As already mentioned, the HSP-70 locus is near the TNF locus (which includes TNF, LTA, and LTB) and includes HSP70A1B, HSP70A1B, and HSP70A1L. We found a significant association between a G to A polymorphism at HSP70A1B +1267 and septic shock in a cohort of CAP patients (69). The association between HSP70A1B + 1267 and shock was even stronger than that with LTA + 250, with which it is in strong linkage disequilibrium. Haplotype analysis suggested that carriage of an adenine at both LTA + 250 and HSP70A1B + 1267 conferred the greatest risk of septic shock. Because HSP70A1B + 1267 is a silent mutation and does not lead

to a change in the amino acid structure of the HSP70 protein, this analysis suggests that the ''real'' polymorphic site is likely to be on the HSP70A1B + 1267 A–LTA + 250 A haplotype.

Interleukin-6 (IL-6)

IL-6 has been demonstrated to be a marker of the severity and outcome of sepsis by a number of groups, but whether this represents an epiphenomenon or a causative relationship is still undetermined. Schluter et al. (70) found the IL-6-174 G to C polymorphism was a risk factor for mortality in a heterogeneous group of patients with severe sepsis. However, Gallagher et al. (71) did not find IL-6-174 G to C influence the severity of disease in 103 patients with CAP.

Interleukin-10

IL-10 is a potent anti-inflammatory protein. Several polymorphisms have been identified in IL-10 gene, including a three-SNP promoter haplotype (72) and microsatellites in both the 3′ and 5′ regions (73). The promoter haplotype influences IL-10 production, with stimulated lymphocytes from subjects carrying IL-10-1082 A/-819C/-592C haplotype producing less IL-10 after Con A stimulation than those carrying the IL-10-1082G/-819C/-592C haplotype (72).

Two recent studies found significant correlations between the IL-10-1082 G to A polymorphism and variable outcome from CAP. Gallagher et al. (71) found that carriage of the G allele of IL-10-1082 was more common in patients with more severe CAP. In a study of patients with pneumococcal pneumonia, Schaaf et al. (74) also found carriers of the IL-10-1082 G allele had a greater risk of developing septic shock. In contrast, Lowe et al. found carriage of the A allele of IL-10-592, which is in linkage disequilibrium with IL-10-1082 A (72), was associated with decreased survival in critically ill patients in an intensive care unit (75).

These disparate findings suggest two things. First, more study is required to dissect the complex relationships between clinical phenotypes and IL-10 genotypes. Second, the consistent findings of associations between important clinical outcomes with polymorphisms in the IL-10 promoter region suggest that these polymorphisms or polymorphisms with which they are in linkage disequilibrium are an important component of hereditary susceptibility to severe pneumonia.

CONCLUSION

Severe pneumonia remains a major clinical problem with little progress having been made in reducing the mortality rate in the past three decades. Many factors can be identified as risk factors for severe pneumonia,

including variation in pathogen virulence, comorbid illnesses, increasing age, and a rise in the recognized number of genetic factors. Our understanding of how these many factors interact and alter immune response to favor the development of severe pneumonia is far from complete, and further research is required before we can hope to improve on current outcomes.

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3

What Is the Role of Mechanical Ventilation in Pneumonia Pathogenesis and How Can Noninvasive Ventilation Be Used to Prevent Nosocomial Pneumonia

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INTRODUCTION

Nosocomial pneumonia is a major cause of morbidity, prolonged intensive care unit (ICU) and hospital stay, increased cost, and mortality (1,2).

The occurrence of nosocomial pneumonia implies the invasion of the lower respiratory tract by bacteria, with a concomitant downregulation of local and systemic host defenses.

In the normal human respiratory tract, defensive mechanisms such as the anatomic barrier, cough reflexes, mucociliary clearance, and cell-mediated and humoral immunity protect the lung from infection (3). When these defenses are impaired or if they are overcome by a high inoculum of organisms or organisms of unusual virulence, pneumonia results. Alterations in the tracheobronchial tree leading to anatomical changes in the epithelial

lining or to localized obstruction increase the vulnerability of the lungs to infection (4).

Airway Management and Risk Factors for Pneumonia

Cook and Kollef analyzed the risk factor for ICU-acquired pneumonia. They searched for cohort studies of ICU patients in whom nosocomial pneumonia was recognized and defined ventilator-associated pneumonia (VAP) as lung infection diagnosed more than 48 hr following endotracheal intubation and mechanical ventilation. Depression of the cough reflexes because of anesthesia, alcoholic intoxication, or convulsions was associated with ICU-acquired pneumonia in several studies reported in this analysis (5). The risk of lung infection was higher in patients with chronic lung disease and ARDS and when the duration of mechanical ventilation was longer (5). Mechanical ventilation and endotracheal intubation are merged as independent risk factors for ICU-acquired pneumonia.

Fagon and collaborators (6) have demonstrated that the risk of pneumonia is incremental in ventilated patients and increases by about 1% per day of continuous invasive ventilation. Manipulation of the airway and ventilator circuit may predispose to aspiration and subsequent VAP. The majority of nosocomial pneumonia appears to result from the aspiration of potential pathogens that have colonized the mucosal surfaces of the upper airways (4–7). Reintubation, tracheostomy, and frequent ventilator circuit changes have also been shown to increase the risk of VAP (4,5).

In 1972, Johanson established that upper airway colonization is a frequent occurrence in ventilated patients. The authors found that Gram-negative bacilli (GNB) colonized 45% of 213 patients admitted to a medical ICU by the end of one week in the hospital, and 23% of these patients developed nosocomial pneumonia. Only four of 118 noncolonized patients had pneumonia (8).

A greater severity of disease, a longer duration in the hospital stay, the prior or concomitant use of antibiotics, azotemia or underlying pulmonary disease, and intubation have been reported as other important risk factors for upper airway colonization and pneumonia development (9).

Experimental investigations have linked some of these risk factors to changes in adherence of GNB to respiratory epithelial cells. Bacterial lectine and receptors on respiratory epithelial cells are important elements in mediating the attachment of Gram-negative bacilli to the mucosal surface. The integrity of fibronectin, a mucosal cell surface glycoprotein, plays an important role in modulating oropharyngeal bacterial ecology and adhesion (3,10).

The use of artificial airways is often associated with potential complications and discomfort (11). At the point of contact between the mucosa of airways and the endotracheal tube (ET) or cuff, ulcerations, edema, and hemorrhage with potential stenosis may occur (12).

Intubation compromises the natural barrier between the oropharynx and trachea and facilitates the entry of bacteria into the lung by pooling and leakage of contaminated secretions around the endotracheal tube cuff (13). Supine position of the patients may facilitate pooling of secretions, stasis, and hypoventilation in the recumbent parts of the lung and aspiration (4,5).

The Problem of Biofilm

Scanning electron microscopy of 25 endotracheal tubes revealed that 96% had partial bacterial colonization whereas 84% were completely coated with bacteria in a biofilm or glycocalyx (14). The authors hypothesized that bacterial aggregates in biofilm dislodged during suctioning might not be killed by antibiotics or be effectively cleared by host immune defenses (14,15). Bacterial biofilm may play an important role in recurrent pulmonary infections of the intubated and mechanically ventilated patient. Common nosocomial pathogens like *Pseudomonas aeruginosa* are known to produce an exopolysaccharide and generate a complex biofilm structure, which allows adhesion to abiotic surfaces and protection against antibiotic action.

Multiple studies have identified bacterial biofilm on the inner lumen of endotracheal tubes that represent a permanent source of infectious material (15,16). Several authors have found that endotracheal tubes removed from patients with ventilator-associated pneumonia are covered more frequently with biofilm than those of uninfected controls (14–16). The endotracheal tube, commonly made of polyvinyl chloride (PVC), is acknowledged as a significant factor in micro-organism colonization (17). Bacteria colonize the biomaterial, thereby adopting a sessile mode of growth, which progresses to the establishment of an antibiotic-resistant biofilm by the accretion of a protective glycocalyx (15–17). Jones and coauthors, in a recent study, have described the physicochemical properties and the resistance to microbial adherence of novel surfactant coatings of the endotracheal tube PVC. Interestingly, the microbial antiadherent properties of the coatings were dependent on the lecithin content (18). It is proposed that these systems may reduce the incidence of ventilator-associated pneumonia when employed as endo- and extraluminal coatings of the endotracheal tube (18).

The Type of Endotracheal Tube May Change the Risk Factors

The type of endotracheal tube may influence the likelihood of aspiration. The use of low-volume, high-pressure endotracheal cuffs reduced the rate of aspiration to 56%, and the advent of high-volume, low-pressure cuffs further diminished this rate to 20% (7).

Continuous or intermittent suction of oropharyngeal secretions has been proposed to avoid chronic aspiration of secretions of intubated patients to an endotracheal tube (19,20). In a 3-year prospective, randomized controlled study, a lower VAP rate was documented when continuous subglottic

suction was applied (18% vs. 33% of the control subjects) (21). However, this difference was significant only for the pneumonia occurring in the first week (three of 76 vs. 21 of 77, $p < 0.009$), whereas late-onset pneumonia was more frequent in the continuous subglottic-suctioning group (11 of 76 vs. four of 77) than in the control group (21).

The source of organisms colonizing the upper airways has been a controversial subject. Interestingly, *Enterobacteriaceae* appear to colonize in oropharynx first, whereas *P. aeruginosa* shows first in trachea (10). Other sources of pathogens causing VAP include the paranasal sinuses, dental plaque, and the subglottic area between the true vocal cords and the endotracheal tube cuff.

Other Risk Factors

In this section, some of the other risk factors for the development of pneumonia are only briefly mentioned.

The relationship between VAP and tracheal, pharyngeal, and/or gastric colonization remains to be elucidated for patients with an endotracheal tube (22). Normally, the stomach maintains near-sterility by acid pH. Several investigators reported a clear sequence of colonization from the stomach to the upper airways in large sets of patients (27–45% of patients) (23). The reduction of gastric acidity for stress ulcer prophylaxis in the intubated ICU patients may result from the decrease of gastric acid production or from the use of antacids or histamine type 2 blockers and is associated with the overgrowth of gastric Gram-negative bacteria and the development of pneumonia. In intubated patients given sucralfate, the rate of pneumonia has been found to be lower than in those given conventional agents (24). Conversely, Cook et al., in a recent large randomized study, concluded that H2 blockers provided an antiulcer prophylaxis more efficent than sucralfate, with no difference in the rate of ventilator-associated pneumonia (25).

Tracheobronchial colonization originates in the stomach in at least 25–40% of the cases. This finding supports the role of the gastric barrier in the pathogenesis of nosocomial pneumonia (4–7). The stomach, with an alkaline pH, may act as a reservoir in which pathogens can multiply and attain high concentrations. However, some authors agree that intragastric acidity influenced gastric colonization, but not that of the upper respiratory tract or the incidence of VAP. De Latorre demonstrated that only 19 of 72 patients developed tracheal colonization by the same organisms that colonized the pharynx or the stomach. In that study, only 10 of the 21 micro-organisms isolated from the 12 patients who developed VAP had previously colonized the pharynx or stomach (26).

Antimicrobial therapy, without decontamination of oropharyngeal cavity, to eliminate the gastric bacterial reservoir has generally failed to prevent VAP (27). Patient care activities, such as bathing, oral care, tracheal suctioning, enteral feeding, and tube manipulations, provide wide

opportunities for transmission of pathogens when infection control practices are inadequate (4,5). Despite improved knowledge on the basic mechanisms underlying ventilator-associated pneumonias, VAP incidence still remains very high (1,3,13). Preventive interventions are aimed to increase host defenses and reduce or avoid invasive mechanical ventilation.

DOES NONINVASIVE VENTILATION PREVENT PNEUMONIA IN PATIENTS WITH ACUTE RESPIRATORY FAILURE?

Pneumonia affects 20–30% of ICU patients and is the leading cause of death (28). The use of an endotracheal tube (ET) to deliver ventilatory support is the single most important predisposing factor for developing nosocomial bacterial pneumonia (29). Nevertheless, those with acute respiratory failure (ARF) often require life-supporting mechanical ventilation (MV). The target points of ventilatory support in ARF patients are both the reduction in the work of breathing and the alveolar recruitment to increase the functional residual capacity.

Recently, several authors had demonstrated that noninvasive mechanical ventilation (NIMV) may represent a valid and alternative approach to conventional ventilation with ET in selected groups of ARF patients (30,31). The application of pressure support ventilation (PSV) and positive end-expiratory pressure (PEEP), delivered by a nasal or a full-face mask, seems to be effective in unloading the respiratory muscles and improving gas exchange by the recruitment of underventilated alveoli (32,33). This approach may have several advantages in terms of infection prevention. Factors involved in reducing the rate of ventilator-associated pneumonia (VAP) include the maintenance of natural barriers provided by the glottis and the upper respiratory tract, the reduction in the need for sedation and endotracheal intubation (ETI), and the shortening of MV duration.

Patients with acute or chronic respiratory failure are the ones most likely to benefit from NIMV treatment in terms of both additive morbidity and mortality (34,35). However, clinical evidence exists to propose NIMV treatment as a first-line intervention in hypoxemic ARF (36,37). Randomized and nonrandomized studies on the application of NIMV in patients with hypoxemic ARF have shown promising results, with reduction of complications, including sinusitis and VAP, and duration of ICU stay (37,38). In the present chapter, the efficacy of NIMV in preventing episodes of pneumonia in patients with ARF is discussed throughout using randomized and nonrandomized studies. Noninvasive mechanical ventilation can be applied differently at different times in ARF: as a means to prevent ETI, an alternative to ETI in the treatment, to wean previously intubated patients from MV, or to avoid reintubation after weaning.

Early NIMV Application as a Means to Prevent Nosocomial Pneumonia: Randomized Studies (Table 1)

Several prospective, randomized studies have evaluated the usefulness of NIMV in avoiding ETI and reducing complications related to intubation in patients with hypercapnic and hypoxemic ARF (35,37,39–42). In a controlled study including 85 patients with COPD, Brochard et al. (35) randomized 43 patients to receive NIMV via face mask for at least 6 hr/day and 42 to receive standard therapy with oxygen supplementation. The authors found that NIMV treatment improved gas exchange and decreased both ETI rate and length of stay in the ICU. There was a trend in the reduction of VAP in the NIMV group in comparison to the patients receiving conventional treatment (5% vs. 17%; $p = \text{NS}$). In this study, the crude mortality was significantly decreased in patients receiving NIMV treatment.

Recently, Conti et al. (39) compared NIMV versus conventional ventilation in 49 patients with COPD exacerbation who failed standard medical treatment in the emergency ward and required mechanical ventilation. Both techniques achieved similar results. The group of patients randomized to receive NIMV showed a trend toward a lower rate of nosocomial pneumonia (3 vs. 9, $p = 0.07$).

Antonelli et al. (37) conducted a prospective randomized trial comparing NIMV treatment via face mask to ETI with conventional ventilation in hypoxemic ARF patients who met well-defined criteria for MV. Sixty-four consecutive patients were enrolled (32 in each arm) and randomly assigned to each group. At study entry, the two groups were similar. After 1 hr from MV, 20 out of the 32 patients (62%) in the NIMV group and 15 out of the 32 patients (47%) in the conventional ventilation group improved their ratio of PaO_2 to FiO_2 (PaO_2/FiO_2) ($p < 0.05$). Subjects in the conventional ventilation group had more serious complications (66% vs. 38%; $p = 0.02$) and ETI-related complications, including pneumonia and sinusitis (31% vs. 3%; $p = 0.003$), than patients in the NIMV group. Among those who failed NIMV treatment and required ETI, 12 patients (38%) developed serious complications. One out of the 12 had pneumonia after 6 days of ETI. Among survivors, patients in the NIMV group had a shorter duration of MV (3 ± 3 vs. 6 ± 5 days; $p = 0.006$) and a shorter stay in the ICU (6.6 ± 5 vs. 14 ± 13 days; $p = 0.002$) than those in the conventional ventilation group. Factors that may have been involved in shortening duration of MV in the NIMV group included avoidance of sedation, a lower rate of VAP, elimination of the extra work imposed by ET, and earlier removal from MV. The authors concluded that NIMV is as effective as conventional ventilation in improving gas exchange in patients with hypoxemic ARF, and that when ETI is avoided, the development of VAP is unlikely.

In a randomized prospective controlled trial, Wood et al. (40) evaluated the effects of early NIMV application to 27 patients with hypoxemic

Table 1 Randomized Studies Evaluating the Usefulness of Early NIMV Treatment as a Means to Prevent Nosocomial Pneumonia

Authors and reference	Year	No. of pts (NIMV vs. ETI)	N (%) PN in CT group	N (%) PN in NIMV group	*P*	% of mortality in CT group	% of mortality in NIMV group	*P*
Brochard et al. (35)	1995	43 vs. 42	17	5	NS	29	9	0.02
Wysocki et al. (59)	1995	21 vs. 20	NR	NR	NR	66	9	NS
Antonelli et al. (37)	1998	32 vs. 32	25	3	0.003	47	28	NS
Wood et al. (40)	1998	16 vs. 11	18	0	< 0.05	0	25	NS
Confalonieri et al. (41)	1999	28 vs. 28	7	0	< 0.05	88.9[a]	37.5[a]	0.05[a]
Martin et al. (42)	2000	14 vs. 11	0	0	NS			
Antonelli et al. (43)	2000	20 vs. 20	20	10	0.047	50	20	0.05
Hilbert et al. (44)	2001	26 vs. 26	35	12	0.05	69	38	0.03

PN = pneumonia; Pts = patients; NIMV = noninvasive ventilation; ETI = endotracheal intubation; CT = conventional treatment; NR = not reported; NS = not significant.

[a]Refers only to patients with chronic obstructive pulmonary disease.

ARF requiring emergency admission. Sixteen patients (59.3%) were randomly assigned to receive conventional medical therapy plus NIMV and 11 (40.7%) to get conventional medical therapy alone. NIMV was delivered by a nasal mask with biphasic positive airway pressure (BiPAP) ventilator. Seven subjects (43.8%) in the NIMV group and five (45.5%) in the group receiving conventional medical therapy alone required ETI and MV [relative risk (RR) = 0.96; 95% confidence interval (CI): 0.41–2.26; $p = 0.930$]. Among patients requiring ETI, those in the NIMV group had a longer delay to intubation (26.0 ± 27.0 vs. 4.8 ± 6.9 hr; $p = 0.055$). The rate of pneumonia was higher in the group receiving conventional medical therapy than in the NIMV group (18% vs. 0%; $p < 0.05$). However, patients randomized to NIMV treatment had a greater hospital mortality (25% vs. 0.0%; $p = 0.123$). A trend toward higher APACHE II scores in patients receiving NIMV treatment may have influenced the final patient outcome (26 ± 14 vs. 19 ± 8; $p = 0.4$).

Confalonieri et al. (41) conducted a multicenter, prospective, randomized study comparing standard treatment plus NIMV delivered through a face mask to standard treatment alone, in patients with ARF caused by severe community-acquired pneumonia. Fifty-six consecutive patients (28 in each arm) were enrolled, and the two groups were similar at study entry. Those randomized to NIMV treatment had a significantly lower rate of ETI (21% vs. 50%; $p = 0.03$) and a shorter duration of ICU stay (1.8 ± 0.7 vs. 6 ± 1.8 days; $p = 0.04$). Noninvasive mechanical ventilation was well-tolerated, safe, did not compromise removal of respiratory secretions, and required an intensity of nursing care similar to standard treatment (with or without MV). Among patients with COPD, those randomized to NIMV treatment had a lower intensity of nursing care workload ($p = 0.04$) and improved 2-month survival (88.9% vs. 37.5%; $p = 0.05$). Timing of ETI was similar in both groups, and the rate of complications developing during intubation did not increase in patients failing NIMV and requiring intubation. The only complication associated with NIMV was one case of gastric distention. No facial skin necrosis occurred. Complications associated with conventional MV included two cases of BAL-proven VAP: one case of otitis and mastoiditis, and another pneumothorax. These complications occurred only in patients originally randomized to standard treatment.

In a prospective randomized trial, Martin et al. (42) compared noninvasive positive pressure ventilation (NPPV) with usual medical care (UMC) in the treatment of patients with ARF of various origins. Thirty-two patients were randomized to receive NPPV and 29 to get UMC. Noninvasive positive pressure ventilation was delivered through a BiPAP system, using initial IPAP and EPAP levels of 5 cm H_2O. A significantly lower rate of ETI was observed in the NPPV group than in the UMC group (6.38 vs. 21.25 intubations per 100 ICU days; $p = 0.002$). Mortality rates in

the ICU were similar for the two treatment groups [2.39 deaths (NPPV group) vs. 4.27 deaths (UMC group) per 100 ICU days, $p = 0.21$]. Patients with hypoxemic ARF in the NPPV group had a significantly lower ETI rate than those in the UMC group (7.46 vs. 22.64 intubations per 100 ICU days, $p = 0.026$); a similar trend was also reported in patients with hypercapnic ARF [5.41 intubations (NPPV group) vs. 18.52 intubations (UMC group) per 100 ICU days, $p = 0.064$]. No infectious complications were present in the two groups.

Noninvasive Mechanical Ventilation in Immunocompromised Patients

Avoiding intubation is a major goal in the treatment of ARF in immunosuppressed patients. Two different randomized studies suggest early NIMV application to be a therapeutic challenge in the patients after transplantation or with immunosuppression of various origins. In a prospective randomized study, Antonelli et al. (43) compared the use of NIMV delivered through a face mask with standard treatment using oxygen supplementation to avoid ETI and decrease duration of ICU stay in 40 patients with hypoxemic ARF (defined as acute respiratory distress, a respiratory rate greater than 35 breaths/min, a ratio of PaO_2 to FiO_2 of less than 200 while the patient was breathing oxygen through a Venturi mask, and active use of the accessory muscles of respiration or paradoxical abdominal motion) after solid organ transplantation. Twenty patients were randomly assigned to each group, and the two groups were similar for baseline characteristics at study entry. All COPD patients were excluded. Within the first hour of treatment, 14 (70%) of the 20 patients in the NIMV group improved their PaO_2/FiO_2 ratio vs. 5 (25%) in the standard treatment group. The improvement of gas exchange over time was more prolonged in the NIMV group than in the standard treatment group (60% vs. 25%; $p = 0.03$). The use of NIMV was well-tolerated, safe, and associated with a significant reduction in the need for ETI (20% vs. 70%; $p = 0.05$) and in the rate of severe sepsis and septic shock, including VAP (10% vs. 20%; $p = 0.047$). Moreover, patients in the NIMV group had lower duration of ICU stay [mean (SD) days, 5.5 (3) vs. 9 (4); $p = 0.03$] and lower rate of ICU mortality (20% vs. 50%; $p = 0.05$) than those in the standard treatment group. Hospital mortality did not differ in the two groups.

Hilbert et al. (44) investigated the use of NIMV to prevent ETI and serious complications in patients with hematological malignancies, immunosuppression, bone marrow transplantation, or HIV. Fifty-two patients were enrolled in the study and randomized (26 in each arm) to receive standard treatment with oxygen therapy through a Venturi mask or standard treatment plus intermittent face mask NIMV. The authors found that patients in the NIMV group required less ETI (46% vs. 77%; $p = 0.03$) and had less

serious complications (50% vs. 81%; $p = 0.02$) than those in the standard treatment group. The early NIMV application was associated with a decrease in the rate of VAP (12% vs. 35%; $p = 0.05$) and ICU and hospital mortality (10 vs. 18 patients; $p = 0.03$ and 13 vs. 21 patients; $p = 0.02$, respectively). These results confirm that early application of NIMV to immunosuppressed patients with hypoxemic ARF may be effective in preventing episodes of VAP by avoiding ETI. Moreover, the reduction in additive morbidity may improve patient survival.

Prevention of Pneumonia During Noninvasive Mechanical Ventilation Application as a Weaning Strategy or a Means to Avoid Reintubation

The rationale for NIMV application as a weaning strategy may be related to the ability of NIMV to decrease the workload of the respiratory muscles and to develop rapid and shallow breathing associated with unsuccessful weaning from MV. Nava et al. (45) conducted a prospective randomized control study to evaluate the use of noninvasive PSV (NPSV) in the weaning of COPD patients with ARF. Fifty patients who had failed a T-piece trial of weaning were randomized (25 in each group) to extubation with immediate application of NIMV or to weaning with ETI. Twenty-two out of the 25 subjects (88%) in the NIMV group were successfully weaned vs. 17 in the invasively ventilated group (68%). None of the patients (0%) in the NIMV group developed VAP, whereas seven (28%) in the invasive weaning group did ($p = 0.005$). The use of NIMV significantly decreased duration of ICU stay (15 ± 5 vs. 24 ± 13 days; $p < 0.05$) and increased 60-day-survival rate (92% vs. 72%; $p = 0.009$). This study showed that the likelihood of weaning success increased, and the additive morbidity and the overall mortality decreased using NIMV as a weaning strategy.

The effect of NIMV application during a persistent weaning failure was evaluated in another randomized (46) clinical trial including 43 patients who had failed a spontaneous-breathing trial for 3 consecutive days. Thirty-three of these had underlying chronic obstructive respiratory failure. Patients were randomly assigned to be extubated with NIMV or to follow a conventional weaning approach. In this study, the authors found that NIMV application was really effective in facilitating the weaning process, and reducing the duration of MV and the need for tracheostomy. Noninvasive mechanical ventilation treatment was associated with a decrease in additive morbidity, including the incidence of VAP, septic shock, and multiple organ failure, and with improvement in the ICU and 90-day cumulative mortality.

NonRandomized Studies

The use of NIMV to prevent nosocomial pneumonia was demonstrated in a prospective epidemiological survey on a cohort of 320 consecutive patients with ARF on more than 48 hr of MV (47).

The authors reported a lower ($p = 0.004$) rate of VAP in noninvasively supported patients (0.16 per 100 days of NIMV) versus those on conventional ventilation (0.85 per 100 days of ETI).

In a prospective study Nourdine et al. (48), compared a group of 159 patients with ARF of various origins treated with NIMV and 607 with ETI and MV. The authors described a significantly lower incidence of VAP (4.4 vs. 13.2 per 1000 patients/days; $p < 0.05$) and infections at all sites in the NIMV group except in the conventional ventilation group. Girou et al. (49) conducted a matched case–control study on 100 patients with acute exacerbation of COPD or hypercapnic cardiogenic pulmonary edema to evaluate whether the use of NIMV was associated with decreased risk of NI and improvement of survival in everyday clinical practice. Among 2441 patients admitted to ICU, 1040 patients needed ventilatory support. Noninvasive mechanical ventilation was delivered in 134 out of the 1040 patients. Only 50 of these patients were eligible as cases that were treated with NIMV for at least 2 hr. Fifty control patients receiving conventional ventilation with ETI were matched to cases for diagnosis, age, simplified acute physiology score II (SAPS II), logistic organ dysfunction score, and no contraindication to NIMV treatment. The 50 patients treated with NIMV developed significantly fewer complications ($p = 0.006$) during their ICU stay and received fewer antibiotics for NI (8% vs. 26%; $p = 0.01$) than controls. Rates of nosocomial infection [18% (NIV group) vs. 60% (ETI group); $p < 0.001$] and pneumonia [8% (NIV group) vs. 22% (ETI group); $p = 0.04$] were significantly decreased when NIMV was applied. Interestingly, the authors also observed that the mean duration of ventilation [mean (SD); 6 (6) vs. 10 (12) days; $p = 0.01$), mean duration of ICU stay [mean (SD); 9 (7) vs. 15 (14) days; $p = 0.02$], and crude mortality (4% vs. 26%; $p = 0.002$) were lower in the NIMV group than in the ETI group.

In a prospective survey among 42 ICUs, Carlucci et al. (50) enrolled 689 patients with ARF who required ventilatory support. In 108 of these patients, NIMV treatment was delivered through a face mask. Among the 581 patients receiving conventional treatment with ETI, 382 were intubated before ICU admission. The incidence of NIMV for patients in the ICU was 35%. Simplified acute physiology score II was significantly higher in patients receiving conventional treatment with ETI [mean (SD); 47 (21) vs. 36 (20); $p < 0.001$] than in those receiving NIMV treatment. Subjects in the NIMV group had a shorter duration of MV delivery [mean (SD); 8 (6.3) days vs. 13.9 (14.5) days; $p < 0.002$] and ICU length of stay [mean (SD); 5.1 (5.7) days vs. 7.8 (9.8) days; $p < 0.04$] than those in the ETI group.

Moreover, 11 patients (10%) in the NIMV group and 72 (19%) in the ETI group developed nosocomial pneumonia ($p = 0.03$). Overall mortality was also significantly decreased in the NIMV group (22% vs. 41%; $p < 0.001$). Failure of NIMV treatment was observed in 52 out of 108 patients in the NIMV group (48%). Major causes of NIMV failure could be ascribed to the inefficacy of the procedure in 84% of the cases, inability to handle tracheobronchial secretions in 32%, poor patient compliance in 22%, and need of a long-term support in 11%. However, NIMV failure was not a risk factor for mortality (9% vs. 12%; $p = \text{NS}$) and pneumonia (12% vs. 9%; $p = \text{NS}$). The authors concluded that NIMV may be successful in selected patients and is associated with a decreased risk of pneumonia and death.

In a prospective multicenter cohort study, Antonelli et al. (51) investigated prospective outcome descriptors for NIMV in a large population of 354 hypoxemic ARF patients of various origins. The authors found that NIMV was successful in 264 (70%) patients, whereas 108 (30%) failed NIMV treatment and required ETI. A multivariate analysis identified age > 40 years (OR = 1.72, 95% CI: 0.92–3.23), SAPS II score ≥ 35, the presence of ARDS or community-acquired pneumonia, and a PaO_2:$FiO_2 \leq 146$ after 1 hr of NPPV as factors independently associated with NPPV failure. Throughout the study period, patients avoiding ETI led to shorter duration of MV [median (range); 48 (1–216) days vs. 24 (1–192) days; $p = 0.06$] and ICU length of stay [median (range); 5 (3–31) days vs. 9 (1–72) days; $p < 0.001$] than those requiring ETI. Successful NIMV was also associated with a significant decrease in the rate of VAP [0.4% (NIMV success) vs. 28% (NIMV failure); $p < 0.01$], severe sepsis, and septic shock [3% (NIMV success) vs. 65% (NIMV failure); $p < 0.01$].

Noninvasive Mechanical Ventilation Approaches with New Interfaces

If disconnection from MV occurs during the early phases of ARF, patients can rapidly deteriorate their gas exchange, with potential life-threatening consequences. The improvement of the patient–ventilator interface seems crucial to achieve a prolonged application of NIMV. Noninvasive mechanical ventilation can fail because of either (a) conditions related to the disease (inability to correct hypoxia, manage copious secretions, etc.) or (b) technical causes (intolerance, skin necrosis). Despite improvements in facial masks characteristics, skin necrosis may occur in 7% of patients treated with NIMV for periods exceeding 72 hr (38). The nasal mask is usually better tolerated, but a full-face mask seems more appropriate for patients affected by severe hypoxemia who are commonly mouth breathers (43–52).

Attempting to improve tolerability of patients, we adopted a transparent helmet (Fig. 1) made of latex-free PVC, which allows patients to

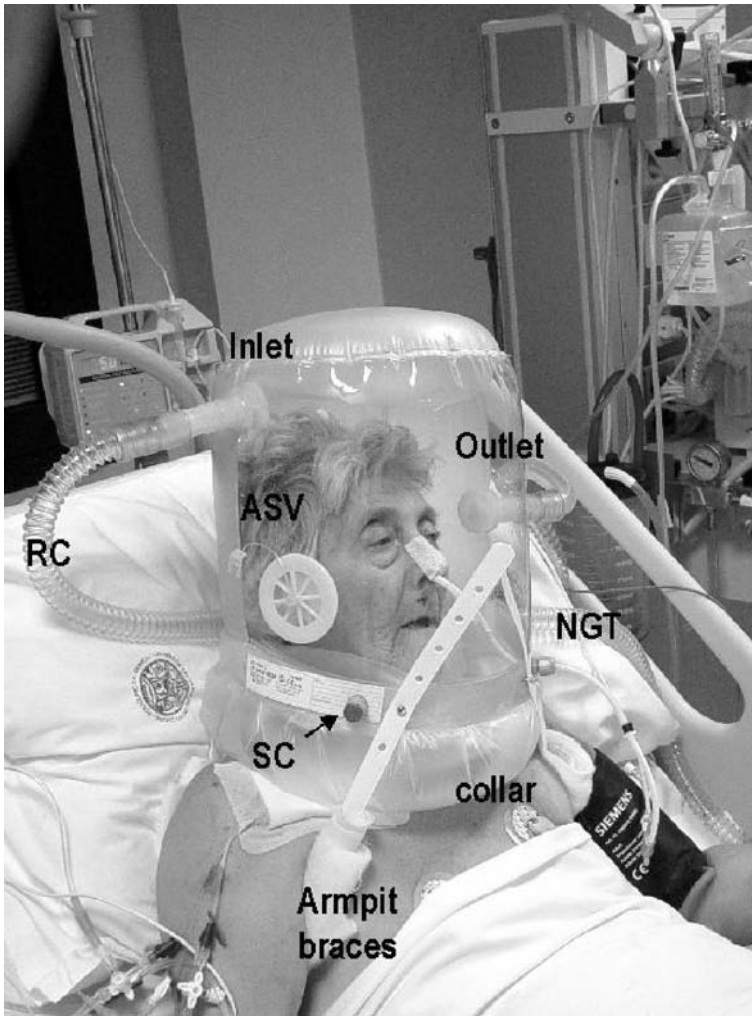

Figure 1 A patient with acute respiratory failure treated with helmet noninvasive ventilation. ASV = antisuffocation valve: this device avoids the risk of asphyxia if a disconnection from the ventilator occurs. The inlet and outlet of the helmet are connected to the inspiratory and expiratory valves of the ventilator through conventional respiratory circuits (RC). The trigger of the system is that of the ventilator. SC = seal connection, which allows the passage of a nasogastric tube (NGT) for enteral feeding or enables the patient to drink through a straw, without interruption of ventilation or air leakage. The helmet is secured to the patient with two armpit braces attached to two metallic hooks of the ring which joins the collar and the helmet.

see, read, and speak during noninvasive positive pressure ventilation. The efficacy of a helmet to deliver continuous positive airway pressure (CPAP), without a mechanical ventilator, was recently tested (53) and the device was successfully applied to deliver CPAP as out-of-hospital treatment for patients with pulmonary edema (54). However, to our knowledge, the helmet was never used to ventilate patients with ARF by NPSV.

In our prospective clinical pilot investigation (55), 33 consecutive non-COPD patients with hypoxemic ARF [defined as severe dyspnea at rest, RR >30 breaths/min, PaO_2:$FiO_2 < 200$, and active contraction of the accessory muscles of respiration (56)] were enrolled. Each patient treated with NPSV by helmet was matched with two controls with ARF treated with NPSV via a facial mask, selected by SAPS II, age, PaO_2/FiO_2, and arterial pH on admission. The 33 patients and the 66 controls had similar baseline characteristics. Both groups improved oxygenation after NPSV. Eight patients (33%) in the helmet group and 21 (32%) in the facial mask group ($p = 0.3$) failed NPSV and were intubated. No patients failed NPSV because of intolerance of the technique in the helmet group in comparison with eight patients (38%) in the mask group ($p = 0.047$). Complications related to the technique (skin necrosis, gastric distension, and eye irritation) were fewer in the helmet group compared to the mask group (no patients vs. 14 patients; $p = 0.002$). Four patients (12%) in the helmet group and 10 (20%) in the mask group developed nosocomial pneumonia after the study entry ($p = 0.3$). Interestingly, three of the four pneumonia patients in the helmet group and six of the 10 nosocomial pneumonia patients in the mask group developed only after the NPSV failure and ETI. The helmet allowed the continuous application of NPSV for a longer period of time ($p = 0.05$). Length of stay in the ICU, intensive care, and hospital mortality were not different in the two groups. We showed that NPSV by helmet successfully treated hypoxemic ARF with better tolerance and fewer complications than facial mask NPSV. When patients with suspected pneumonia are approached with this technique, NIMV delivered by helmet can be used to allow diagnostic bronchoscopy, thereby avoiding gas exchange deterioration and allowing the identification of the responsible pathogen (57).

In a recent multicenter cohort investigation (58), we studied 33 COPD patients with acute exacerbation, admitted to four ICUs and treated with helmet noninvasive positive pressure ventilation over a 4-month period. They were compared to 33 historical controls treated with noninvasive positive pressure ventilation delivered through a facial mask (FM), matched for SAPS II, age, $PaCO_2$, pH, and PaO_2:FiO_2. Ten patients in the helmet group and 14 in the FM group ($p = 0.22$) were intubated. In the helmet group, no patients failed noninvasive ventilation because of intolerance, whereas five required intubation in the mask group ($p = 0.047$). After 1 hr of treatment, both groups had a significant reduction of $PaCO_2$ and improvement of pH; $PaCO_2$ decreased less in the helmet group ($p = 0.01$). On discontinuing

support, $PaCO_2$ was higher ($p = 0.002$) and pH lower ($p = 0.02$) in the helmet group than in the control group. Length of ICU stay, and ICU and hospital mortality were similar. The number of nosocomial pneumonia was relatively low and not different between the two groups [5 (15%) vs. 4 (12%), $p = 0.5$]. All the pneumonia occurred after the failure of noninvasive ventilation and endotracheal intubation. If larger studies confirm these preliminary data, the helmet could become another valid therapeutic option to deliver noninvasive positive pressure ventilation in patients with acute respiratory failure.

CONCLUSIONS

Randomized and nonrandomized clinical studies (36–38) conducted on more than 2200 patients have demonstrated that NIMV is really effective in the clinical management of patients with ARF. Recent studies (37,38) have also reported that NIMV treatment may be attempted as first-line intervention for hypoxemic acute respiratory failure with significant reduction in nosocomial infections, including VAP, antibiotic use, duration in ICU stay, and overall mortality.

As NIMV is successful and ETI is avoided, the development of nosocomial pneumonia is unlikely.

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4

Community-Acquired Pneumonia: Defining the Patient at Risk of Severe Illness and the Role of Mortality Prediction Models in Patient Management

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INTRODUCTION

"Whether impending death, in pneumonia, can ever be averted is an interesting and important question. That positions of great peril may be relieved in some cases I am firmly convinced (1)."

One hundred years ago, Edward Wells addressed an issue that remains central to the management of the patient with community-acquired pneumonia (CAP). Are there clinical features that aid discrimination between those at increased risk of death and those who will have an uncomplicated clinical course? If so, are there steps that can be taken that might then prevent that death? In those 100 years, much research has been undertaken into the assessment of CAP severity. Wells' question has now been widened into the identification of low- and high-severity patients for the application of different management strategies, and these have been assessed against a number of outcome measures, not just death. This document reviews this

research and describes whether this, together with the advances in management that have occurred, has provided an answer to Wells' question.

WHY MIGHT WE NEED SEVERITY ASSESSMENT?

Prediction of severe illness not only predicts those at risk of death but also those at risk of increased use of healthcare resources and costs by way of need for hospital and intensive care unit (ICU) admission and for the time required to stay in hospital. If we have methods of treatment available that, while not required in nonsevere illness, might alter outcome in severe illness, then severity assessment can be used to direct these interventions. Expensive resources are thereby not wasted unnecessarily on those at low risk and can be appropriately provided for those at high risk. An additional role for severity assessment rules is in the stratification of patients in clinical trials and for comparison of cohorts of patients to determine whether comparable groups are being studied.

Data on severity endpoints vary from study to study and country to country. Hospital admission rates range from 9% (2) to 58% (3) of cases. Intensive care unit admission rates in prospective studies range from 3.1% (4) to 16.2% (5), rising to 24% in patients with CAP, complicating COPD (6) (Table 1) of those admitted to the hospital. Patients admitted to an ICU in one hospital may be very different from those in another hospital. A recent North American study found an average ICU admission rate of 12.7%, but with variation of 8.8–26.1% between participating centers (13). This may partly be because of the provision of varying services in different ICUs. The wide variation between ICUs in the rates of intubation and assisted ventilation illustrates this. In recent studies, intubation rates have

Table 1 ICU Admission Rates in Recent Prospective Studies of Adults Admitted to the Hospital with CAP

First author	Patients	Country	ICU admission (%)
Neill (4)	Adults	New Zealand	3.1
Espana (7)	Adults	Spain	4.1
Lim (8)	Adults	UK	6
Roson (9)	Adults	Spain	8
Kamath (10)	Adults	UK	10
Sopena (11)	Adults	Spain	9.8
Ewig (5)	Adults	Spain	12.9
Ewig (5)	Adults	Spain	16.2
Ewig (12)	Elderly	Germany	15.7
Torres (6)	COPD	Spain	24

Table 2 Frequency of Admission of Low-Risk Patients (PSI I–III) in Recent CAP Studies

First author	Country	Year	PSI I–III (%)
Marras (21)	Canada	2000	29
Meehan (22)	United States	2001	30
Stauble (23)	Switzerland	2001	39
Roson (9)	Spain	2001	44
Espana (7)	Spain	2003	45
Dedier (24)	United States	2001	48
Lim (25)	N.Z.	2003	51
Lim (25)	U.K.	2003	55
Lim (25)	The Netherlands	2003	56
Marrie (26)	Canada	2000	59 and 63 in two cohorts
Atlas (27)	United States	1998	66

ranged from 50% (14) to 96% (15) of ICU admissions for CAP. One important recent change in management, which will impact on this, is the introduction of noninvasive ventilation, which may be used to a varying extent in different centers and may be applied in different settings in different centers (e.g., specialist respiratory ward, high dependency unit, or intensive care unit). Death rates for patients admitted to the hospital also vary from 4% (16) to 15% (17). These variations are likely to be influenced by differences in CAP definition, differences in the populations covered, and differences in healthcare structures and practices. However, some of these variations are likely to be because of inadequate use of severity assessment and inappropriate patient admission to the wrong management setting. Evidence to support this comes from studies that have found both under- (4,18) and overestimation (19) of illness severity using routine clinical practice. One study of medical patients, including many with CAP, in the period before their admission to the ICU has found that such admission may have been avoidable in up to 41% of cases if pre-ICU management had been improved (20). Use of severity prediction tools (see later) shows that the proportion of low-risk patients admitted to hospital varies by a factor of 2 between studies (Table 2). It will be very important in the future for studies of CAP patients in management settings for them to define precisely the services provided, especially with respect to noninvasive ventilation and intubation rates.

SOME BASIC PRINCIPLES

Severity assessment must be applicable to the setting in which it is to be used, which means that it has to be proven to work in that setting. This

not only means that outcome is predicted, but also that it is practical to use in the clinical setting. While it would be convenient if one severity measure is applicable in all settings, healthcare structures vary from country to country, and for this reason, a severity assessment approach applicable in one country may not work in the healthcare system of another. Severity tools derived from a population in an intensive care unit cannot be automatically applied to population attending the emergency room, and those derived in the young adults cannot be used in the elderly, unless they have also been validated in those populations.

Depending on the setting, the arbiter of severity may vary. In community studies, it might be hospital admission in the emergency room, hospital admission in the intensive care unit admission, or endotracheal intubation and in these situations, it might be death. Results may then not be translatable between institutions because of variations in admission or clinical practice. Only death provides a hard endpoint, which might translate between institutions; however, even this may be influenced by differing application of "do not resuscitate" orders. Nevertheless, death remains the ultimate arbiter of CAP severity.

Severity assessment can be useful at different stages of patient care, but it is most useful when the patient first presents to a medical facility. This is because most ICU admissions occur within the first 24 hr of hospital admission, and up to one-half of deaths occur in this time period. For assessment to operate adequately at this time, it must be based on variables that are rapidly available. Subsequent reassessment may be based on variables that evolve or only become available later.

DEFINING THE PATIENT AT RISK: PRESENTATION TO HOSPITAL

There have been many studies of populations of patients with CAP, either presenting to the emergency room or admitted to hospital that have identified features that, on univariate analysis, are statistically related to outcome. The reproducibility of these findings varies partly for the reasons stated earlier and also mainly because of comparison of different patient populations. Some 40 different variables have been found to be associated with outcome, but this is of little use to the average medical practitioner managing a patient with CAP. Of these, nine factors or areas have been consistently identified as being linked to outcome on multivariate analyses: patient age, comorbid illness, blood pressure, respiratory rate, mental function, gas exchange, peripheral blood leukocyte count, radiographic changes, and microbial etiology (28). The latter is not known on admission and is often never known and is therefore of limited value. No single variable has adequate operating characteristics to allow accurate distinction of the severely ill patient from the nonseverely ill. For this reason, attempts have

been made to combine different variables identified on multivariate analysis to produce severity scoring tools.

Early studies compared CAP-specific with generic severity of illness scores. A small South African study (34 patients) found that the generic APACHE score significantly underestimated death rates, and hence they proposed a CAP-specific score based on six variables (29). A year later, a 12-variable score was proposed by another group (30) and compared with the acute physiology score (APS) and the simplified APS (SAPS) in 96 ICU admissions with pneumonia. All three scores were found to have similar operating characteristics. A later paper suggested that SAPS poorly discriminated those at risk of death because it did not account for bacteremia, which was the most important risk for death (31). However, the presence of bacteremia is not known at the time of admission. Better performance of a CAP-specific score compared to a generic illness severity score was found in another study (32).

Two broad approaches to CAP-specific severity scores have been adopted: one for the prediction of cases at high risk of death that require hospital admission and consideration for intensive care unit management, and the other for the prediction of low-risk patients, who might reasonably be managed at home. Two landmark studies are the platform for most subsequent work on CAP severity assessment. The first was performed by the British Thoracic Society and published in 1987 (33). This multicenter study, of 453 adults admitted to hospital, identified 32 variables (from 90 studied) to be related to five different outcome measures on univariate analysis. Of these, seven [age, lack of alcohol intake, absence of chest pain, absence of vomiting, respiratory rate, diastolic hypotension, and raised blood urea (>7 mmol/L)] were related to risk of death on multivariate analysis. From these, three different discriminant rules were constructed, separating severe CAP from nonsevere CAP, each based on three or four variables available on or shortly after admission (Table 3), and have come to be known as the "BTS Rules." Rule 1 had the best operating characteristics with death occurring in one of five of those fulfilling the rule and only one in 100 of those who did not fulfill the rule.

The second landmark study set out to identify low-risk patients who might reasonably be managed in the community (34) and was based on earlier studies on outcome prediction in CAP by the same authors. Application of severity scoring from these early studies was shown to overpredict death rates by a factor of 2.4 when applied to a different population (35). A severity prediction rule was derived from the records contained within an insurance database of 14,199 adults admitted with CAP to 78 hospitals. It was then validated in a separate database of hospitalized CAP patients, as well as in a prospectively collected cohort of CAP patients from the PORT study, which included patients managed in the community. A two-step prediction rule was developed that separated patients into one of five risk classes

Table 3 The British Thoracic Society Severity Prediction Rules (33)

Rule 1
Two of three criteria:
Respiratory rate $\geq$30/min
Diastolic blood pressure $\leq$60 mmHg
Blood urea >7 mmol/L (during admission)
Rule 2
Two of three criteria:
Respiratory rate $\geq$30/min
Diastolic blood pressure $\leq$60 mmHg
Confusion
Rule 3
Three of four criteria:
Confusion
$PaO_2 \leq 6.6$ kPa
White blood cells $\leq 10 \times 109$/l or lymphocytes $\leq 1 \times 109$/L
Blood urea >7 mmol/L (during admission)
Modified BTS Rule
Two or more of four criteria on admission
Respiratory rate $\geq$30/min
Diastolic blood pressure $\leq$60 mmHg
Blood urea >7 mmol/L
Confusion (mental score quotient $\leq$8)

(Fig. 1). The first step, which separated Class I from Classes II–V, was based on clinical variables. Separation of Classes II–V was based on scores calculated from 20 clinical and laboratory variables. Mortality was similarly low in Classes I–III, all of which had low rates of ICU admission and shorter hospital stays than Classes IV and V, suggesting that patients in Classes I–III could be managed at home, whereas those in IV and V required hospital admission.

Subsequent studies have set out to further assess the validity of these rules in different population groups at different times. Initial studies confirmed the BTS Rule 1 to be a predictor of severe illness where its main quality was a high negative predictive value (97–99%), indicating that those who did not fulfill the rule were unlikely to die (36,37). However, its positive predictive value was low as in the derivation study.

A German study of 92 hospitalized patients, with a higher overall mortality than previous studies, found that a rule using heart rate, systolic blood pressure, and serum lactate dehydrogenase had a higher positive predictive value (42%) but at the expense of a lower negative predictive value (93%) (12). A New Zealand study amalgamated the three BTS Rules into what became known as the modified BTS (mBTS) Rule (4). In this rule, severe CAP was defined by the presence, on admission, of two or more conditions

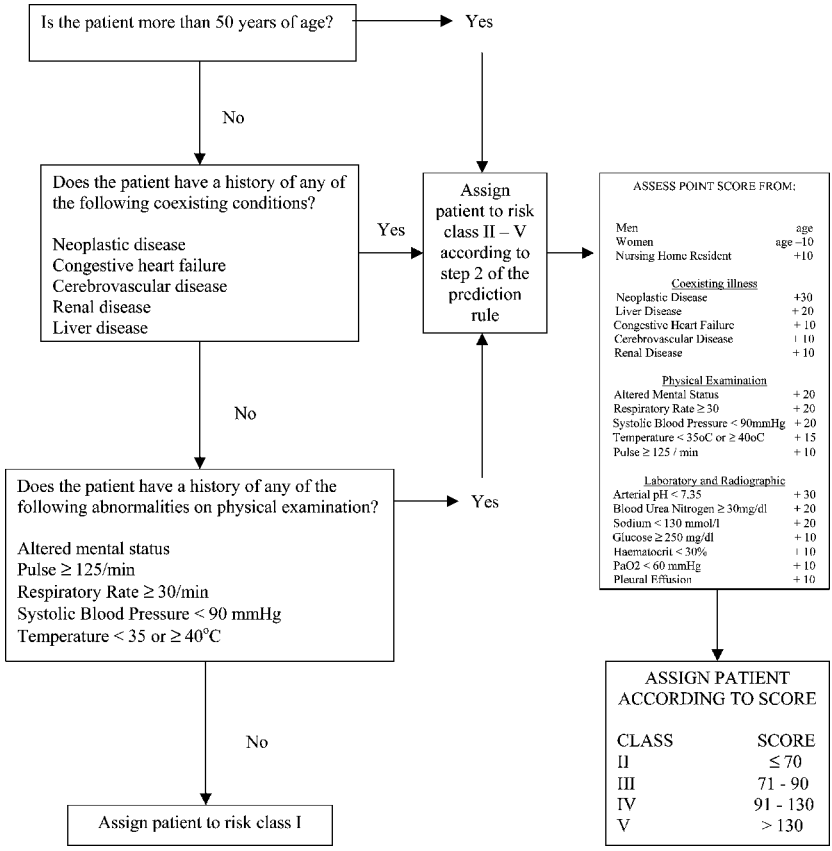

Figure 1 The pneumonia severity index (34).

of: respiratory rate $\geq$30/min, diastolic blood pressure $\leq$60 mmHg, blood urea $>$7 mmol/L, and confusion (defined as mental score quotient $\leq$8/10). Those with one or less of these features were deemed to be nonseverely ill. In a population of 255 adults admitted to hospitals with CAP, this rule had an improved sensitivity compared to the BTS Rules 1–3, but reduced specificity and positive predictive value while maintaining a high negative predictive value. The improved sensitivity was deemed to make it more clinically useful than the previous rules. A consistent criticism of the original BTS study was the exclusion of patients older than 74 years, leading to concerns about the value of the BTS rules in older patients. The New Zealand study included older patients and suggested therefore that the mBTS Rule might be useful in this population.

While other small studies have supported the validity of the mBTS Rule (10), larger validation studies supported concerns over its validity in the elderly. In a retrospective, case-control study of older patients including

122 deaths from CAP compared to 122 controls, neither diastolic nor systolic blood pressure was found to be related to death. The sensitivity (66%) and specificity (73%) of the mBTS Rule were lower than in studies of younger age groups (38). A second retrospective, case-control study by the same authors was confined to the $\geq$75 age group, and it was found that three (respiratory rate, blood urea, and confusion) of the four features in the mBTS Rule were not associated with death (39). Not surprisingly, the mBTS Rule performed poorly in this group with positive and negative predictive values of 60% and 66%, respectively. An earlier study in elderly patients had come to a similar conclusion (40). A more recent prospective cohort study, however, found a better negative predictive value in elderly patients of 86% (8).

A limitation of all of the "BTS Rules" is the separation of patients into only two risk groups (severe and nonsevere), which does not equate with the three common clinical sites of management in most healthcare systems, namely, the patient's home, the ordinary hospital ward, or the ICU. The last study found a stepwise relationship between the number of factors present in each patient from the mBTS Rule and outcome (8). Those with no factors present had a 2.7% mortality rising to 83% in those with four features present. The use of these four features was suggested as a more discriminating CURB (Confusion, Urea, Respiratory rate, and Blood pressure) score. A more recent study built on these results to develop a severity scoring system linked to the three management options of home, hospital, and ICU. This study used pooled data on 1068 patients from three prospectively collected CAP databases from the U.K., the Netherlands, and New Zealand, which were split into derivation and validation cohorts (25). It began by confirming the validity of each component of the CURB score as a predictor of 30-day mortality. The presence of two or more mBTS (or CURB score) variables had a sensitivity of 75% and specificity of 69% in the validation cohort. After adjustment for the CURB score, both serum albumin $<$30 g/dL and age $\geq$65 remained independently associated with 30-day mortality. Serum albumin was discarded as it is often not available at the time of admission, but age was added to create a six-point CURB65 score. This allowed patients to be stratified into three groups according to number of factors present from 0 to 1 (1.5% mortality), 2 (9.2% mortality) to 3 or more (22% mortality). This model performed equally well in the validation cohort and provided a bigger range of sensitivities for specificity than the mBTS score. It was proposed that those with score 0 or 1 might be managed at home, 2 in hospital, and 3 or more be considered for ICU management.

The PSI has been validated in studies in the U.K., the Netherlands, New Zealand (25), Spain (7,41), Italy (42), Japan (43), and in elderly patients in Germany (40) as well as in studies in North America (24). All have found that the five risk classes are predictors of mortality, length of hospital stay,

and ICU admission rates, and in general have found Classes I–III to be similar with respect to outcome.

A separate approach was used by the American Thoracic Society in its 1993 CAP Guidelines (44). In this guideline, the presence of any one of 10 criteria (each having been found to be related to outcome in one or more CAP studies) defined severe illness. It was recommended that ICU admission be considered for such patients. One major difference in their approach was the use, in addition to parameters immediately available on admission, of factors that might only have become apparent as the illness evolved in hospitals. Ewig and colleagues (5) set out to validate this severity rule against ICU admission in a prospective study of 422 consecutively admitted adults (64 admitted to ICU) with CAP within one institution. They confirmed that three of the factors were often only present as the disease evolved with requirement for mechanical ventilation, septic shock, and renal failure being present only after 4 hr of admission in 53%, 29%, and 32%, respectively. More importantly, they also found that while each individual factor was associated with death, the relative risks of death for each factor varied widely from 1.3 ($PaO_2/FiO_2 < 250$) to 82.2 (requirement for mechanical ventilation). Only requirement for mechanical ventilation and septic shock was related to outcome on multivariate analysis. While the "ATS Rule" had a high negative predictive value (99%), its positive predictive value was low (19%). These authors suggested a modification of the "ATS Rule" (Table 4) such that severe CAP was defined by the presence of at least two minor and one major criteria. This improved the positive predictive value to 75% with only a small reduction in negative predictive value (95%). This approach was adopted in the revised ATS guidelines (45). A criticism of this severity prediction tool is that the use of "requirement for mechanical ventilation" is an endpoint in itself, and it is often the failure to predict this need that has led to late ICU admission in the past. Also, this endpoint may now be interpreted differently because of the use of noninvasive ventilation for patients that might previously have been intubated.

Table 4 The Modified American Thoracic Society Severity Prediction Rule (5)

Severe pneumonia is present in the presence of:
≥ Two of three minor admission criteria
Systolic blood pressure <90 mmHg
Multilobar involvement
PaO_2/FiO_2 <250
or
≥ One of two major criteria
Requirement for mechanical ventilation
Septic shock

Table 5 Comparison of Operating Characteristics of Severity Prediction Rules in the PORT Patient Cohort (13)

Event	Sensitivity	Specificity	ROC	PPV	NPV	RR
ICU admission						
Original ATS	82	43	0.61	17	94	3.0
Modified ATS	71	72	0.68	26	95	4.9
BTS Rule 1	40	78	0.58	20	90	2.1
PSI IV or V	73	53	0.6	19	93	2.7
Mechanical ventilation						
Original ATS	86	42	0.64	10	98	4.2
Modified ATS	100	73	0.74	22	100	4.2
BTS Rule 1	51	78	0.64	15	95	3.3
PSI	54	51	0.63	8	94	1.2
Medical complication						
Original ATS	69	71	0.6	89	40	1.5
Modified ATS	67	62	0.6	84	39	1.3
BTS Rule 1	28	87	0.57	84	33	1.3
PSI	58	77	0.65	90	35	1.4
Death						
Original ATS	80	41	0.6	9	97	2.6
Modified ATS	40	68	0.63	8	94	1.3
BTS Rule 1	56	78	0.62	16	96	4
PSI	94	53	0.75	13	99	16.8

Attempts to compare these severity prediction rules have been few, and early studies may have been invalidated by evolution of the rules with time. A recent study retrospectively compared the original and revised ATS criteria, the original BTS "Rule 1" and the PSI in the Pneumonia Patient Outcomes Research Team (PORT) patient cohort against ICU admission, mechanical ventilation, medical complication, and death (13). No clinical prediction rule appeared to be particularly accurate, with the modified ATS criteria being the best predictor of ICU admission and mechanical ventilation (but mechanical ventilation is one of the criteria), and the BTS Rule and PSI the best predictors of medical complications and death (Table 5).

DEFINING THE PATIENT AT RISK: PRESENTATION TO THE ICU

A number of studies have sought factors that predict poor outcome in CAP patients who reach the ICU. These results must be treated with some caution as the patient populations admitted and the types of care administered

Table 6 Features Related to Death in Patients Admitted to the ICU

Feature	References
Increased age, variously defined	14, 47–51
Immune compromise	14, 47, 49
Reduced alertness	50
Anticipated death within 4–5 years	14, 47, 52
Bacteremia	14, 50, 52
Albumin <45	14
Low admission neutrophil or leukocyte count	14, 49
Bilateral radiographic shadowing or radiographic spread	14, 52, 53
Inadequate initial therapy	14, 52
Measures of inadequate gas exchange, e.g., assisted ventilation, PEEP	14, 47, 50, 52, 53
Specific microbial causes (*P. aeruginosa*, *S. pneumoniae*, Gram-negative enterobacteria)	50, 52
ARDS	52
Septic shock	14, 50, 52, 53
Extrapulmonary organ failure	47
Complications	14, 53

have varied between the institutions covered by the studies. While two studies found no features to predict outcome (15,46), others have noted a number of features to be significantly related to the outcome as listed in Table 6. One study, confined to mechanically ventilated patients, developed an equation, which correctly predicted outcome in 88% of patients (47). Five factors, hypoxemia index, number of failed nonpulmonary organ systems, immunosuppression, age >80, and pre-existing medical prognosis of <5 years, were used to create a predictive score. This rule has not however been validated prospectively, nor in other populations.

DEFINING THE PATIENT AT RISK: PRESENTING IN THE COMMUNITY

In many healthcare systems, it is to the community physician, rather than the emergency room, where most patients will initially present. This is one of the least studied interfaces with respect to severity assessment. There are two important differences between this setting and those described earlier. The first is that the question to be answered is whether to *refer* the patient to hospital or to manage at home, and the second is that this decision often has to be made without access to hospital investigations including a chest radiograph. This usually means that only clinical information can be used to guide the decision, although research studies may have used investigations not usually available to the community physician at the time of

decision-making. A U.K. study of 236 adults (52 admitted to hospital) with CAP in the community identified home consultation, chronic disease, cough, fever >37.5°C, respiratory rate >30/min, confusion, and reduced conscious level to be related to hospital admission (54). Another study found living alone, chronic diseases (especially cardiovascular), and tachypnea to relate to hospital admission (55). A study in the elderly found only respiratory rate and consultation in the evening (56), while a population-based study found age and FEV1 to relate to admission (57). Of the three prospective clinical studies, respiratory rate appears to be the common factor predicting hospital admission. However, as indicated earlier, the hospital admission decision may vary between healthcare settings; hence, care is urged in trying to combine these results.

Where community-based studies have used death as an endpoint, age (57,58), coexisting illness (58), employment status (54), home consultation (54), absence of upper respiratory symptoms (54), respiratory rate >30/min (54,58), reduced conscious level (54), and FEV1 (57) have been the features associated with outcome.

While none of these have attempted to develop rules for severity prediction, it can be seen that many of the features are common to the hospital-based severity prediction rules, including both the PSI and the mBTS/CURB rules. It might therefore be reasonable to extrapolate from this to use, where practical, these hospital-based rules in the community. The first step of the PSI is based on clinical features, and the low mortality of Class I patients suggest that for patients aged <50 without comorbid disease or vital sign abnormality home management might be suitable (34). However, many Class II and III patients can also be managed at home, but this cannot usually be determined from data available in the community. Similarly, those who had less than two of the BTS Rule 2 features might be manageable at home. The CURB65 Rule suggests that those with none or only one feature could be suitable for home management (25). These authors, although studying patients admitted to hospital, also developed a further model based on features available on clinical assessment (confusion, respiratory rate ≥30/min, blood pressure (diastolic ≤60 mmHg or systolic <90 mmHg) and age ≥65—CRB65). This was found to correlate with mortality and need for mechanical ventilation. These suggestions now need prospective evaluation in a community population.

DOES SEVERITY ASSESSMENT ALTER OUTCOME?

The critical test for severity assessment rules is whether they can be used in routine clinical practice and whether outcomes are actually altered. In Britain, most hospitals have adopted CAP antibiotic guidelines based on severity assessment (59), but their impact has not been assessed. A North American study showed that adoption of a CAP practice guideline based

on the PSI altered physician beliefs about CAP management, but it did not address whether these were put into practice (60).

There are no prospective studies on clinical outcomes of application of the BTS Rules, the CURB/CURB65 scores, the ATS severity score, or the use of severity rules outside the hospital. One study of CAP patients admitted to an ICU found, compared to an earlier study on the same unit (48), a reduction in admissions as a result of cardiorespiratory arrest from 25% to 7% ($p \leq 0.02$) after adoption of CAP guidelines suggesting better severity assessment (15).

The PSI was developed primarily to identify low-risk CAP patients who might be managed at home. Most studies of the application of PSI-based guidelines have therefore used this endpoint. An initial study found that 33% of hospitalized CAP patients were low risk on day 3 and, although managed in hospital for longer than this, had the potential to have been able to be discharged at this time (61). A prospective study found that compared to retrospective controls, use of PSI-based guidelines increased the proportion of cases managed as outpatients from 42% to 57% (27). However, only 30% of potentially eligible patients were entered into this study, and the readmission rate for those managed at home was increased by the guideline from 0% to 9%. Another study, based in an urban urgent care clinic, also showed a reduction in admissions for CAP from 14% to 6% of total CAP cases, which was presumed to be because of severity assessment (62). Interestingly, introduction of the guideline was associated with a 33% increase in CAP case numbers in this study. There might be many explanations for this including natural variation in numbers. However, it is possible that the reduction in proportion admitted was because the increase in total numbers was simply because of increased identification of nonseverely ill cases.

A separate uncontrolled audit of the use of the PSI to aid home management in Hong Kong found that nine of 72 low-risk cases required readmission, and that none died. The authors interpreted these results to suggest safety of the approach, but some might consider this readmission rate high. Also, because Classes I and II were considered low risk, Class III patients were recommended for admission (63). A further study, which used non-PSI-based guidelines, found improved speed of antibiotic administration, blood culture performance, and oxygen assessment, but was associated with a trend for an increase in low-risk admissions from 30% to 39% (22). Perhaps the best evidence in support of this approach also comes from the study with the best methodological design. In a Canadian study, a critical care pathway for CAP was used in nine intervention hospitals, and patients were compared prospectively to those in 10 control hospitals (26). The care pathway included severity assessment using the PSI, levofloxacin monotherapy, an IV to oral switch protocol, and explicit discharge criteria. The proportion of low-risk patients admitted to hospital was 31% in the intervention compared to 49% in the controls ($p = 0.01$). Despite a higher PSI score in the admitted

patients, the length of stay was lower in the intervention hospitals. Interestingly, in the control hospitals, retrospective baseline data showed that 63% of low-risk patients were being admitted, suggesting improvement in these hospitals even without the intervention of guideline introduction.

In summary, these studies do suggest that the PSI can be used to safely increase the proportion of low-risk patients managed at home in some settings. Whether such changes can occur everywhere is unclear and may depend on current levels of practice. As indicated earlier (Table 1), the proportion of low-risk patients admitted to hospital varies widely. In some situations where the rate is already low (21,23), further reductions may or may not be achievable by objective severity scoring. It remains a concern that a significant number of low-risk patients do require admission for reasons unrelated to severity (e.g., comorbid disease, social factors), and this proportion will vary between healthcare settings. It is also a concern that some home-managed patients require readmission and some low-risk admitted patients suffer complications (7). A recent Spanish study has suggested that the application of a further eight clinical factors, to Class I–III patients may help to select low-risk patients who require admission (7). However, this is making a complex tool even more complex, which may reduce its applicability.

Although not designed specifically for the purpose, guidelines using the PSI have been assessed against other endpoints. A study assessing process of care markers found that the mean time to antibiotic administration and first blood culture was significantly shorter in Class V than in Class I, suggesting that physicians were using severity to guide management (24). In a study in which patients managed by physicians using a guideline within one healthcare scheme were compared with those managed by physicians outside that healthcare scheme, a statistically significant fall in 30-day inpatient mortality from 13.4% to 11% was found in those managed by the healthcare scheme physicians, but not in those managed by the nonhealthcare scheme physicians (64). Overall inpatient mortality and overall 30-day mortality, however, were unchanged. The practice guideline in this study included both CAP-specific interventions and general management interventions, including prophylactic heparin. Hence, it is not clear whether there was a real mortality reduction, and if so, whether this was because of better CAP management or just the prevention of pulmonary venous thromboembolism.

An important factor to take into account about these studies is the setting in which they were performed and importantly the steps that were taken to facilitate severity prediction introduction. Information about both is important to assess the applicability of the results to the reader's clinical practice. Such an introduction must initially involve an education and information phase, whereby healthcare personnel are informed. This may need to be backed up by repeated reinforcement and result feedback. In the above studies, other inducements have included free antibiotic provision (27), free

software provision (22), nurse training in PSI calculation (26), and increased nurse visiting and access to a primary care physician (27).

A final issue is the general educational effect that publicity about issues related to good medical practice, such as severity prediction, has on medical practice in general, leading to gradual secular changes in management. Improvement in the control group compared to historic controls referred to above (26) may have been because of this.

HOW TO USE SEVERITY PREDICTION RULES IN PRACTICE

A fundamental issue that all authors have made efforts to point out is that severity prediction rules cannot replace clinical judgment, but may be a useful guide to that judgment. Populations, healthcare systems, hospitals, community care schemes, and ICUs may all have varying operating characteristics and different accepted practices, which may mean that patients are managed differently in each setting. While a single prediction rule might help in all settings, it may be that different prediction rules have their place in varying settings—this remains to be defined. Each of the clinical prediction rules described above has been validated as predictors of severity. It is currently not clear whether small differences in sensitivity, specificity, positive or negative predictive values are clinically of any relevance. More studies addressing alterations in outcome associated with severity assessment introduction are needed. It may be that in some settings, where admitting healthcare staff has to deal with the whole range of acute medical condi-

Table 7 Comparison of Severity Prediction Rules

	mBTS	PSI	Modified ATS
Number of variables	4	20	5
Need for laboratory results	No	Yes	Yes
Information available at admission	Yes	Yes	No
Confirmed by >1 study	Yes	Yes	No
Outcomes improved by prospective implementation	Not studied	Unnecessary hospital admission? Death	Not studied
Risk groups defined	Severe and nonsevere	Five risk classes. I–III nonsevere, IV–V severe	Severe and nonsevere

tions, the use of a generic severity prediction rule, while less accurate than a CAP-specific rule, may be more practical. The early warning score (EWS) is an example of such a tool (65). Healthcare workers should choose prediction rules relevant to their work setting, ideally with studies of that rule having been performed in that or a similar setting. A summary of relevant features of the different rules to help guide the reader appears in Table 7. Prediction tools are currently evolving rapidly, with little information available about their risks and benefits in clinical practice with which to make a truly informed decision about the best approach.

CONCLUSIONS

While progress has been made, we do not yet have the answer to the question posed by Edward Wells. Illness severity in CAP can be predicted, but whether "positions of great peril can be relieved" is yet to be proved. Prediction of CAP severity has been accepted as an important step in patient management with CAP that may guide therapeutic interventions. A number of prediction tools have and are being developed, with varying amounts of information currently available about their individual value. Further developments are to be expected from forthcoming studies, especially with respect to their impact on outcome. This information is vital to guide their use in the future. Clinical expertise will remain the final arbiter of decision making.

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5

The Bacteriology of Severe Community-Acquired Pneumonia and the Choice of Appropriate Empiric Therapy

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INTRODUCTION

Community-acquired pneumonia (CAP) is a common illness, with an estimated incidence of 2–12 cases/1000 persons/year. Most of these cases are successfully managed on an outpatient basis; however, 20% will still require hospital admission. Severe CAP is considered a distinct clinical entity, which usually requires intensive care unit (ICU) management, has a particular epidemiology, and a somewhat different distribution of etiologic pathogens, compared with the other less severe forms of community-acquired pneumonia. Severe CAP may represent 10% of the total admissions of a specialized ICU (1), and the mortality of these patients is also high. Although less than 5% of outpatients with CAP die as a result of this illness, the meta-analysis performed by Fine et al. (2) found a mortality rate of 36.5% in ICU-admitted CAP patients, with a range of 21.7–57.3%.

Taking into account the potential evolution of this disease, the prompt institution of antimicrobial therapy is mandatory, even before any information regarding the etiologic diagnosis is available (which could take hours or even days). Empiric therapy, which does not cover the implicated pathogen, is known to be an independent predictor of poor outcome (1,3,4).

Moreover, subsequent changes in antibiotic therapy based on culture results also have a significant mortality (5,6). These adverse implications of inadequate empiric therapy make it necessary that the empirical antibiotic regimen chosen covers, as much as possible, the most likely pathogens. During the process of choosing the empirical therapy, current available epidemiological information about the spectrum of microbial etiology must be taken into account.

In this chapter, we review the most important pathogens implicated in the etiology of severe CAP. Some factors that may modify the spectrum of involved pathogens, like advanced age, nursing-home stay, chronic obstructive pulmonary disease (COPD), alcohol ingestion, and human immunodeficiency virus (HIV) infection will be approached separately. Finally, we discuss the treatment recommendation of available guidelines for the treatment of severe CAP.

ETIOLOGY OF SEVERE CAP

Over the last couple of years, numerous studies have been published about the bacteriology of severe CAP. Even though the percentage of pathogens differs in each publication, the overall distribution of these micro-organisms remains relatively constant. The most frequently identified pathogens include *Streptococcus pneumoniae*, *Legionella pneumophila*, *Haemophilus influenzae*, Gram-negative enteric bacilli (GNEB), *Staphylococcus aureus*, *Mycoplasma pneumoniae*, and respiratory-tract viruses. Interestingly, up to 20% of severe CAP episodes are caused by mixed infection.

In most patients with severe CAP, the responsible pathogen is not isolated in 50–60% of the cases, even when extensive diagnostic procedures are performed. The high proportion of subjects that usually receives prior antibiotic treatment may explain the low diagnostic yield of culture results. Besides, no single diagnostic test currently available can identify all possible involved pathogens.

In Table 1, a summary of the results of some series about the etiology of severe CAP is given.

Streptococcus pneumoniae

S. pneumoniae is by far the most frequently isolated pathogen among patients with CAP, independent of the severity of illness. It is present in up to one-third of the cases of CAP among those requiring ICU admission (1,8,13). The importance of *S. pneumoniae* in the etiology of CAP is not only because of its high prevalence, but is also related to its association with worse outcomes (9,16). Four variables have been found to be independently associated with the risk of severe pneumococcal CAP by Georges et al. (12), including male gender, nonaspiration pneumonia, septic shock,

Table 1 Microbial Patterns, Over the Years, of Severe Community-Acquired Pneumonia[a]

First author	Torres (1)	BTSRC (7)	Pachon (8)	Moine (9)	Leroy (4)	Rello (10)	Feldman (11)	Georges (12)	Ruiz (13)	Marik (14)	Rello (15)
Country	Spain	UK	Spain	France	France	Spain	S. Africa	France	Spain	USA	Spain
Year of publication	1991	1987	1990	1994	1995	1993	1995	1999	1999	2000	2003
No. of patients	92	60	67	132	299	58	259	505	91	148	204
S. pneumoniae (%)	29	24	34	41	31	37	45	41	32	19	35
H. influenza (%)	—	15	6	13	10	—	2	11	8	13	9
Legionella (%)	27	15	20	4	—	23	1	—	3	5	20
S. aureus (%)	—	7	3	5	22[b]	—	5	16	3	18	4
GNEB (%)	8	2	14	13	18	14	35	16	8	23	4
P. aeruginosa (%)	10	2	—	—	3	—	1	3	6	7	7
Atypical pathogens[c] (%)	12	20	3	13	3	3	3	3	31	—	2
Undetermined (%)	48	42	52	28	34	40	39	73	46	48	43

[a]Results are expressed as percentual of isolated pathogens.
[b]*Staphylococcus* spp.
[c]*M. pneumoniae, C. pneumoniae, C. burnetii,* viruses.

and lack of previous antibiotic use. This information provides an additional clue to the choice of initial empiric antimicrobial treatment in CAP.

Of great importance is the magnitude of the antibiotic resistance problem. Since the first description of an *S. pneumoniae* isolated with diminished susceptibility to penicillin in 1967 (17), resistance to penicillin and other antibiotics has been increasing worldwide (18,19), even though a prominent variation is found in the incidence of drug-resistant *S. pneumoniae* (DRSP) in different geographic areas (20–24). Identified risk factors for drug-resistant *S. pneumoniae* include age >65 years, alcoholism, noninvasive disease, β-lactam therapy within 3 months of infection, multiple medical comorbidities, exposure to children in a daycare center, and immunosuppressive illness, including therapy with corticosteroids (25).

The National Committee for Clinical Laboratory Standards (NCCLS) currently categorizes pneumococcal isolates as penicillin-susceptible if MIC is not greater than 0.06 μg/mL, of intermediate susceptibility if MIC is 0.1–1.0 μg/mL, and resistant if MIC is not less than 2.0 μg/mL. Even though these cut-offs may have clinical relevance in the presence of acute otitis media or meningitis (26,27), they do not seem to be appropriate for guiding the treatment of pneumonia.

Studies comparing patients infected by penicillin-susceptible strains with those with intermediate-susceptibility strains provide strong evidence that no increased mortality or treatment failure is associated with MICs of 0.1–1.0 μg/mL (28–31). Controversial results are found with penicillin MIC levels higher than 2.0 μg/mL. Some evidence suggests that there is an increased risk of mortality (30), a higher risk of suppurative complication (32), and a prolonged length of hospitalization (31,33), among those with penicillin MIC of 4.0 μg/mL or greater. However, other data indicate that there is no difference in outcomes at penicillin MIC of 2.0–4.0 μg/mL (34,35).

The report from the Drug-Resistant Streptococcus Pneumoniae Therapeutic Working Group recommends that in the future the susceptibility cut-offs for cases of pneumonia should be shifted upward so that the susceptible categories include all isolates with MICs of 1.0 μg/mL, the intermediate categories those of 2.0 μg/mL, and the resistant category includes those of at least 4.0 μg/mL (36). At the moment, NCCLS classification still prevails.

Resistance to macrolides has also become a worldwide problem over the last few years (37,38), concomitant with the increase in the use of macrolides (38). Erythromycin-resistant strains are also resistant to other macrolides and also to penicillin (39). A 2-year study in the United States found that 5% of the penicillin-susceptible strains of *S. pneumoniae* were also macrolide resistant, compared with 37% of the intermediate isolates and 66% of the resistant isolates (40).

The emergence of resistance to new fluoroquinolones has already been described in the Americas, Western Europe, and East Asia (41–44). The

highest resistance rate to date is reported from Hong Kong: 13% of fluoroquinolone nonsusceptibility (levofloxacin MIC $>4\,\mu g/mL$), which increased to 27% among penicillin-resistant strains (44). Risk factors associated with infection with levofloxacin-resistant strains include chronic obstructive pulmonary disease, nosocomial origin of the infection, residence in a nursing home, and, most importantly, exposure to quinolones (42,45). Many reports have been published to date describing cases of levofloxacin failure in treating pneumococcal respiratory-tract infections, even with previously susceptible strains (46–48).

Of great importance is the fact that the incidence of fluoroquinolone-resistant *S. pneumoniae* is likely to increase, especially with the rising empirical use of these drugs for the treatment of respiratory-tract infections, together with the evidence that strains under selective pressure of quinolone use will be able to acquire sequentially, several mutational resistance mechanisms (49).

Of the previously mentioned studies on etiology of severe CAP, only Ruiz et al. (13) described the percentage of isolated resistant *S. pneumoniae*. They found 32% (10 of 31) with drug resistance in the following distribution: 70% with intermediate and 20% with high-level penicillin resistance, 30% with intermediate cephalosporin resistance and 50% with macrolide resistance.

Legionella

Since its discovery in 1976, *L. pneumophila* has been recognized as an important cause of CAP. Over the last few years, studies of severe CAP have shown *Legionella pneumonia* as the second most common cause of admission to an ICU, after pneumococcal pneumonia (1,50). Nevertheless, the incidence of *Legionella* as causative organism of severe CAP widely changes according to the study and the geographic area where the study was performed. In Spain, *Legionella* spp. is the most frequent etiology after *S. pneumoniae* (1,8), whereas in the United States (51) and Great Britain (7), the incidence appears lower. Because pneumococcal pneumonia has an overall incidence of at least five-fold greater than that of *L. pneumophila*, the high frequency of *Legionella* in severe CAP implies that this micro-organism produces more severe forms of CAP.

Overall, mortality of *L. pneumonia* is high. Marston et al. (52) reported a mortality rate of 24%, Hubbard et al. (53) 27%, Pedro-Botet et al. (54) 18%, Moine et al. (9) 25%, and el-Ebiary et al. (55) 31%. This last study evaluated prognostic factors of severe *Legionella* pneumonia and found that serum sodium levels <136 (RR, 21.3) and APACHE score >15 at admission (RR, 11.5) were the only independent factors related to death. Conversely, improving pneumonia was associated with better outcome in Legionnaires' disease (RR, 0.02).

Interestingly, two studies have demonstrated a reduction, over time, in the incidence of *L. pneumophila*. In the Spanish study (13), the decrease in incidence of *Legionella* in patients with severe CAP (14%, 1984–1987 vs. 2%, 1996–1998) occurred concomitant with the increase of another atypical pathogen, *C. burnetii* (0%, 1984–1987 vs. 7%, 1996–1998). The higher prevalence of other atypical pathogens like *C. pneumoniae* and viruses in the second study period must be interpreted with caution because they were not tested in the first period. Similarly, the British study (56) also found a reduced prevalence of *Legionella* over time in the same ICU (30%, 1972–1981 vs. 16%, 1984–1993). A possible explanation for this decreasing incidence of severe legionellosis may be the more widespread early use of macrolides, or the so-called "rise and fall of legionellosis."

Staphylococcus aureus

The frequency of *S. aureus* in severe CAP is variable, ranging from 1% to 22% of all patients (25). Most patients with *S. aureus* pneumonia are elderly and have serious underlying disorders such as cardiovascular disease, malignant disease, chronic pulmonary disease, or diabetes mellitus, and recent influenza infection (57). The mortality rate of this infection ranges from 30% to 80% (58).

It has been suggested that *S. aureus* rarely causes severe CAP among healthy adults who live independently. However, over the last decade, *S. aureus* strains carrying a Panton–Valentine leukocidin (PVL) have been progressively isolated among immunocompetent children and young adults. This PVL-positive *S. aureus* causes a severe form of necrotizing pneumonia, usually in individuals with previous influenza infection, which rapidly progresses to acute respiratory distress syndrome (59,60). Gillet et al. (61) compared patients with pneumonia caused by PVL-positive and PVL-negative strains of *S. aureus*, and confirmed the high lethality of this entity (75% among PVL-positive vs. 47% among PVL-negative strains). In addition, they found that young and previously healthy patients had a worse prognosis compared with those with comorbidities and with advanced age.

Gram-Negative Enteric Bacilli

Community-acquired pneumonia by GNEB occurs more frequently in patients treated in the intensive care setting than in those treated elsewhere. However, there seem to be differences in its prevalence worldwide. Previous studies, particularly from Spain (8,10) and South Africa (62,63), have suggested the important role of GNEB in the etiology of severe CAP. Conversely, in the studies from the United Kingdom (7,50), these pathogens were not as commonly implicated in the etiology of severely ill patients. Feldman et al. (11) discussed this feature and proposed some explanations for the differences in etiology noted within these studies: different number of

patients with underlying disorders, known to be associated with increased colonization and/or invasive disease with GNEB; greater alcohol consumption; and different methodology utilized because the use of more invasive techniques for the diagnosis of pneumonia may be associated with the documentation of more GNEB infection.

A study by Ruiz et al. (13) found that GNEB caused 11% of CAP in patients requiring ICU admission. The mortality in this subgroup was 55.5%, the highest case fatality rate for any etiology. Gram-negative pathogens, in another study, were also associated with severe CAP and shock, with a mortality rate of 50% (14).

The current ATS guidelines (25) suggest that *P. aeruginosa* should be considered only when specific risk factors are present, and these risks include: chronic or prolonged (>7 days within the past month) broad-spectrum antibiotic therapy, presence of bronchiectasis, malnutrition, or diseases and therapies associated with neutrophil dysfunction (such as >10 mg of prednisone per day). As discussed later, HIV infection has also been identified as a risk factor for severe CAP due to *P. aeruginosa* (64).

Another Gram-negative bacillus, *Acinetobacter baumannii*, usually considered as a nosocomial pathogen, has been implicated in the etiology of CAP over the last several years (14,65). A recent publication described a series of patients with severe community-acquired *Acinetobacter pneumonia*, in which 85% of the patients acquired the infection between the months of April and October, reflecting the inclination of this micro-organism for warm and humid environments (66). This pathogen was also more frequent among young alcoholic patients; clinical course was usually fulminant, with respiratory failure and septic shock. Mortality of community-acquired *Acinetobacter pneumonia* ranges from 40% to 64%, significantly higher than overall mortality resulting from severe CAP (66).

SPECIFIC RISK GROUPS

Elderly

A few studies addressed CAP in the elderly (67–71), but the major limitation of most of these studies is the use of expectorated sputum for etiological diagnosis. Only two studies have evaluated the etiology among elderly with severe CAP with invasive diagnostic techniques (72,73). However, these studies revealed different etiologic profiles, with a high prevalence of GNEB (15.8%) and *Legionella* (8.8%) found by El-Solh and coworkers. In fact, the authors justified the unexpected prevalence of *Legionella* because of prolonged corticosteroid therapy, which most of the patients were receiving. The most common isolated pathogen by Rello et al. was *S. pneumoniae* (48.6%), followed by GNEB (13.5%) and *H. influenzae* (10.8%). Of note is that patients originally from a nursing home were excluded, as were those

with a diagnosis obtained exclusively by sputum, because these agents are frequently recovered from sputum specimens of elderly patients with pneumonia, increasing the difficulty in differentiating colonization from infection. Both studies also evaluated the prognostic factors of elderly with severe CAP. Rapid radiological spread, shock, immunosuppression, acute renal failure, APACHE score >22, and inadequate antibiotic coverage were independently associated with poor prognosis. Extraordinarily, the presence of comorbidities did not seem to influence outcome.

Nursing Home-Acquired Pneumonia

Nursing home-acquired pneumonia (NHAP) has been considered to be different from CAP in terms of severity and etiology. Nursing home-acquired pneumonia patients are more likely to present with severe pneumonia than controls aged more than 65 years admitted to the hospital from the community (74). Only one study carefully studied the etiology in this specific group of patients with severe CAP. El-Solh et al. (73) compared the etiology of severe CAP in patients older than 75 years from both the community and the nursing home. They found that *S. pneumoniae* was the most frequent etiology in those admitted from the community, followed by GNEB and *Legionella*. Distribution of pathogens in NHAP was significantly different: *S. aureus* was the leading etiology, followed by GNEB and *S. pneumoniae*. In this study, 21% of the isolated *S. aureus* were methicillin resistant, similar to the findings of Muder et al. (75), who reported that up to one-third of invasive staphylococcus infections in nursing-home patients could be because of methicillin-resistant strains. Muder et al. also reported a mean prevalence of S. aureus pneumonia approaching 9% in the nursing home setting, but with a wide range—from 0% to 33%. In elderly patients with severe CAP who have aspiration risks, Gram-negative organisms predominate.

Alcoholics

Alcoholics are a subgroup of the population who suffer from severe CAP. Even though its specific incidence has not been described, the ingestion of 80 g/day of alcohol is a well-known factor independently associated with severe CAP (13,76). Factors responsible for this increased incidence of pneumonia among alcoholics have been previously investigated. The alcohol itself is known to depress ciliary function, inhibit surfactant production, retard the migration of neutrophils in the lung, and impair the activity of macrophages. Besides, other factors like poor nutrition, aspiration, excessive smoking, and alcoholic cirrhosis often play additional roles in the increased rate of pneumonia in alcoholics (77).

The most common etiologic agents of pneumonia among alcoholics are *S. pneumoniae*, *Klebsiella*, and *H. influenzae*. *K. pneumoniae* has long been considered to be the most frequently encountered causative micro-organism

of pneumonia in alcoholics, even though the high prevalence of pharyngeal colonization by this bacillus among these patients (78) is the only satisfactory explanation for this finding. Mortality rate among alcoholics with *Klebsiella* pneumonia is around 50–60%; however, it is remarkably higher (89–100%) when bacteremic *Klebsiella pneumonia* is present (79).

Chronic Obstructive Pulmonary Disease

Chronic obstructive pulmonary disease is a common illness, affecting up to 15 million persons in the United States (25), and these patients commonly develop pneumonic and nonpneumonic exacerbation of their illness. Besides, among those patients with severe CAP who require hospitalization and admission to ICU, COPD is one of the most frequent underlying diseases (1,13,62,80). Even though some studies have also attributed a higher mortality to the presence of COPD among these patients, others have not confirmed this fact (1,4,80). The number of published articles on CAP in patients with COPD is relatively small. Furthermore, nobody has yet specifically evaluated the population of COPD patients with severe CAP.

Lieberman et al. (81) evaluated patients with pneumonic and nonpneumonic acute exacerbations of COPD. They found significantly more patients with pneumonic acute exacerbation of COPD admitted to ICU (26% vs. 7%). These patients also had a higher mortality rate (13% vs. 1%). Ruiz De Ona et al. (82) also found more severe forms of CAP among patients with COPD, but mortality was greater only in COPD patients who were receiving domiciliary oxygen therapy, had greater airflow obstruction or respiratory deterioration upon admission.

Human Immunodeficiency Virus

Immunocompromised patients, especially those with human immunodeficiency virus (HIV), have become recognized as a particularly important population not only because of their increased risk for CAP (29,83) but also for the expanded spectrum of potential causes of CAP. However, clinical information regarding this group of patients is sparse. Besides, the published CAP management guidelines have excluded HIV-positive patients from consideration. Few studies have specifically evaluated the etiology of severe CAP in HIV-positive patients.

Park et al. (84) evaluated a cohort of patients with CAP, and among those, 92 patients with severe CAP (72 HIV-negative and 20 HIV-positive). Opportunistic infection was the most important cause of CAP among HIV-positive patients. *Pneumocystis carinii* pneumonia (PCP) was the most common etiology of severe CAP among HIV-infected patients, especially in those with lower CD4 lymphocyte counts. Severe PCP prevalence was similar to that of bacterial pneumonia (30% vs. 35%). Infection by *Cytomegalovirus* and *Mycobacterium avium* accounted for 15% and 10%

of the etiologies respectively. There was also a higher prevalence of *P. aeruginosa* (15% vs. 0%), as found by others (85). Besides, in accordance with the findings of Mundy et al. (86), the prevalence of *Legionella* pneumonia was not higher among HIV-positive patients, as previously suggested by the CDC study (52). The uncommonly low prevalence of *S. pneumoniae* (5%) among HIV-positive patients could probably be explained by the high rate of previous use of antibiotics of these patients. Moreover, Janoff et al. (87) had earlier found a higher risk of pneumococcal infection and bacteremia associated with HIV infection. Cordero et al. (88) also evaluated a cohort of HIV patients with bacterial CAP, 214 with severe CAP. There was no difference in the microbial profile of those patients with severe CAP or not. *S pneumoniae* was the most prevalent micro-organism (33%) among those with severe CAP, followed by *P. aeruginosa* (20%) and *H. influenzae* (14%).

It should also be kept in mind that patients with unknown HIV infection may present with severe CAP. One study of 385 patients in 1991 showed that 46% of patients had HIV infection and 19% of these patients were unaware of their HIV status at the time of admission (86). Many authors have also emphasized this information. Hirani and Macfarlane (56) found in their study that 5% of patients with severe CAP were infected by *P. carinii*, while Rello et al. found 8% in 1993 (10) and 5% in 2003 (15); all of them were not aware of their immunosuppression until hospitalization.

Table 2 Distribution of Pathogens According to the Presence of Modifying Factors[a]

	Elderly (73)	Elderly (72)	Nursing home (73)	HIV[b] (88)	HIV (84)
Country	USA	Spain	USA	Spain	USA
Year	2001	1996	2001	2000	2001
No. of patients	57	95	47	214	20
S. pneumoniae (%)	21	49	9	33	4
H. influenzae (%)	13	11	—	14	—
Legionella (%)	10	8	31	—	4
S. aureus (%)	10	3	2	8	—
GNEB (%)	21	8	15	6	4
P. aeruginosa (%)	3	8	4	20	14
Atypical pathogens[c] (%)	5%	11%	—	2%	23%

[a]Results are expressed as percentual of isolated pathogens. The lack of specific studies evaluating the etiology of severe CAP among COPD and alcoholics justifies their exclusion from this table.

[b]Only bacterial pneumonia.

[c]*M. pneumoniae, C. pneumoniae, C. burnetii,* viruses.

Table 2 exhibits the distribution of pathogens according to the presence of modifying factors.

TREATMENT OF SEVERE CAP

One of the most problematic issues in severe CAP treatment is that the antibacterial has to be initiated on an empirical basis. To be able to start an effective empiric therapy, it is necessary to predict the micro-organisms or the mixture of these, which are likely to be the etiology of the current illness. Multiple guidelines (Table 3) have been published in the last few years to help physicians choose the right antibacterial (89). The different recommendations are based on the severity of illness, comorbidities, and modifying factors that the patient has for specific micro-organisms. In addition, resistance patterns of each geographic area need to be taken into account. Timing of initial empiric therapy is very important, because there are data showing a reduced risk of complications and mortality at 30 days if hospitalized patients receive their first dose of antibiotic therapy within 4–8 hr of arrival at the hospital (90). Besides time of initial antibiotic therapy, the administration of an appropriate antibacterial is a key factor associated with a shorter course, lesser risk of complications and lower mortality, understanding that when host factors become more complex, or the severity of illness increases, a more aggressive and broad-spectrum regimen is recommended. Many studies of patients with severe CAP have emphasized the importance of adequate empirical treatment in reducing disease-related mortality. In severe CAP, mortality can be as low as 10% if initial empirical therapy is adequate. But if there is no clinical response by 72 hr, even if culture data explain why initial therapy is inadequate, mortality can be as high as 60% (4).

ATS Guidelines

In accordance with the ATS guidelines for the management of adults with community-acquired pneumonia (25), initial empirical therapy should be directed against *S. pneumoniae*, *Legionella* (and other atypicals), and *H. influenzae*. However, the patients should be stratified on the basis of risks factors for *P. aeruginosa*.

In the absence of pseudomonal risk factors, therapy should be with a β-lactam, which would be active against DRSP plus either an intravenous macrolide (azithromycin) or a quinolone. These β-lactam agents should be effective against pneumococcus, but those that are also active against *P. aeruginosa* (cefepime, piperacillin/tazobactam, imipenem, meropenem) are not recommended as primary in this group of patients. They should be reserved for those with pseudomonal risks.

Patients with pseudomonal risk factors should be treated with two antipseudomonal agents and with the use of agents that also provide coverage for DRSP and *Legionella*. The options include selected β-lactam agents

Table 3 Initial Empiric Antimicrobial Therapy According to Different Guidelines

Organization	Preferred	Alternative or special consideration
ATS	IV β-lactam (cefotaxime, ceftriaxone)+ IV macrolide (azithromycin) or IV fluroquinolone	IV antipseudomonal β-lactam (cefepime, imipenem, meropenem, piperacillin/ tazobactam)[a] + IV antipseudomonal quinolone (ciprofloxacin) or IV antipseudomonal β-lactam plus IV aminoglycoside + either IV macrolide (azithromycin) or IV nonpseudomonal fluoroquinolone
BTS	IV broad-spectrum β-lactamase stable antibiotic (amoxicillin/ clavulanic acid, cefuroxime, cefotaxime, ceftriaxone)+ macrolide ± rifampicin	Antipneumococcal fluoroquinolone + benzylpenicillin
IDSA	Extended spectrum cephlosporin (cefotaxime, ceftriaxone) or β-lactam/ β-lactamase inhibitor + antipneumococcal fluoroquinolone or macrolide	Antipseudomonal agents[b] plus a fluoroquinolone (including high-dose ciprofloxacin)
		Antipneumococcal fluoroquinolone ± clindamycin[c]
		Antipneumococcal fluoroquinolone ± clindamycin or metronidazole or β-lactam/ β-lactamase inhibitor[d]

[a]Risks for *P. aeruginosa*.
[b]Structural lung disease.
[c]β-Lactam allergy.
[d]Suspected aspiration.
Abbreviations: ATS, American Thoracic Society (25); BTS, British Thoracic Society (91); IDSA, Infectious Disease Society of America (89).

(cefepime, piperacillin/tazobactam, imipenem, meropenem) plus an antipseudomonal quinolone (ciprofloxacin), or a selected β-lactam agent plus an aminoglycoside and either azithromycin or a nonpseudomonal quinolone. In the β-lactam allergic patient, aztreonam can be used and combined with an aminoglycoside and an antipneumococcal fluoroquinolone.

IDSA Guidelines

According to these guidelines (89), the goal of therapy is to provide optimal coverage for the two most commonly identified causes of lethal pneumonia, *S. pneumoniae* and *Legionella*. The alternatives include the use of a β-lactam (cefotaxime, ceftriaxone, ampicillin–sulbactam, or piperacillin–tazobactam) combined with a fluoroquinolone or a β-lactam combined with a macrolide. Patients with risk factors for *P. aeruginosa* (e.g., structural disease of the lung) should be covered with a regimen which will be active against this microorganism: piperacillin, piperacillin–tazobactam, a carbapenem or cefepime, plus a fluoroquinolone (including high-dose ciprofloxacin).

BTS Guidelines

Initial empirical treatment in these guidelines (91) includes combination therapy with broad-spectrum β-lactams (cefuroxime, ceftriaxone, or cefotaxime) and a macrolide. While *S. pneumoniae* remains the predominant pathogen, *S. aureus* and Gram-negative enteric bacilli, although uncommon, carry a high mortality (2)—hence the recommendation for broad-spectrum β-lactam regimens in those with severe CAP. Patients admitted to hospital with CAP caused by *Legionella* species are more likely to have severe pneumonia; hence, the initial empirical antibiotic regimen should also include this pathogen within its spectrum of activity. Retrospective studies suggest a reduction in mortality for those treated with a third-generation cephalosporin plus a macrolide (92,93), although no additional benefit has been noted in another study (94). For life-threatening infection where *Legionella* species could be present, the addition of rifampin is recommended, despite the absence of clinical data showing benefit.

Guidelines-Based Therapy and Outcomes

Different scientific societies have published several clinical guidelines (25,89,91) in CAP like the ones mentioned earlier, to guide and assist physicians in choosing the appropriate initial antibiotic regimen to be followed. However, they leave some degree of uncertainty arising from the heterogeneity of patients' clinical condition, the differences in etiologic micro-organisms, and the quality of the evidence backing their recommendations. Herein, there is no firm evidence that acceptance of and compliance with guidelines leads to an improvement in the patients' prognosis with CAP or has an impact on relevant social and economic variables such as health care-related costs or length of stay. It remains to be determined whether the strict adherence to the recommendations is the best therapeutic option in each and every patient.

A study (94) evaluated the degree of adherence to American Thoracic Society guidelines and the influence of adhering to these guidelines on mor-

tality and length of hospitalization in 295 patients. Class IV and V of Pneumonia Severity Index (PSI) accounted for 58% of all patients, and adherence to ATS guidelines in these groups was 87.6% and 87.8%, respectively. Mortality was found to be significantly higher in class V (most severe group) patients receiving treatment who did not adhere to ATS guidelines (25% vs. 66%, $p < 0.05$; RR 2.6, 95% IC 1.2–5.6). Logistic regression analysis to predict mortality showed that both the PSI score and adherence to the ATS guidelines were significant and independent variables associated with decreased mortality (RR 0.3; 95% IC 0.14–0.9 for ATS). The mean length of hospital stay did not show statistically significant difference according to the ATS guidelines.

Hirani and Macfarlane (56) published an article several years ago about the impact of 1993 BTS management guidelines on the outcome of severe community-acquired pneumonia. They evaluated 57 patients—52% fulfilled Rule 1 of the BTS criteria for severe infection at admission. Most of the patients received a β-lactam agent on admission; 39 (68%) received ampicillin and 17 (30%) cefuroxime or cefotaxime. Erythromycin was administered to 91% of patients on arrival at hospital and to all patients upon ICU admission. Only four patients received flucloxacillin on admission and 21% an aminoglycoside, including the one case of *P. aeruginosa* infection. They found that the guidelines were practical and widely adopted locally, but there was no reduction in mortality.

Additionally, an article by Marras and Chan (95) evaluated the use of ATS guidelines in CAP patients admitted to the general medical ward. One-hundred-twenty-two patients were prospectively described and another 130 patients were identified retrospectively. There was no difference in guidelines' adherence between the prospective and retrospective groups (81% vs. 80%, $p = 0.94$). When physicians believed that they were following guidelines, this was true in 88% of the cases. When they felt they were deviating, they were actually adhering 46% of the time. There was no significant difference in length of stay or in-hospital mortality, regardless of guideline adherence. However, this study does not specify the severe CAP subgroup. A paper by Gordon et al. (96) also showed in 4339 non-ICU patients that recommended therapy options are associated with a lower mortality than other therapeutic options, and there are no significant differences in mortality among guideline-recommended β-lactams when they are used as monotherapy for nonsevere CAP. Finally, one study reported a 4.4-fold reduction in mortality if the ATS therapy guidelines for hospitalized CAP were followed, rather than using alternative antibiotic regimens. Noncompliance with the guidelines was greater in the ICU-admitted patients because the selected therapy did not provide coverage for atypical pathogens, *P. aeruginosa*, or both. Nonetheless, the study included only 52 severe CAP cases, of whom only 10 were mechanically ventilated (97).

Empirical Antimicrobial Therapy and Outcome in Global Studies of Severe CAP

As previously mentioned, it is essential that the initial antimicrobial therapy in severe CAP be effective against the causative pathogen. Even though the guidelines can help choose the appropriate antibiotic, they cannot capture every clinical situation. Hence, it remains the responsibility of the physician to balance the history and clinical features, assess the importance of risk factors, and interpret local epidemiology and laboratory data to make the best judgment for an individual patient (98). Herein, an empiric treatment which deviates from the guidelines could be initiated. Several studies have attempted to evaluate the associations between initial empirical antibiotic therapy and primary outcomes, without paying attention to guideline recommendations.

A recently published study by Rello et al. (99) in a group of 460 severe CAP patients showed that the most frequently prescribed empirical regimen in Spain (56.7% of cases) included a combination of a β-lactam with an intravenous macrolide, and it was associated with 27.2% mortality. The lowest overall mortality was associated with initial treatment with a macrolide plus another agent (or alone). The excess mortality for initial treatment with an aminoglycoside was significantly higher (14.2%; IC 95% 27.3–1.1) than the overall mortality rate between patients receiving a macrolide plus another agent. No significant differences were documented when mortality was adjusted for intubated patients or APACHE II at admission. In an editorial comment (100), it is clear that one confounding factor was that the patients receiving a macrolide/β-lactam combination had a lower frequency of shock or intubation than those receiving an aminoglycoside. The latter could be a reflection of the possibility that aminoglycosides were used in sicker patients or that therapy with an aminoglycoside led to a worse outcome than therapy with alternative regimens. Unfortunately, the authors did not separate out these explanations.

Gleason et al. (101) published a study of 12,945 Medicare inpatients ($>$ or $=$ 65 years of age) with pneumonia: 75.3% were community dwelling and 68.3% were in the two highest severity risk classes (IV and V) at initial examination. The three most commonly used initial antimicrobial regimens were a nonpseudomonal third-generation cephalosporin only (26.5%), a second-generation cephalosporin only (12.3%), and a nonpseudomonal third-generation plus a macrolide in 8.8%. Initial treatment with a second-generation cephalosporin plus macrolide [hazard ratio (HR), 0.71; 95% confidence interval (CI), 0.52–0.96], a nonpseudomonal third-generation cephalosporin plus macrolide (HR, 0.74; 95% CI, 0.60–0.92), or a fluoroquinolone alone (HR, 0.64; 95% CI, 0.43–0.94) was independently associated with lower 30-day mortality. Yet, only 15% of all patients received one of these three initial regimens, whereas higher 30-day mortality rates were

observed among patients treated with a β-lactam/ β-lactamase inhibitor plus macrolide (HR, 1.77; 95% CI, 1.28–2.46) and an aminoglycoside plus another agent (HR, 1.21; 95% CI, 1.02–1.43). Separate analysis of association between initial therapy and 30-day mortality performed for patients in severity risk classes IV and V had a similar direction and magnitude of effect as those derived from the model in the total study population. No regimen was associated with a significantly shorter length of stay. Although the study by Stahl et al. (102) did not include ICU patients, the average mortality risk class was IV. The latter study concluded that patients who received macrolides within the first 24 hr of admission had a markedly shorter length of stay (2.8 days) than those not so treated (5.3 days; $p = 0.01$). Including ceftriaxone as part of the initial therapy did not appear to affect LOS.

A controversial issue in the Gleason study is the association between β-lactamase inhibitors/ β-lactam agents used with macrolides and a poorer outcome. Neither the study by Rello et al. (99) nor Stahl's showed such association. The importance of atypical pathogens was shown in one series that reported finding these organisms in about 20% of ICU-admitted CAP patients (13). But, if the treatment of these micro-organisms is critical, why do these studies show opposite results and why do Gleason's results not apply to other macrolide-combination regimens? One possible explanation for the counterintuitive findings on outcomes studies is that clinicians select the initial antibiotic regimen in a patient-based policy after carefully classifying them according to risk factors for specific pathogens and prognosis, rather than by following general guidelines. It is unclear if all these studies have evaluated the impact of therapy on the severity of illness or the impact of severity of illness on therapy choices. Additionally, the retrospective nature of the most of outcome papers is another potential limitation to interpret their findings.

Pneumococcal CAP Outcomes and Therapy

As previously described, *S. pneumoniae* is consistently identified as the most common pathogen in CAP accounting for 9–55% of cases among patients requiring hospitalization (103). Surveillance data collected from 27 institutions in the United States from February through June 1997 revealed that 28% of respiratory-tract isolates of *S. pneumoniae* had penicillin MIC no less than 0.1 μg/mL and 16% had penicillin MIC no less than 2 μg/mL, and recent data suggest higher rates of resistance (104). Some studies of pneumococcal pneumonia among children and adults indicate that pneumococcal resistance to penicillin does not have a deleterious impact on treatment outcome (28). However, other studies (30) and case reports suggest that pneumococcal resistance may have an impact on mortality and other outcome measures in pneumonia. Although this issue remains

debated, resistance has been shown to influence which antimicrobial agents clinicians must choose for treatment of pneumococcal pneumonia. Also, there has been some controversy about what are the best MICs to define resistance and susceptibility to penicillin, evidence now indicates that patients hospitalized for pneumococcal pneumonia caused by strains currently defined as having intermediate susceptibility to penicillin (MIC 0.1–1.0 μg/mL) respond well to treatment with adequate intravenous doses of β-lactams (e.g., 15 million units per day of penicillin G). Additionally, several studies comparing patients infected by penicillin-susceptible strains with patients infected by intermediate-susceptibility strains provide strong evidence that there is no increased mortality or treatment failure associated with strains currently defined as having intermediate susceptibility to penicillin (105).

The empirical therapy of pneumococcal pneumonia in the drug-resistant pneumococcal era should include an intravenous β-lactam, such as ceftriaxone or cefotaxime, and an intravenous macrolide. Alternatively, intravenous ceftriaxone or cefotaxime and a fluoroquinolone with antipneumococcal activity may be an option. The antipneumococcal activity differs slightly between each agent (i.e., gemifloxacin is superior to moxifloxacin, which is superior to grepafloxacin, which is superior to levofloxacin (106).

Macrolides do not provide optimal coverage of penicillin-resistant pneumococci, because macrolide resistance is common among such strains (approximately 60%) (107), and also macrolide resistance is often high level, when present (22). Existing data are insufficient to determine whether macrolides can be used effectively against macrolide-resistant pneumococcal strains in which lower-level resistance results from increased drug efflux (mef E-encoded resistance), with resulting MIC values of 1–32 μg/mL. Adequate concentrations of macrolides in lung tissue may be able to overcome this resistance. However, when macrolide resistance is caused by a ribosomal methylase encoded by ermAM, with resulting MIC values generally being no less than 64 μg/mL (108), resistance presumably cannot be overcome by increasing the dosage.

Two recently published studies found important issues about bacteremic pneumococcal pneumonia. The mortality rate of this pneumonia has shown little improvement in the past 3 decades, remaining between 19% and 28% (109). Waterer et al. (110) showed in a retrospective study the influence of initial empiric monotherapy on the outcome of bacteremic pneumococcal pneumonia. Of the 255 patients identified, 99 were classified as receiving single effective therapy (SET), 102 for dual effective therapy (DET), and 24 for more than DET effective therapy (MET). Those who received MET were significantly sicker than the ones who received SET or DET as measured by the PSI ($p = 0.04$) and APACHE II-based predicted mortality ($p = 0.03$). Mortality within the SET group was significantly higher than those within the DET group [$p = 0.02$, odds ratio, 3.0 (95%

confidence intervals, 1.2–7.6)], even when the DET and MET groups ($p = 0.04$) were combined. In a logistic regression model including antibiotic therapy and clinical risk factors for mortality, SET remained an independent predictor of mortality with a predicted mortality-adjusted odds ratio for death of 6.4 (95% confidence intervals, 1.9–21.7).

To assess the association between inclusion of a macrolide in a β-lactam-based empirical antibiotic regimen and mortality among patients with bacteremic pneumococcal pneumonia, Martinez et al. (111) analyzed 10 years of data from a database. Of the 409 patients analyzed, 238 (58%) received a β-lactam plus a macrolide and 171 (42%) a β-lactam without a macrolide. Multivariate analysis revealed four variables to be independently associated with death: shock ($p < 0.0001$), age $>$ or $=$65 years ($p = 0.02$), infections with pathogens that have resistance to both penicillin and erythromycin ($p = 0.04$), and no inclusion of a macrolide in the initial antibiotic regimen ($p = 0.03$). For patients with bacteremic pneumococcal pneumonia, not adding a macrolide to a β-lactam-based initial antibiotic regimen was an independent predictor of in-hospital mortality. This work has the shortcomings common to any observational study in which empirical antimicrobial therapy has not been selected at random.

Fluoroquinolone Therapy and Outcome

Nowadays, a debated aspect in severe CAP therapy is whether fluoroquinolone monotherapy can be effective for patients admitted to the ICU with CAP. In the ATS guidelines and other recently published recommendations, no ICU-admitted patient is to receive monotherapy, even with one of the new quinolones. To our knowledge, there are no prospective randomized trials that have evaluated this issue, and these studies should also address whether quinolone monotherapy would be effective for patients with drug-resistant pneumococcal pneumonia, complicated by meningeal infection. In the study by Rello et al. (99), mortality with quinolone monotherapy was comparable to that with a β-lactam/macrolide combination, but the number of patients treated with this regimen was small (2.3%).

In a prospective, randomized, double-blind, multicenter trial (112), intravenously administered ciprofloxacin (400 mg every 8 hr) was compared with imipenem (1000 mg every 8 hr) for the treatment of severe pneumonia. A total of 405 patients with severe pneumonia were enrolled and 78% had nosocomial pneumonia. Two-hundred-and-five patients (98 ciprofloxacin-treated patients and 107 imipenem-treated patients) were evaluable for the major efficacy endpoints. The primary and secondary efficacy endpoints were bacteriological and clinical responses at 3–7 days after completion of therapy. Ciprofloxacin-treated patients had a higher bacteriological eradication rate than did imipenem-treated patients (69% vs. 59%; 95% confidence interval of -0.6%, 26.2%; $p = 0.069$) and also a significantly higher clinical

response rate (69% vs. 56%; 95% confidence interval of 3.5%, 28.5%; $p = 0.021$). A drawback of this study is that those with *P. aeruginosa* recovering from initial respiratory-tract cultures failed to achieve bacteriological eradication and developed resistance during therapy in both treatment groups (67% and 33% for ciprofloxacin and 59% and 53% for imipenem, respectively). There is also controversy about whether ICU-admitted patients should be routinely treated for *P. aeruginosa*, or such therapy should be limited to specific populations at risk for infection with this organism, such as those with bronchiectasis, prolonged antibiotic therapy, chronic steroid therapy, and malnutrition (25).

Finch et al. (113) compared the efficacy, safety, and tolerability of moxifloxacin (400 mg) given intravenously (i.v.) once daily followed by the oral form (400 mg) for 7–14 days with the efficacy, safety, and tolerability of coamoxiclav (1.2 g) administered by i.v. infusion three times a day followed by its oral form (625 mg) three times a day, with or without clarithromycin (500 mg) twice daily (i.v. or orally), for 7–14 days, in adult patients with community-acquired pneumonia requiring initial parenteral therapy. A total of 628 patients were enrolled in the trial, and 622 were valid for the intention-to-treat (ITT) analyses. More than half ($n = 321$) of the patients in the ITT and safety analyses had a diagnosis of severe CAP. The results showed statistically significantly higher clinical success rates (for moxifloxacin, 93.4%, and for comparator regimen, 85.4%; difference (Delta), 8.05%; 95% CI, 2.91–13.19%; $p = 0.004$) and bacteriological success rates (for moxifloxacin, 93.7%, and for comparator regimen, 81.7%; Delta, 12.06%; 95% CI, 1.21–22.91%) for patients treated with moxifloxacin. This superiority was seen irrespective of the severity of the pneumonia and whether or not the combination therapy included a macrolide. The rates of drug-related adverse events were comparable in both groups (38.9% in each treatment group). An important aspect of the study is that only 28% of patients in the moxifloxacin group had pre-existing bronchopulmonary disease. This limits interpretation of the results for severe CAP patients with *Pseudomonas spp*. infection risk. Additionally, in the study by Frank et al. (114) in hospitalized patients with moderate-to-severe CAP, levofloxacin monotherapy was at least as effective as a combination regimen of azithromycin and ceftriaxone in providing coverage against the current causative pathogens in CAP. In addition, levofloxacin was as well tolerated as the combination of azithromycin and ceftriaxone. It remains unclear if levofloxacin should be dosed at 500 mg or 750 mg daily in severe CAP, but the higher dose has been used in nosocomial pneumonia.

All these studies offer the possibility of treating the patients with severe CAP with fluoroquinolone monotherapy unless they have specific risks factors for *Pseudomonas infection*.

CONCLUSION

The most common etiologic agents in severe CAP are *S. pneumoniae*, *L. pneumophila*, *H. influenzae*, Gram-negative enteric bacilli (GNEB). One must be aware of risk factors such as advanced age, admission from a nursing home, alcohol ingestion, COPD, and HIV that may modify the spectrum of predicted pathogens. Regarding the treatment, it is important to promptly begin an antibiotic regimen, which adequately covers the most frequent pathogens, and also taking into account the presence of risk factors and the resistance pattern of each community.

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6

Risk Factors for Ventilator-Associated Pneumonia: A Complex and Dynamic Problem

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Remember how much you don't know.

– William Osler (circa. 1895)

Clinical medicine seems to consist of a few things we think we know (but probably don't), and lots of things we don't know.

– CD Naylor (1995)

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INTRODUCTION

A patient's risk of pneumonia is increased 6 to 21-fold with intubation and mechanical ventilation (1–3). Ventilator-associated pneumonia (VAP) is defined as new pneumonia, which develops more than 48–72 hr after intubation (1). Early-onset VAP, which occurs within the first 5 days of intubation, carries a better prognosis and is more likely to be caused by aspiration of antibiotic-sensitive bacteria colonizing the oropharynx than late-onset VAP (4–6). The latter, which occurs more than 5 days after intubation, is often caused by nosocomial pathogens that are often multidrug-resistant (MDR), and has a higher mortality and morbidity than early-onset disease. Exceptions to this include patients who have received antibiotics earlier, and those with prior hospitalization, or residence in a chronic care or nursing home facility who may have pathogens similar to those with late-onset VAP (6).

Several excellent, detailed review articles on risk factors for nosocomial pneumonia and VAP are available, and the updated 2003 Centers for Disease Control (CDC) and Hospital Infection Control Practices Advisory Committee (HICPAC) *Guidelines for Prevention of Healthcare-associated Pneumonia* have been published (1,2,5,7–11). This article provides an overview of risk factors for VAP in adults, highlights current, evidence-based prevention strategies, and addresses problems related to extrapolating data from clinical studies into guidelines for the clinical care and prevention (1,2,7).

EPIDEMIOLOGY

Nosocomial pneumonia accounts for 13–18% of all nosocomial infections. The reported incidence of VAP is variable and depends on the population being studied, the definition of VAP being utilized, and the diagnostic methods. Most studies have suggested that VAP develops in 8–28% of mechanically ventilated patients. In a recent retrospective cohort study in which data from 9080 patients who were mechanically ventilated for >24 hr were reviewed, VAP developed in 9.3% (12). The risk of VAP increases with the duration of mechanical ventilation. However, at least one study has suggested that the incremental risk remains constant at $\sim$1% per day, and an additional study has suggested that the daily incremental risk may actually decline after day 5 (13,14). However, as with the overall incidence, the daily risk of VAP depends on many factors, including the use of antibiotics in the intensive care unit (ICU) population being studied.

Crude mortality rates of up to 70% have been reported for VAP; however, in this critically ill population, the mortality attributable to pneumonia has been difficult to assess and mortality rates vary considerably with the

population (13). Most studies have suggested that mortality rates of ICU patients with VAP exceed that of those without pneumonia. Craven et al. (15) observed a mortality rate of 44% in patients with VAP compared to 19% in those without VAP, corresponding to a risk ratio of mortality of VAP patients of 2.3. However, in a recent case–control study in which 816 mechanically ventilated patients with VAP were matched to 2243 without VAP, no significant difference in mortality was observed (30.5% vs. 30.4%, respectively) (12). Interestingly, in this study, patients with VAP required on average 9.6 additional days of mechanical ventilation, 6.1 additional days in the ICU, and 11.5 additional days of hospitalization. Their inpatient billed charges were US $40,000 greater than those without VAP. These statistically significant outcomes suggest that although the crude mortality rate was not affected by VAP, patients with VAP had a more complicated clinical course. These results also reflect the significant burden of VAP on the healthcare system.

Over the past two decades, there has been a substantial change in the natural history of VAP (Fig. 1). The patient population admitted to hospitals in the United States today is older with more severe chronic diseases, prior hospitalizations, residence in chronic care facilities. More of these patients have had surgery, organ transplants, invasive devices, and prior antibiotics or immunosuppressive medications. These changes have resulted in increased rates of bacterial colonization and infections with MDR bacterial pathogens (16). Multidrug-resistant strains include a spectrum of Gram-negative bacilli, such as *Pseudomonas aeruginosa* and

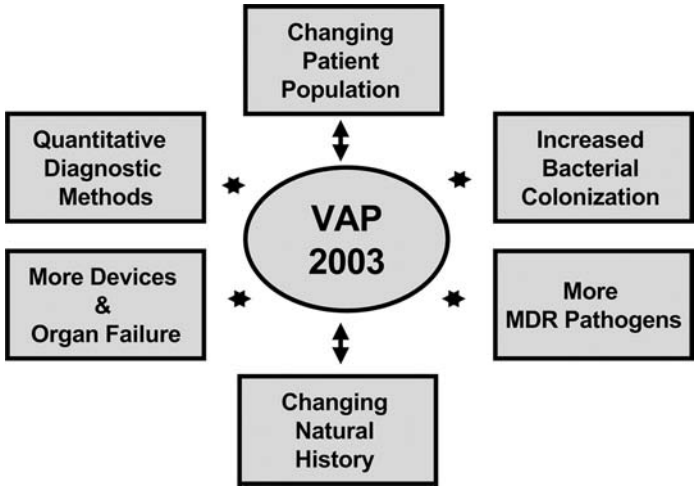

Figure 1 Factors related to the changing epidemiology of VAP in 2004.

Acinetobacter spp., and methicillin-resistant *Staphylococcus aureus* (MRSA). Recent reports of vancomycin-resistant *S. aureus* (VRSA) raise concern for the future (16–18).

PATHOGENESIS

A clear understanding of VAP pathogenesis is helpful in understanding potential risk factors and strategies for prevention. Risk factors may vary by patients' population and the pathogenic route of infection. Most bacteria causing VAP enter the lower respiratory tract from the oropharynx; bacteremia and translocation of bacteria are less important routes of infection (Figs. 2 and 3).

For each patient, there is usually a combination of known risk factors that increase oropharyngeal colonization and the possibility of aspiration. Bacterial adherence to oropharyngeal epithelial cells is a prerequisite for host colonization and is related to a patient's severity of disease. In one study, 16% of moderately ill patients compared to 57% of critically ill subjects were colonized with Gram-negative bacilli, and rates of pneumonia were increased six-fold in colonized patients (19).

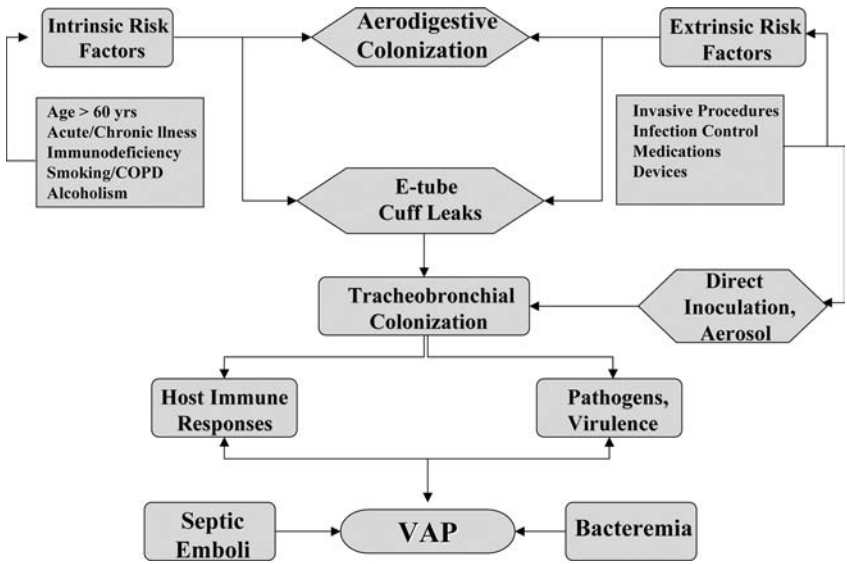

Figure 2 Intrinsic and extrinsic risk factors and their relation to the pathogenesis of VAP. Modified from Ref. 8. COPD = chronic obstructive lung disease and E-tube = endotracheal tube.

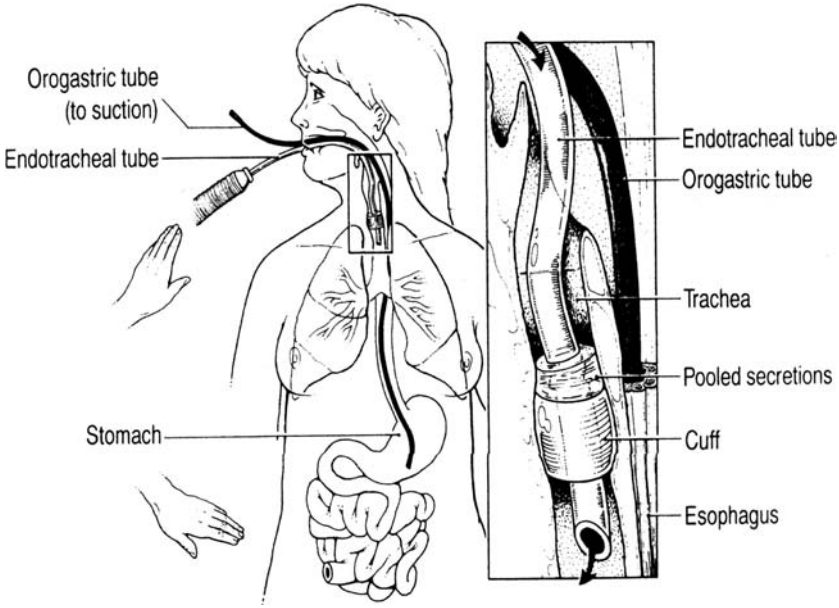

Figure 3 Schematic of an intubated patient with nasogastric tube. Colonization of the trachea usually results from leakage of contaminated subglottic secretions around the cuff of the endotracheal tube into the trachea. (Source: Ref. 9)

Although controversial, sinusitis and the gastrointestinal tract are other potential reservoirs for bacterial pathogens entering the lower respiratory tract (4,5,8,20–24).

Key points in pathogenesis of VAP include host risk factors, use of invasive devices, specific microbial colonization, and the pulmonary host defenses (4,5,15,21–23,25–33). The use of invasive devices, such as endotracheal and nasogastric tubes, increases bacterial access to the lower respiratory tract (Fig. 3) (27,28). Local trauma and inflammation from the endotracheal tube and the leakage of contaminated secretions around the cuff into the upper trachea serve as a major source of tracheal colonization, tracheobronchitis, and VAP (19,34,35). In addition, biofilm in the endotracheal tube, encased with bacteria, may be embolized into the alveoli after suctioning or bronchoscopy (36). The development of VAP usually requires either the entry of a large number of organisms into the lower airway or a smaller number of more virulent organisms that then overcome the multiple mechanical host defenses (ciliated epithelium, mucus), humoral components (antibody and complement), and cellular defenses (polymorphonuclear leukocytes, macrophages lymphocytes, and their respective cytokines) (9,10).

ETIOLOGIC AGENTS

Risk factors for VAP and strategies for prevention are also often related to the etiologic agent, method of diagnosis, and time of onset. Ventilator-assisted pneumonia may be caused by multiple organisms, especially if the diagnosis is made clinically, without the use of quantitative microbiology (2,5,7,8,37,38).

Early VAP is often caused by *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Moraxella catarrhalis,* if the patient has not received recent antimicrobial therapy or had been previously hospitalized (4–6,39). By comparison, late-onset VAP is often caused by more MDR strains of aerobic Gram-negative bacilli (*P. aeruginosa*, ESBL *Klebsiella pneumoniae,* or *Acinetobacter* spp.) and *MRSA.* Anaerobic bacteria are not important as a cause of VAP. *Legionella pneumophila* occurs episodically, usually in hospitals with colonized water supplies (1,9,40).

All bacteria are not created equal, even if they are in the same genus and species. Some bacteria, such as *S. pneumoniae* (pneumococci), *K. pneumoniae*, and *S. aureus*, are more virulent because of their specific polysaccharide capsules that impair phagocytosis and killing (5,9). Others may rely on adherence factors to host cells to enhance colonization or may contain exotoxins that cause damage to lung tissue and pulmonary host defenses. Recent data, based on sequencing of bacterial genes, suggest that there are many new virulence factors for MRSA and indicate that certain exotoxin-producing strains of *P. aeruginosa* are more virulent and increase patient mortality (41,42).

DIAGNOSIS OF VAP

Establishing the diagnosis of VAP requires discriminating between tracheal colonization or tracheobronchitis from leakage of infected secretions around the endotracheal tube and infection involving lung parenchyma. Ventilator-assisted pneumonia should be suspected with clinical symptoms and signs of lower respiratory tract infection. These include elevated or occasionally low temperature, purulent sputum with respiratory pathogens on smear or culture, an abnormally high or low leukocyte count, impaired or reduced oxygenation, and a new infiltrate on chest X-ray. However, sputum culture, although sensitive, lacks specificity when compared to quantitative methods of sputum analysis.

Quantitative methods of diagnosing VAP have also increased and improved its diagnostic specificity (Fig. 1) (2,5,43–45). These include the use of bronchoscopy with bronchoalveolar lavage (BAL) and/or protected specimen brush (PSB) samples, blind BAL/PSB, or quantitative endotracheal aspirates (QEA) (5). In one randomized clinical trial in France, decreased incidence of polymicrobial VAP and resultant mortality were observed

in patients diagnosed by bronchoscopy with bronchoalveolar lavage or protected specimen brushes compared to those managed by a clinical diagnosis and routine endotracheal aspirates (43). However, to date, the widespread use of quantitative techniques for the diagnosis of VAP has been limited.

RISK FACTORS AND PROPHYLAXIS

Several authors have examined risk factors for VAP, and a summary of independent risk factors from the literature was published in a recent state-of-the-art review by Chastre and Fagon (Table 1) (5,8,27,29). Analysis of these risk factors is complex, and results may change with time and patient population, method of diagnosis, duration of exposure, and type of microbial colonization (Fig. 1).

In contrast to the term ''prevention,'' we prefer prophylaxis with its connotation of active intervention. We suggest forming a multidisciplinary

Table 1 Independent Risk Factors for Ventilator-Associated Pneumonia Identified by Multivariate Analysis from Selected Studies[a]

Host factors	Intervention factors	Other factors
Serum albumin, $<2.2\,g/dL$	H^2 blockers $\pm$ antacids[a]	Season: Fall, winter
Age >60 years	Paralytic agents, continuous intravenous sedation	
ARDS	>4 units of blood products	
COPD, pulmonary disease	Intracranial pressure monitoring	
Coma or impaired consciousness	MV >2D	
Burns, trauma	Positive end-expiratory pressure	
Organ failure	Frequent ventilator circuit changes	
Severity of illness	Reintubation	
Large-volume gastric aspiration	Nasogastric tube	
Gastric colonization	Supine head position	
Upper respiratory tract colonization	Transport out of the ICU	
Sinusitis	Prior antibiotic or no antibiotic therapy	

[a]Definition of abbreviations: ARDS = acute respiratory distress syndrome; COPD = chronic obstructive pulmonary disease; ICU = intensive care unit; MV = mechanical ventilation.
Source: Ref. 5.

"team" comprising critical care and infectious disease physicians, nurses, respiratory therapists, and administrators to evaluate and implement hospital-specific prophylaxis (Fig. 4). In general, we have highlighted strategies for prophylaxis of VAP that are practical, cost effective, and based on our current perspectives on pathogenesis and "modifiable" risk factors (Tables 2 and 3) (also see the chapter by Bontent Weinstein). Major targets include reducing the duration of intubation, minimizing the use of all invasive devices, implementing infection control policies, and developing antibiotic reduction strategies (2,12–14).

Infection Control

Effective targeted surveillance for high-risk patients coupled with staff education and use of proper infection control practices are the cornerstones for prevention of nosocomial pneumonia (40,46,47). Hospitals with effective surveillance and infection control programs have rates of pneumonia

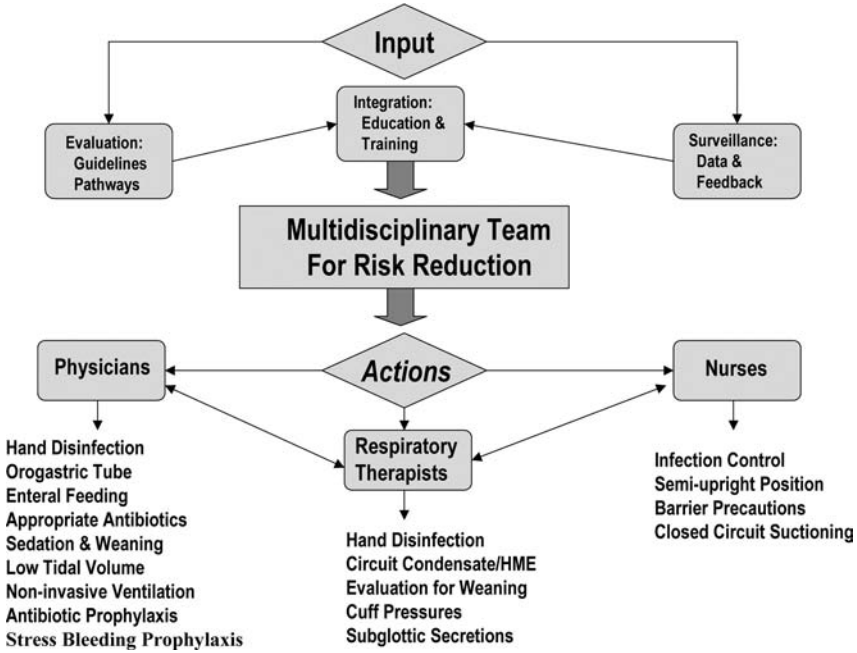

Figure 4 Prophylaxis requires a multidisciplinary team to evaluate input data that can be translated into actions for physicians, nurses, and respiratory therapists. (Modified from Ref. 8.) CASS = continuous aspiration of subglottic secretions, HME = heat-moisture exchanger.

Table 2 Selected Risks Factors and Prophylaxis for Ventilator-Associated Pneumonia (VAP)

Risk factor	Preventive measure	CDC/ HICPAC (NP)[a]	Kollef (VAP)[b]
Age	Primary prevention; healthcare maintenance	NS	NS
Underlying disease	Ambulation; incentive spirometry post surgery	IB	NS
	Influenza, pneumococcal vaccination	IA	D
Immunosuppression	Minimize duration of neutropenia ± GCSF	NR	D
Environmental	Awareness of seasonal pathogens (Influenza, RSV)	NS	NS
Depressed consciousness	Cautious use of CNS depressants	NS	NS
	Position patient upright at 30–45°	II	B
Oropharyngeal colonization	Chlorhexidine gluconate (0.12%) oral rinse (cardiac surgery)	II	B
	Oral hygiene program—cleaning	II	
Cross-infection	Educate and train personnel	IB	NS
	Cleaning and steam sterilization of equipment	IA	
	Appropriate hand washing/use of gloves and gowns	IA/IB	B
	Feedback of surveillance data to staff	IB	NS
Enteral feeding	Verify tube placement	IB	U
	Assess intestinal motility and adjust feeding accordingly	IB	
	Preferential use of small-bore tubes	NR	D
	Acidification of gastric feedings	NR	U
	Intermittent vs. continuous enteral feedings	NR	NS
Mechanical ventilation	Noninvasive ventilation if possible	IB	
	Preferential use of orotracheal intubation	IB	
	Continuous aspiration subglottic secretions	II	
	Avoid repeat endotracheal intubation	II	

(*Continued*)

Table 2 Selected Risks Factors and Prophylaxis for Ventilator-Associated Pneumonia (VAP) (*Continued*)

Risk factor	Preventive measure	CDC/ HICPAC (NP)[a]	Kollef (VAP)[b]
Avoid aspiration	Remove tracheal and gastric devices as soon as indicated	IB	B
	Position patient upright at 30–45°	II	
Antibiotic administration	Antibiotic prophylaxis for NP in high-risk patients	NR	U
	Judicious administration of appropriate antibiotics	NS	C
	Rotation of empiric antibiotic regimens	NR	C

Prevention recommendations from the Center for Disease Control and the Hospital Infection Control Practices Advisory Committee (CDC/HICPAC) and of Kollef for VAP (1,7).
Adapted from D. E. Craven, K. A. Steger, O. C. Tablan. Preventing Nosocomial Pneumonia: Guidelines for Health Care Workers. Taken with permission from Saunder's Infection Control Reference Service. (Abrutyn E, Goldmann DA, Sheckler WE, eds. 2nd ed. Philadelphia, PA: WB Saunders, 2000.)
[a]CDC/HICPAC Category IA, strongly recommended for all hospitals and strongly supported by well-designated experimental or epidemiologic studies; Category IB, strongly recommended for all hospitals and viewed as effective by experts in the field and a consensus of HICPAC based on strong rationale and suggestive evidence, even though definitive scientific studies may not have been done; Category II, suggested for implementation in many hospitals. Recommendations may be supported by suggestive clinical or epidemiologic studies. A strong theoretical rationale or definitive studies applicable to some but not all hospitals. No recommendation (NR) unresolved issue is defined as "practices for which insufficient data or a lack of consensus regarding efficacy exists"; NS, not specified by CDC/HICPAC guideline.
[b]Kollef grading criteria: A, supported by at least two randomized, controlled investigations; B, supported by at least one randomized, controlled investigation; C, supported by nonrandomized, concurrent-cohort investigations, historical-cohort investigations, or case series; D, supported by randomized, controlled investigations of other nosocomial infection; U, undetermined or not yet studied in clinical investigations.
COPD: chronic obstructive pulmonary disease; G-CSF: granulocyte-colony stimulating factor; RSV: respiratory syncytial virus; CNS: central nervous system; MDR: multidrug resistant.

that are 20% lower than those without such programs. Monitoring of MDR pathogens and device-related infections should be carried out hospital-wide.

Cross-infection is an important source of all pathogens including nosocomial MDR strains of Gram-negative bacilli and *S. aureus* (48,49). Hands or gloves of hospital personnel are potential reservoirs for spread, and clinical data have indicated that rates of all nosocomial infection may be significantly reduced by the use of alcohol-based hand disinfection (50). Gloves should be changed between patients, as they may become colonized.

Table 3 Selected Device-Related and Pharmacologic Risks Factors and Prophylaxis Measures for Nosocomial Pneumonia (NP) and Ventilator-Associated Pneumonia (VAP)

Risk factor	Preventative measure	CDC/ HICPAC	Kollef category (VAP)
Device-related			
Invasive devices	Appropriate cleaning and sterilization	IB	NS
	Expeditious removal	IB	NS
Spirometer/O_2 sensor	Clean, sterilize/disinfect between patients	IA	NS
Resuscitation bag	Clean, sterilize/disinfect between patients	IA	NS
Nasogastric tube	Refer to enteral feeding (above)	IA	
	Remove tube as soon as feasible	IA	C
Endotracheal intubation	Continuous aspiration of subglottic secretions	NR[a]	A
	Adequate cuff pressure at all times	IB	C
	Oral intubation	NR	D
Ventilator circuits	Do not change more often than every 48 hr	IA	A
	Use heat-moisture exchanger (HME)	NR	A
	Scheduled drainage condensate away from patients	IA	C
In-line nebulizer	Disinfect between treatments	IB	NS
	Sterilize between patients	IB	NS
Suction catheter	Aseptic technique	IA	NS
	Sterile single-use catheter for open system	II	NS
	Closed circuit tracheal suction catheter	NR	NS
Tracheostomy care	Use aseptic technique when changing trach tubes	IB	NS
Immobility	Lateral rotational bed	NR	NS
	Semirecumbent positioning	NS	B
Cross-infection	Hand washing; glove and gown	IA	B
	Infection control program	IA	C
Pharmacological			
Orogastric colonization	Selective digestive decontamination not recommended	NR	A

(*Continued*)

Table 3 Selected Device-Related and Pharmacologic Risks Factors and Prophylaxis Measures for Nosocomial Pneumonia (NP) and Ventilator-Associated Pneumonia (VAP) (*Continued*)

Risk factor	Preventative measure	CDC/ HICPAC	Kollef category (VAP)
Stress bleeding prophylaxis	Use nonalkalinizing cytoprotective agents	II	B
Bacterial resistance	Antibiotic class rotation	NS	C

[a]Prevention recommendations from the Center for Disease Control and the Hospital Infection Control Practices Advisory Committee (CDC/HICPAC) and of Kollef for VAP (1,7).
See Table 2 for definitions and source for this table.

Host Factors

Some of the intrinsic and extrinsic host risk factors (Fig. 1) are difficult to modify acutely and therefore should be considered as part of a long-term strategy of prevention (12–14). Many of these, such as age or chronic disease, are not preventable; however, every effort should be made to prevent pneumonia before it occurs. Prevention of the initial episode of pneumonia or recurrent pneumonia includes routine healthcare maintenance, such as exercise, weight reduction, and vaccinations with influenza and pneumococcal vaccines (51,52). Smoking cessation should be encouraged in all patients who have had VAP, as they are at a higher risk of developing a subsequent pneumonia.

Postoperative patients, notably those who have undergone thoracic, abdominal, head, or neck surgery, require special attention to prevent VAP (53). Postoperative atelectasis, retained secretions, and pain may further increase the risk of VAP by impairing the host's ability to clear bacteria and secretions effectively. Preventive measures include maintaining semiupright patient position to reduce aspiration, limited sedation, frequent coughing, chest physiotherapy, and early ambulation to prevent atelectasis and retained secretions. Recent data suggest that maintaining better glucose control may also reduce the risk of nosocomial infection and improve outcomes in surgical ICU patients (54).

Clinical studies have identified the supine body positioning as a risk factor for VAP, and additional studies using radioactively labeled gastric contents have demonstrated that reflux can be reduced and subsequent aspiration avoided by positioning mechanically ventilated patients in a semirecumbent position (7,55–57). Drakulovic et al. (56) conducted a randomized controlled study of body position in mechanically ventilated patients and demonstrated that a semirecumbent position was associated with a

significantly reduced incidence of VAP compared to a supine position. This benefit was greatest in those receiving enteral nutrition.

Device-Associated Risk Factors (Table 3)

Several devices have been associated with a greater risk of VAP. Hence, proper use and care of these devices coupled with the shortest duration of use should be emphasized.

Endotracheal Tube

Endotracheal intubation facilitates the entry of bacteria into the trachea, decreases clearance of bacteria and secretions from the lower airway, and acts as a surface on which bacteria may collect and form a protective biofilm (36). Leakage around the endotracheal tube cuff enables pooled secretions and bacteria to enter the trachea, increasing tracheal colonization and leading to VAP. This may be prevented by maintaining appropriate cuff pressures and by the continuous aspiration of subglottic secretions (CASS). An endotracheal tube that incorporates a separate dorsal lumen ending in the subglottic area and opens above the cuff allowing continuous aspiration of secretions is available in the United States. Valles et al. (58) reported that CASS significantly reduced the incidence of VAP from 39.6 episodes/1000 days in controls to 19.6 episodes/1000 ventilator-days in the CASS group. Efficacy was most pronounced during the first 2 weeks after intubation, and in 85% of infections the causative organism was previously isolated in cultures of subglottic secretions, indicating their importance in the pathogenesis of VAP.

Colonization of the surface of the endotracheal tube may be an important risk factor for VAP (36,59). Endotracheal tubes become rapidly colonized with nosocomial pathogens that are encased in a biofilm, which protects the bacteria from both antibiotics and host defenses (36,59). These aggregates of bacteria may become dislodged from the endotracheal tube by ventilation flow, tracheal suctioning, or bronchoscopy, and embolize to the lower respiratory tract. Over 95% of the endotracheal tubes examined by scanning electron microscopy in one study had partial bacterial colonization, and 84% were completely covered by bacteria encased in a biofilm or glucocalyx (59). Research is in progress to alter the composition of the endotracheal tube to be more resistant to colonization and biofilm formation.

The removal of the endotracheal tube and good weaning protocols that help to prevent reintubation are important for reducing VAP. Because reintubation has also been shown to be a risk factor for VAP, early extubation to minimize duration of ventilation must be weighed against the risk of reintubation (60). Clearly, all eligible patients should be evaluated for noninvasive ventilation as it has been associated with significant reductions

in pneumonia and improved outcomes in terms of pneumonia, reduced antibiotic use, and decreased costs and ICU stay (61).

Nasal Intubation and Sinusitis

Nasal intubation was a risk factor for both nosocomial sinusitis and VAP in some studies (20,62). In one study, maxillary sinusitis, diagnosed by baseline and serial computer axial tomographic scan and needle aspiration, was linked to the placement and duration of nasotracheal and nasogastric intubation (20). Ventilator-associated pneumonia occurred significantly more frequently in the patients with maxillary sinusitis, and the organisms isolated from maxillary sinus aspirates, *P. aeruginosa, Acinetobacter* spp., and *S. aureus*, correlated well with those causing VAP. Placement of oral-tracheal and orogastric tubes significantly decreased the incidence of bacterial maxillary sinusitis. Although demonstrating a causal link between sinusitis and VAP is difficult, we suggest the use of oral rather than nasal tubes when possible.

Bronchoscopy

Bronchoscopy is frequently performed in mechanically ventilated patients for diagnostic or therapeutic purposes. The introduction of a large volume of BAL fluid may decrease bacterial clearance in the alveolar spaces (45,63). Care of these is important, as they have been demonstrated to be a source of nosocomial respiratory tract pathogens, such as *P. aeruginosa*, *Mycobacterium tuberculosis,* and other pathogens (64). Bronchoscopy may also predispose to VAP by dislodging biofilm-encased bacteria from the endotracheal tube into the lower airway. Although the data are not conclusive and further prospective studies are needed, it seems prudent to reserve the use of bronchoscopy for absolute indications in mechanically ventilated patients (64).

Ventilator Tubing Condensate and Heat-Moisture Exchangers

Mechanical ventilators may generate condensate, which may be contaminated by the patient's oropharyngeal flora and can be flushed into the lower respiratory tract when the ventilator tubing is manipulated (65). Hence, tubing condensate should be drained regularly, and healthcare workers should be instructed to drain the condensate away from the patient. Other measures that minimize the generation of condensate within ventilator circuits are heated ventilator tubing and heat-moisture exchangers (HME) (1,9,66). Studies confirm that there is no benefit in routinely changing ventilator circuits or HMEs more than every 72 hr because they become rapidly colonized (1,67–71).

Lowering of tidal volume in patients with ARDS or acute lung injury and the daily interruption of sedative infusions to awaken patients have also been shown to be effective in reducing VAP (72). A protocol-driven daily

screening of the respiratory function of mechanically ventilated adults may also reduce the duration of mechanical ventilation (73).

Nebulizers and Miscellaneous Respiratory Therapy Equipment

Appropriate cleaning, sterilization, or disinfection of all reusable respiratory-therapy equipment is essential to reduce the nosocomial transmission of infectious agents. Small volume "in-line" medication nebulizers inserted into the mechanical ventilator circuit are readily colonized from contaminated condensate, and allow bacterial aerosols direct access to the lower airway, bypassing the normal host defenses (46,74,75). Both handheld and "in-line" nebulizers should be sterilized between patients and their use limited to clear indications. Resuscitation bags, spirometers, temperature sensors, and oxygen analyzers, if not properly sterilized or if transferred between patients, are also potential sources of cross-infection (1,46). Tracheal suction catheters may inoculate bacteria directly into the respiratory tract and aseptic technique is critical during suctioning. A closed, multiuse suction system may be more convenient than a single-use catheter and may cause less hypoxia for the patient; however, it has not been shown to decrease the risk of VAP (1,76).

Enteral Feeding

Nasogastric tubes may increase nasopharyngeal colonization, cause reflux of gastric contents, and act as a conduit for bacteria to migrate from the oropharynx (20,25,27,34). The administration of enteral feedings may also predispose to VAP by elevating gastric pH, and increasing gastric colonization, distention, reflux, and aspiration (1,57,77–84). In one study, oropharyngeal reflux was described in approximately 70% of patients receiving tube feedings—40% of whom had evidence of pulmonary aspiration (84). However, when compared with parenteral nutrition, enteral feeding had a lower risk of VAP and early feeding may help maintain the gastrointestinal epithelial barrier and reduce bacterial translocation (57,85). In a recent meta-analysis of enteral nutrition with immune-enhancing feedings in critically ill patients, there was no effect on mortality. But significant reductions were noted in infection rates, ventilator days, and hospital length of stay (72,86).

Maintaining patients in a semirecumbent vs. supine position during enteral feeding significantly reduces the incidence of VAP (56). Sterile water should be used both for preparation of enteral feeding solutions and flushing the tube, as tap water may be a potential source of nosocomial enteric Gram-negative bacilli and Legionella (78). Measures that may decrease the risk of reflux include monitoring residual volume in the stomach and removal of gastric residual if the volume is large or bowel sounds are absent (1,33,83,84,87). Acidification of enteral feeds may reduce gastric colonization in ill, ventilated patients, but has not been shown to decrease the

incidence of VAP (88). In a recent randomized trial, metoclopromide delayed the development of nosocomial pneumonia but did not decrease mortality in critically ill patients receiving enteral feedings (89).

Medications

There are several different medications that may increase the patient's risk of pneumonia and the duration of mechanical ventilation.

Sedatives and Neuromuscular Blockers

Sedatives may increase the risk of aspiration, decrease cough and clearance of secretions from the lower respiratory tract, and delay weaning from mechanical ventilation. This effect is most profound in elderly patients or those with impaired swallowing. Prevention strategies should include the judicious use of sedation and the proper positioning of patients in a semirecumbent position to minimize the risk of aspiration. In mechanically ventilated patients, the choice of sedatives may influence clinical outcome. Barrientos-Vega et al. (90) reported that propofol decreased weaning time and was economically more favorable than midazolam. Although more studies are required, it appears that careful use of sedatives may decrease the incidence of NP and VAP.

Limited data are available on neuromuscular blockers as a risk factor for VAP. In a retrospective review of patients with severe head injuries, the occurrence of pneumonia was significantly higher (29% vs. 15%) in those pharmacologically paralyzed on admission compared to the nonparalyzed group. The implications from this study are limited by its design and the absence of uniform diagnostic criteria for pneumonia. Prekates and coworkers (91) studied risk factors for VAP in postoperative trauma patients. Independent predictors of VAP, after stepwise logistic regression, were flail chest ($p < 0.001$) and the use of neuromuscular blockers ($p < 0.001$). Although it is difficult to make specific recommendations regarding the use of neuromuscular blocking agent, these agents should be used cautiously after sedation, and analgesia has been maximized in accordance with the practice guidelines published by the Society of Critical Care Medicine (92).

Stress Bleeding Prophylaxis

Antacids and histamine type 2 (H2) blockers are administered for prevention of stress bleeding in critically ill patients. They act by increasing gastric pH, which may result in the bacterial colonization of the stomach. Whether these agents predispose to NP is controversial, but several studies have reported significantly lower rates of clinically diagnosed VAP in patients prophylaxed with sucralfate, a nonalkylinizing cytoprotective agent (4,23,24,93,94). In the largest study to date, sucralfate had the greatest effect on reducing

late-onset VAP with no difference noted for early-onset VAP (4,95). The difference in the observed outcomes among groups prophylaxed with sucralfate, antacids, and H2 blockers may be related to the gastric pH, reflux, level of bacterial overgrowth, or the bactericidal activity of sucralfate (4,22,23,93,96). Several investigators have reported no superiority of sucralfate in different patient populations, and some data suggest that it may be less effective in preventing clinically significant bleeding than H2 blockers and must be given enterally (21,96,97). As the risk of stress ulcers appears to have decreased substantially, we recommend that stress bleeding prophylaxis be limited to high-risk, ventilated patients, and when indicated either nonalkalinizing agents or H2 blockers should be used.

Antibiotic Dilemmas

The prophylactic use of antibiotics to prevent VAP in susceptible patients is not recommended, as antibiotic exposure is a significant risk factor for colonization and infection with nosocomial, MDR pathogens (29,33,39,98). However, intravenous cefuroxime reduced early-onset VAP in coma patients, but these data may not be applicable to other patients (99).

The judicious use of appropriate antibiotics, especially in the ICU, may reduce patient colonization and subsequent infections with MDR pathogens (43,100). Recent data suggest that a spectrum of antibiotics have been associated with the emergence of MDR pathogens (6,101). Although antibiotic control strategies, such as restriction with approval and practice guidelines, may be efficacious in preventing nosocomial infections, they are often contentious and may result in delay of therapy and overall poorer outcomes (102). However, with the increasing prevalence of MDR nosocomial infections, more stringent and widespread control of antibiotic misuse may become necessary (53). We advocate broad-spectrum coverage for suspected VAP and streamlining of therapy based on the patient's clinical response and organisms isolated. In addition, data from a randomized study of the duration of therapy for VAP have suggested that shorter courses of antibiotics may be effective (8 vs. 14 days).

Changing or rotating the standard groups of antibiotics used for empiric therapy has also been efficacious in limited studies (103,104). In one study, the change of empiric therapy regimens for suspected Gram-negative bacterial infections in postoperative ICU patients ("crop rotation") reduced the incidence of VAP significantly (103). Further studies are needed to confirm these results, evaluate the effectiveness over longer time periods, and specify the exact terms, e.g., frequency of regimen change, before widespread use of this practice can be recommended (104).

Combinations of local and systemic antibiotics for selective decontamination of the digestive tract (SDD) have been advocated to reduce or prevent VAP and other nosocomial infections (105,106). A recent meta-analysis showed a significant reduction of respiratory tract infections [odds

ratio (OR) = 0.35; 95% confidence interval (95% CI) 0.29–0.41] and mortality (OR = 0.80; 95% CI 0.69–0.93) with the use of combined topically and systemically administered antibiotic prophylaxis for adult ICU patients. When topical antibiotics alone were used, the incidence of respiratory infections was also reduced (OR = 0.56; 95% CI 0.46–0.68); but little influence on mortality was noted (OR = 1.01; 95% CI 0.84–1.22) (107). These promising results have to be weighed against the considerable risk of long-term selection of drug-resistant organisms (106,108). For this reason, selective decontamination is not recommended and should be reserved for selected patients or for the eradication of a virulent multidrug-resistant nosocomial pathogen (1,7).

RISK FACTORS ARE DYNAMIC

New intervention strategies have changed the natural history of VAP and its risk factors. For example, in the 1960s and 1970s, the use of respiratory therapy equipment with nebulizers was a major contributor to the incidence and risk for VAP because of Gram-negative bacilli (109). The subsequent widespread use of respiratory therapy equipment with humidifiers rather than nebulizers decreased the risk of contaminated bacterial aerosols and VAP (34). Likewise, the use of heat-moisture exchangers eliminates the risk of flushing contaminated condensate directly into the endotracheal tube (65,110). In addition, maintaining the patient in the semiupright position during enteric feeding decreases aerogastric colonization and VAP (56). Improved hand disinfection decreases colonization rates and the risk of nosocomial infections, such as pneumonia (50).

Defining risk factors for pneumonia is important for patient management. Risk factors may be used to stratify patients and to target strategies for managing and preventing VAP in selected patient populations (7,8). Recently, the clinical pulmonary infection score (CPIS), originally described by Pugin and modified by Singh et al. (100), was helpful in identifying patients with a low risk of pneumonia. When these patients were randomized to receive short course therapy with ciprofloxacin vs. standard combination, the results were sobering. The group randomized to ciprofloxacin monotherapy had significantly decreased antibiotic use, superinfections, complications, shorter ICU stays, and lower mortality. These data suggest that inappropriate, multidrug therapy used for longer periods has important consequences for the patient. In addition, the CPIS performed sequentially may be able to identify patients with poorer outcomes (111). Of the CPIS variables monitored, poor oxygenation appeared to be valuable for defining progression of disease and also as a marker for poorer outcomes from VAP.

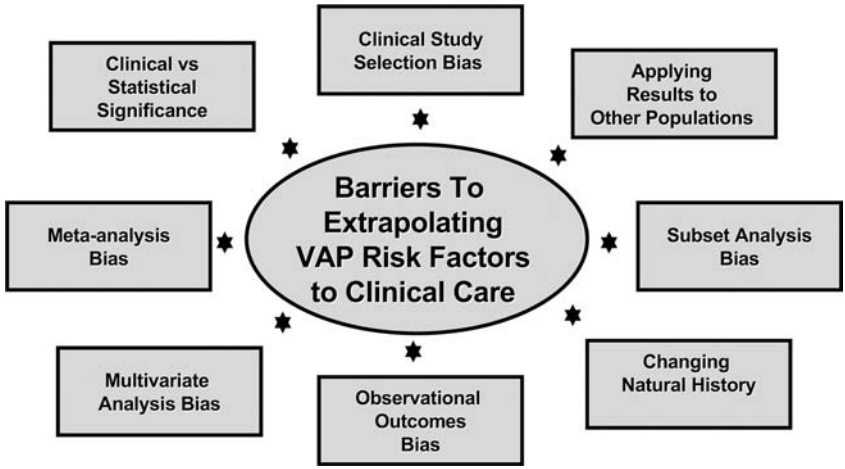

Figure 5 Some of the issues related to extrapolating clinical data into guidelines for preventing VAP.

Pitfall for Weighting Risk Factors

Weighting risk factors for VAP is complicated and becomes confusing by extrapolating data from different studies having varying study designs, patient populations, several definitions of VAP, methods used for statistical analysis, and various standards of care within ICUs (Fig. 5). These may lead to confusion over the level of importance of specific risk factors. For example, the use of selective decontamination of the digestive tract (SDD) or continuous aspiration of subglottic secretions alters the natural history of VAP and the relative importance of specific risk factors and the types of bacteria causing VAP.

An Approach to the "Gray Areas"

Although this review is focused on risk factors for VAP, many of the principles and problems defining risk factors are shared with other diseases. The difficulties of applying evidence collected in clinical trials to patient care have been recently voiced by others (112,113). ''What appears black and white in a clinical trial, may rapidly become grey in practice.'' Some of the clinical trials data are derived from studies that have flawed study design, focus on a specific at risk population, and often the trials are small and have a follow-up that is too short. These issues raise an important question: ''Can we extrapolate data from trials conducted in a highly selected subset of patients to a broader population of patients who do not meet the trial eligibility criteria?'' (113). In addition, standards of ICU care and other

variables, such as staffing, weaning protocols, and variations in respiratory care, are not measured in clinical trials of VAP.

Data suggest that risk factors for nosocomial infections and VAP may vary between medical and surgical patients. Trauma patients who are often young and healthy, with head injury or seizures may have specific risk factors that may require general and targeted interventions. Because each patient is a special situation in risk profile, we need better insight to be able to quantify and combine risk factors for VAP and mortality. The barriers are formidable.

Assessing clinical and evidence-based risk factors for VAP in adults in a changing patient population exposed to a spectrum of MDR bacteria with different virulence factors and changing host defenses will be difficult to analyze and synthesize into guidelines. With these limitations and the myriad of either confounding or unknown variables, it is not surprising that there is no consensus of opinion on many of the risk factors for VAP. Hence, we must focus on effective interventions that fit with our concepts of pathogenesis, and have a good risk and cost benefit ratio. Furthermore, there is a need to affirm uncertainty and gray areas, welcome new ideas and concepts, reach for the growing scientific opportunities, and heed the words of Dr. William Osler who declared at the beginning of the 20th century, "good clinical medicine (and prevention) will always blend the art of uncertainty with the science of probability."

SUMMARY

Despite an increased understanding of the pathogenesis of VAP and advances in diagnosis and treatment, the risk, cost, morbidity, and mortality of VAP remain unacceptably high. Realizing that the pathogenesis of VAP requires bacterial colonization, the subsequent entry of bacteria into the lower respiratory tree helps highlight the role of cross-infection and the importance of standard infection control procedures. Other simple, cost-effective interventions that have recently been shown to be useful in preventing VAP include positioning of patients in a semirecumbent position, appropriate use of enteral feeding, reducing antibiotic days, and limiting the duration when medical devices are in place.

We suggest that prophylaxis of all nosocomial infections in the ICU is best carried by a multidisciplinary management "team," which reviews the current guidelines, establishes pathways, and sets standards for short- and long-term prophylaxis. Team policies should be monitored, measured for impact, and replaced when necessary.

Finally, better research is needed to delineate the most effective and feasible strategies for prophylaxis of VAP. To date, progress in the battle against nosocomial infections has been compromised by denial, insufficient funding, inadequate investment in science, and randomized multicenter

studies to identify the best strategies for management and prevention. Although Sir William Osler warned healthcare providers over 100 years ago to "Remember how much you don't know," we would add that significant advances in our knowledge about risk factors and prophylaxis of VAP have occurred over the past 20 years that should be implemented now, and that more work is needed.

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7

Attributable Mortality and Mortality Predictors in Ventilator-Associated Pneumonia

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Ventilator-associated pneumonia (VAP) is reported to be the most common hospital-acquired infection among patients requiring mechanical ventilation. In contrast to other nosocomial infections, for which mortality is low, ranging from 1% to 4%, the mortality rate for VAP ranges from 24% to 50% and can reach more than 75% in some specific settings or when lung infection is caused by high-risk pathogens (1). Despite major improvement in the diagnosis, treatment, and prevention of VAP, the mortality rate has not declined in the last several decades. However, previous studies have not clearly demonstrated that pneumonia itself is actually responsible for the high mortality rate of these patients. Because the risk factors for VAP and death are directly related, the severity of the underlying disease can influence both events. Thus, it is difficult to determine whether such patients would have survived if VAP had not occurred. The concept of ''attributable mortality,'' defined as the percentage of deaths that would not have occurred in the absence of this infection, has been developed. Studies on the attributable mortality of VAP are difficult to compare not only because of the varied definitions of VAP based on different diagnostic criteria and

patient populations, but also because of the several methods employed to control for confounding factors; as a consequence, they provided conflicting results. Some authors failed to demonstrate an excess death rate, whereas others found that 25–50% of all deaths in patients with VAP were the direct result of pulmonary infection.

ATTRIBUTABLE MORTALITY

Crude ICU mortality rates of 24–76% have been reported for VAP at various institutions (Table 1) (2–15). ICU-ventilated patients with VAP appear to have a two- to 10-fold higher risk of death compared to patients without pneumonia. In 1974, fatality rates of 50% for ICU patients with pneumonia vs. 4% for those without pneumonia were reported (16). The results of several studies conducted between 1986 and 2003 have confirmed the following observation: despite variations among studies that partly

Table 1 Incidence and Crude Mortality Rates of VAP

First author	Year of publication	No. of patients	Incidence (%)	Diagnostic criteria	Mortality rate (%)
ICU Patients					
Salata	1987	51	41	Clinical-autopsy	76
Craven	1986	233	21	Clinical	55
Langer	1989	724	23	Clinical	44
Fagon	1989	567	9	PSB	71
Kerver	1987	39	67	Clinical	30
Driks	1987	130	18	Clinical	56
Torres	1990	322	24	Clinical-PSB	33
Baker	1996	514	5	PSB/BAL	24
Kollef	1993	277	16	Clinical	37
Fagon	1996	1118	28	PSB/BAL	53
Timsit	1996	387	15	PSB/BAL	57
Cook	1998	1014	18	Clinical-PSB/BAL	24
Tejada Artigas	2001	103	22	PSB	44
ARDS Patients					
Sutherland	1995	105	15	PSB/BAL	38
Delclaux	1997	30	60	PTC/BAL	63
Chastre	1998	56	55	PSB/BAL	78
Meduri	1998	94	43	PSB/BAL	52
Markowicz	2000	134	37	PSB/BAL	57

PSB, protected specimen brush; BAL, bronchoalveolar lavage; PTC, plugged telescoping catheter.

reflect the populations considered, overall mortality rates for patients with or without VAP were: 55% vs. 25% (5), 71% vs. 28% (3), 33% vs. 19% (4), 38% vs. 9% (11), 44% vs. 19% (13), and 50% vs. 34% (17), respectively. These rates correspond to increased risk ratios of mortality of VAP patients of 2.2, 2.5, 1.7, 4.4, 2.3, and 1.5, respectively.

In addition, nosocomial pneumonia has been recognized in several studies as an important prognostic factor for different groups of critically ill patients, treated with mechanical ventilation or not, including cardiac surgery patients (18,19) or those with acute lung injury (20), and immunocompromised patients, e.g., those with acute leukemia (21), lung transplantation (22), or bone-marrow transplantation (23). In contrast, in patients with extremely severe medical conditions, like those surviving cardiac arrest (24), or in young subjects with no underlying disease, such as those admitted after trauma (10,25,26), nosocomial pneumonia does not seem to significantly affect prognosis.

Despite these difficulties and limitations, several arguments support the notion that the presence of VAP is an important determinant of the poor prognosis of patients treated with MV.

Multivariate Analyses

Multivariate analyses have been conducted to evaluate the independent role played by VAP in inducing death in overall populations of ICU patients, in patients treated with mechanical ventilation, and/or in subgroups of patients admitted to the ICU for specific diseases (Table 2). Craven et al. (5) found that VAP was associated with mortality in univariate analysis but was not among the seven variables identified by multivariate analysis. Similarly, Kollef's multivariate analysis of 227 ventilated patients failed to identify VAP as a variable independently associated with mortality (11). In contrast, the results of the EPIC study demonstrated that ICU-acquired pneumonia increased the risk of ICU death with an odds ratio of 1.91 (95% CI, 1.6–2.3), independent of clinical sepsis and bloodstream infections, as evidenced by stepwise logistic regression analysis (27). Fagon et al. (14) studied 1978 ICU patients, 1118 of whom were treated with mechanical ventilation, and demonstrated that in addition to the severity of the underlying medical condition measured by the Acute Physiology and Chronic Health Evaluation (APACHE II) score, the number of dysfunctional organs or infection (ODIN) score, the criteria of McCabe and Jackson (stratifying the underlying disease as fatal, ultimately fatal, or not fatal), and nosocomial bacteremia, nosocomial pneumonia independently contributed to ICU patient mortality and to ventilated patient mortality. By using the Cox model as the statistical method, Timsit et al. (12) demonstrated that VAP, clinically diagnosed and bacteriologically confirmed, was independently associated with increased mortality (relative risk, 2.1; $p < 0.0001$

Table 2 Results of Multivariate Analysis to Identify Significant Variables Independently Associated with Death in Mechanically Ventilated Patients

First Author	Year of publication	No. of Patients	Variables selected by the model	Adjusted odds ratio	*p* Value
Craven	1986	233	Creatinine >1.5 mg/dL	3.3	0.0002
			Admitted with pneumonia	4.9	0.0002
			No nebulized bronchodilatator	4.2	0.0004
			Duration of mechanical ventilation	1.2	0.005
			No abdominal surgery	3.2	0.03
			Transferred from ward	2.9	0.003
			Coma of admission	2.6	0.009
Kollef	1993	227	OSFI ≥3	16.1	<0.001
			Lifestyle score ≥2	3.2	0.012
			Head not elevated	3.1	0.016
Kollef	1996	314	OSFI ≥3	3.4	<0.001
			Nonsurgical diagnosis	2.1	0.002
			Premorbid lifestyle score ≥2	1.8	0.015
			VAP because of high-risk pathogens	3.4	0.025
			Received antiacids or H2 blockers	1.7	0.034
Vincent	1995	1038	Age	1.7	<0.05
			Organ failure on admission	1.68	<0.05
			APACHE II score	15.55	<0.05
			Prolonged ICU stay	2.52	<0.05
			Pneumonia	1.91	<0.05
			Clinical sepsis	3.5	<0.05
			Bloodstream infection	1.73	<0.05
			Carcinoma	1.48	<0.05
Fagon	1996	1118	APACHE II score	1.06	<0.001
			ODIN score	1.36	<0.001
			Nosocomial bacteremia	2.12	<0.001

(*Continued*)

Table 2 Results of Multivariate Analysis to Identify Significant Variables Independently Associated with Death in Mechanically Ventilated Patients (*Continued*)

First Author	Year of publication	No. of Patients	Variables selected by the model	Adjusted odds ratio	*p* Value
			Fatal underlying disease	1.60	<0.001
			Nosocomial pneumonia	1.51	0.007
Timsit	1996	387	APACHE II score	NG	<0.0001
			MacCabe classification	NG	<0.0001
			Shock on admission	NG	0.0001
			Sedatives	NG	0.02
			Enteral nutrition	NG	0.04
			VAP	1.8	0.007

APACHE, acute physiologic and chronic health evaluation; NG, not given; ODIN, number of dysfunctional organs or infection; OSFI, organ system failure index

for clinical diagnosis; relative risk 1.7; $p = 0.01$ for bacteriologic diagnosis). These data have been confirmed by a study conducted by Kollef et al. (19), evaluating the effect of late-onset VAP in determining patient mortality in 314 patients. They identified VAP caused by high-risk pathogens (*Pseudomonas aeruginosa*, *Acinetobacter* spp., *Stenotrophomonas maltophilia*) as independently associated with ICU patient mortality, in addition to the severity of underlying medical condition, a nonsurgical diagnosis, and treatment with antacids or H2 blockers. All these studies only partially elucidated the complex relationship between severity of underlying disease, occurrence of nosocomial pneumonia, and death.

Analysis of Cause-of-Death Data

These are only a few reports on mortality as a result of nosocomial pneumonia in which autopsy material from patients who died during their hospital stay was examined. In a study of 200 consecutive hospital deaths, Gross et al. (28) concluded that nosocomial pneumonia contributed to 60% of the fatal infections and was the leading cause of death from hospital-acquired infection. Matching half of these patients who died in the hospital with controls of similar age, gender, department, primary discharge diagnosis, and severity of primary diagnosis, the same authors found that lower respiratory tract nosocomial infection occurred in 18% of the patients in the case group and in only 4% of the those in the control group ($p < 0.005$). Among the subjects who did not have a terminal condition on admission, nosocomial infections

were four times more common among those who died than among those who survived, and nosocomial pneumonia was present in most patients who died (29). These data confirm the results of the study by White (30); by using death-certificate data as the source of information on nosocomial infections as the contributing cause of death, this author analyzed 2,171,196 deaths, of which 9,415 had a nosocomial infection listed as a contributing cause (3.83 per 100,000 person-years). Pneumonia represented 55.1% of all nosocomial infections causing or contributing to death (vs. only 27.7% for surgical wound infection) (30).

Case–Control Studies

Another methodological approach is the use of case–control studies to evaluate mortality attributable to nosocomial pneumonia, i.e., the difference between the mortality rates of study patients (patients with pneumonia) and control patients (those without pneumonia). This method is based on the quality of the matching process, thereby controlling for other confounding factors. Bregeon et al. (31) conducted a matched-paired, case–control study between patients who died and those who were discharged from the ICU. They studied 108 pairs of survivors–nonsurvivors. There were 39 patients who developed VAP in each group. Multivariate analysis showed that renal failure, treatment with corticosteroids, and bone marrow failure, but not VAP, were independent risk factors for death. The results of other matched cohort studies evaluating mortality and relative risk attributable to nosocomial pneumonia are also available (10,32–37). Of seven other studies, five concluded that VAP was associated with a significant attributable mortality. For example, it was reported that the mortality rate attributable to VAP exceeded 25%, corresponding to a relative risk of death of 2.0 (with respective values of 40% and 2.5 for cases of pneumonia caused by *Pseudomonas* or *Acinetobacter* spp.) (32).

Interventional Studies to Prevent VAP

Theoretically, the optimal study design to assess attributable mortality is a randomized controlled trial of an effective prevention for VAP. The largest number of published randomized trials has evaluated selective digestive decontamination (SDD). Since 1984, when Stoutenbeck et al. (38) published their original study demonstrating a decrease in overall infection rate from 81% in 59 control subjects to 16% in 63 patients receiving SDD, more than 50 studies including more than 6000 patients, and eight meta-analyses have been published (39–46). Two major conclusions concerning mortality can be drawn from the meta-analyses: a combination of topical and systemic prophylactic antibiotics reduces respiratory tract infections and overall mortality in critically ill patients. A treatment based on the use of topical prophylaxis alone reduces respiratory infections but not mortality. In the

most recent meta-analysis from Liberati et al. (46), SDD resulted in a significant reduction of both respiratory tract infections (odds ratio, 0.35) and mortality (odds ratio, 0.78). Five patients needed to be treated to prevent one infection, and 21 patients to prevent one death.

However, SDD is not widely used in most parts of the world, because of the limitations and deficiencies of these studies, including: (1) the use of a clinical diagnosis of pneumonia as a study endpoint, often in a nonblinded study design, which led to data of uncertain value, because of the possibility of a subjective bias in the diagnosis of pneumonia; in blinded studies, the incidence of pneumonia was not always reduced, particularly when invasive methods were used to define the presence of pneumonia; (2) the heterogeneity of patient groups studied: e.g., Nathens and Marshall (47) have found the greatest benefit of SDD among critically ill surgical rather than medical patients; (3) varying oral regimens and the inconsistent addition of systemic antibiotics used in these studies; and (4) persisting concerns about long-term microbial resistance patterns and antibiotic cost.

MORTALITY PREDICTORS IN VAP PATIENTS

Most authors emphasize the complex relationships among the responsible pathogen(s), the severity of underlying disease leading to ICU admission and treatment with mechanical ventilation, the severity of pneumonia itself, the time of onset, the diagnostic techniques used to identify lung infection, and the adequacy of initial antibiotic treatment (Fig. 1A). These studies, based on multivariate analyses and other research conducted in specific populations of ICU patients, and/or evaluating specific factors, identified the following variables as possible contributors to the mortality of VAP.

Type of Patients

Medical vs. Surgical Patients

Several studies showed a significantly higher mortality rate for medical ICU patients than for surgical ICU patients. Kollef (11) identified nonsurgical diagnosis as one of the factors independently associated with mortality in patients with late-onset pneumonia. Similarly, Heyland et al. (36) showed an attributable mortality, which was higher for medical patients than for surgical patients, with a relative risk increase of 65% vs. −27.3%; $p = 0.04$. Such data are a possible explanation for discrepant results reported in research evaluating attributable mortality of VAP: the studies conducted by Baker et al. (10) and Papazian et al. (35) that showed no attributable mortality, enrolled 0% and 26% of medical patients, respectively. In contrast, in those conducted by Fagon et al. (32) and Heyland et al. (36), there were 44% and 61% medical patients.

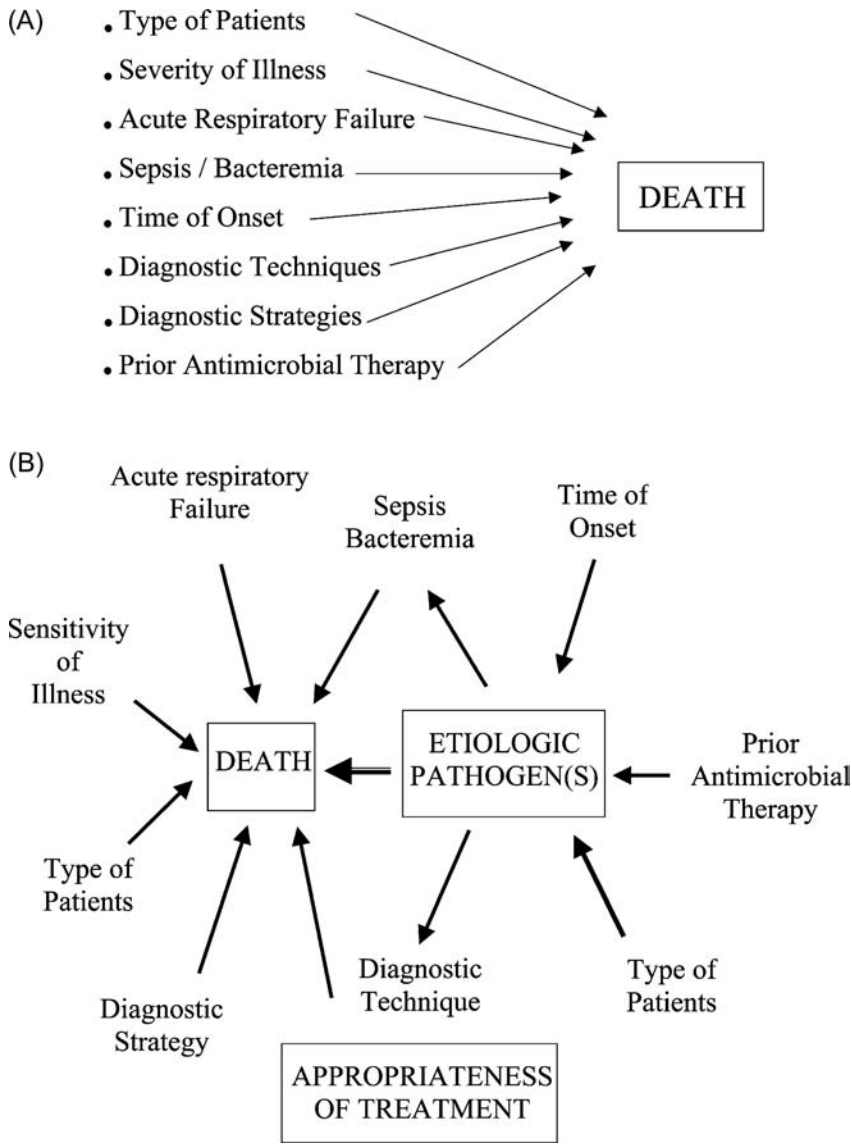

Figure 1 Factors contributing to the mortality in patients with VAP. (A) List of factors; (B) inter-relationship between factors.

Acute Respiratory Distress Syndrome Patients

As in other patients with extremely severe medical conditions, VAP does not appear to markedly influence survival of patients with ARDS, as documented in several studies (48–53). For example, overall mortality rates for

ARDS patients with or without VAP were 78% and 92% in the study by Delclaux et al. (50), 52% and 72% in Chastre et al. (49), and 57% and 59% in Markowicz et al. (51). However, studies evaluating excess mortality attributed to VAP in patients with ARDS are difficult to interpret because most VAP in this subset of patients occurs late in the course of the disease. In contrast, patients with ARDS who do not develop VAP frequently die earlier than non-ARDS patients, thus having little opportunity to develop nosocomial infection.

Severity of Illness

The responsibility of severity of illness is difficult to assess: the more severe the illness at admission, the higher the risk of death in ICU patients. Numerous studies have demonstrated that severe underlying illness predisposes subjects treated with mechanical ventilation to the development of pneumonia, and their mortality rates are consequently high (11,27,54–58). Three types of data explain the relationship between severity of illness, VAP, and death. Using multivariate analysis, Torres et al. (4) identified ultimately or rapidly fatal underlying medical condition as an independent risk factor for dying in 78 patients with VAP. In cardiac surgery patients, an organ system failure index of ≥ 3 was the most important determinant of mortality (11). Comparing patients with and without a terminal condition on admission, Gross and Van Antwerpen (29) showed a significantly higher number of infections in nonsurvivors than in survivors, but only in patients without terminal conditions (45% vs. 11%), whereas the rates of infections were 29% in nonsurvivors and 29% in survivors in the group of patients with terminal conditions. Finally, Bueno-Cavanillas et al. (59) found that patients at the extremes of disease severity (APACHE II score ≤ 10 or ≥ 30) did not have excess mortality from nosocomial infection, while those with an intermediate level of severity had a significantly higher risk of death (APACHE II score between 11 and 21, RR = 4.53; APACHE II score between 21 and 30, RR = 2.19).

Unfortunately, clinical scoring systems that are evaluated on admission (or during the first 24 hr following admission) do not predict the impact on outcome of the development of VAP during the ICU stay. These observations suggest that methods of matching could be improved by matching unexposed patients on the day their individual pair develops the infection, with a similar severity of illness, and not by matching only on admission. They also suggest that the difference between observed mortality and the mortality predicted by an admission scoring system is a possible measure of the impact of VAP on the outcome in critically ill patients.

Severity of Pneumonia

The clinical severity of the infection itself has a significant prognostic influence on the outcome of ICU patients with VAP. Clearly, pneumonia associated with worsening acute respiratory failure and shock (4,60), presence of signs of sepsis (61), bilateral chest X-ray involvement, and severity of hypoxemia (55) is of poorer prognosis than that without concomitant signs of respiratory and/or cardiovascular failure and/or sepsis syndrome. Froon et al. (62) showed that the SAPS II score on the day of diagnosis of VAP correlated well with the clinical severity of infection or mortality. Systemic levels of inflammatory mediators did not predict patient outcome better than SAPS II score.

The impact of bacteremia on outcome has not been directly evaluated by comparison of mortalities of bacteremic pneumonia vs. nonbacteremic pneumonia. However, analysis of nosocomial bloodstream infections suggests that pneumonia as the source of bacteremia was associated with higher mortality than secondary bacteremia because of other sources (urinary tract, catheter infection) (63).

Time of Onset

As compared with early-onset pneumonia, late-onset pneumonia seems to be associated with significantly higher mortality, probably because it is often caused by resistant organisms that are difficult to treat (3,16,32,36,60,64,65), and may result in delayed or ineffective antibiotic therapy. However, the influence of time of onset of pneumonia per se, relative to other confounding factors such as resistance, inappropriateness of antibiotic therapy, and reduction of physiological reserves after prolonged ICU stay (patients treated with mechanical ventilation for more than 96 hr represent a subgroup of ICU patients with persistent underlying disease and reduced host defenses) is unclear (19). Heyland et al. (36) and Mosconi et al. (66) did not show that patients with late-onset pneumonia had greater mortality than those with early-onset pneumonia.

Diagnostic Techniques—Diagnostic Strategies

Diagnostic techniques used to identify patients with VAP have no direct impact on the mortality of patients with true lung infection. The higher the specificity of the diagnostic techniques used, the higher is the likelihood of true (bacteriologically confirmed) pneumonia, and thus the higher the probability to identify deaths directly related to pneumonia. In contrast, by using techniques with high sensitivity and low specificity, it is harder to distinguish infection from colonization, and deaths because of pneumonia from those because of other causes. Bregeon et al. (31) did not identify a difference in mortality between protected brush-positive and brush-negative

patients. Timsit et al. (12) reported similar mortality rates between subjects with clinically suspected VAP and those with bacteriologically confirmed VAP. Finally, Heyland et al. (36) showed that mortality attributable to VAP was similar in the case of clinical evaluation, positive protected specimen brush or bronchoalveolar lavage, or adjudication. In fact, such studies did not evaluate the outcome consequences of the diagnostic techniques used. They only compared the mortality of different subgroups of ICU patients with fever, leukocytosis, change in chest X-ray, with or without bacteriologic confirmation of the presence of pneumonia.

In contrast, diagnostic strategies used to optimize the management of patients seem to have an impact on the outcome. Fagon et al. (67) demonstrated that a strategy based on fiberoptic bronchoscopy with direct microscope examination of BAL and/or PSB specimens to guide in the choice of antimicrobial therapy in patients with positive results, and quantitative culture results of obtained specimens, led to a reduction in antibiotic use and a lower mortality rate at day 14 than a strategy based on clinical evaluation (16% vs. 25%, respectively; $p = 0.02$).

Prior Antimicrobial Therapy

Ten years ago, Rello et al. (68) studied the impact of previous antimicrobial therapy on the outcome of VAP. In 54 out of 129 episodes of VAP, patients received antimicrobial therapy; among them, the incidence of *Pseudomonas aeruginosa* was 40.3% (vs. 4.9% in patients with previous antibiotics). Univariate analysis identified age, COPD, use of steroids, prior antibiotics, and shock as significantly more frequent in nonsurvivors. Multivariate analysis selected previous antimicrobial therapy as the only factor independently associated with death (OR = 9.2; $p < 0.0001$). The use of antibiotics has been repeatedly identified as the major risk factor for the emergence of drug-resistant bacteria (11,67,69,70). It is probably the predominant cause of its impact on mortality.

Responsible Pathogen(s)

The prognosis for aerobic, Gram-negative bacilli (GNB) VAP is considerably worse than that for infection with Gram-positive pathogens, when these organisms are fully susceptible to antibiotics. Death rates associated with *Pseudomonas* pneumonia are particularly high, ranging from 70% to >80% in several studies (3,16,32,68). According to one study, mortality associated with *Pseudomonas* or *Acinetobacter* pneumonia was 87% compared with 55% for pneumonias because of other organisms (3). Similarly, Kollef et al. demonstrated that patients with VAP because of high-risk pathogens (*P. aeruginosa*, *Acinetobacter* spp., and *Stenotrophomonas maltophilia*) had a significantly higher hospital mortality rate (65%) than those with late-onset VAP because of other microbes (31%) or subjects without late-onset pneumonia (37%) (19). In a study of ICU

patients with VAP because of *P. aeruginosa*, all of whom received early and appropriate antimicrobial therapy, the mortality rate attributed to the pulmonary infection was 13.5% (71). In this investigation, by excluding patients who did not receive adequate antimicrobial treatment, the true impact of *P. aeruginosa* VAP, despite the use of accurately targeted therapy, could be assessed. Concerning Gram-positive pathogens, in a study comparing VAP because of methicillin-resistant *Staphylococcus aureus* (MRSA) or methicillin-sensitive *S. aureus* (MSSA), mortality was found to be directly attributable to pneumonia for 86% of the former cases vs. 12% of the latter, with a relative risk of death equal to 20.7 for MRSA pneumonia (72).

Appropriateness of Treatment

To correctly interpret data concerning the treatment of VAP, the definition of the appropriateness (or adequacy) of antibiotic therapy has to be limited to the intrinsic antibacterial activities of antimicrobial agents relative to the etiologic pathogens, i.e., sensitivity patterns from in vitro tests. No data, in the literature, have evaluated the prognostic impact of other parameters such as underdosing, inadequate modalities of administration, choice of drugs with nonoptimal pharmacokinetic properties, lung penetration, or duration of treatment. Only one recent study has compared the outcome of patients treated with different durations of treatment (73). In this study, an 8-day regimen had no significant adverse consequences on the outcome of those with VAP, compared with a 15-day regimen. Finally, even the antibacterial activity is a criterion that is difficult to interpret: in a patient with VAP, the number of putative etiologic agents is largely different depending on the type of bacteriological sample. For example, in the study comparing two different strategies for managing patients suspected of having VAP, the number of potentially responsible pathogens was 126 in 204 patients diagnosed with bronchoscopic techniques compared to 312 in 209 patients diagnosed using qualitative cultures of tracheal aspirate (67). Considering such bacteriological results, the appropriateness of antimicrobial therapy may be interpreted differently.

Nevertheless, appropriateness of antibiotic therapy is obviously a major prognostic factor in bacterial infection. Lujan et al. (74) recently showed that clinical outcome is worse in patients with bacteremic pneumococcal pneumonia receiving antimicrobial therapy, which in vitro testing suggests would be ineffective. Similarly, the important prognostic role played by the appropriateness of the initial empiric antimicrobial therapy for VAP was analyzed by several investigators and is summarized in Table 3. These results suggest that an excess mortality of about 20–30% was directly associated with the inappropriateness of initial antimicrobial therapy. One major point, underlined by Iregui et al. (75) and Leroy et al. (76), is the importance of both timing and efficacy of initial treatment: for example, Iregui et al. reported a hospital mortality of 69.7% in the case of

Table 3 Mortality Rates According to Initial Empiric Antibiotic Therapy

First author, Ref.	Inadequate antibiotic therapy	Adequate antibiotic therapy	p Value
Luna	92.2% ($n = 34$)	37.5% ($n = 15$)	<0.001
Alvarez-Lerma	34.9% ($n = 146$)	32.5% ($n = 284$)	NS
Rello	63.0% ($n = 27$)	41.5% ($n = 58$)	0.06
Kollef	60.8% ($n = 51$)	26.6% ($n = 79$)	0.001
Sanchez-Nieto	42.9% ($n = 14$)	25.0% ($n = 24$)	NS
Ruiz	50.0% ($n = 18$)	39.3% ($n = 28$)	NS
Dupont	60.7% ($n = 56$)	47.3% ($n = 55$)	NS

initially delayed ($\geq$24 hr) appropriate antibiotic treatment, compared to only 28.4% in the cases of immediate appropriate treatment ($p < 0.01$). This factor, poorly investigated until now, could explain differences observed in mortality rates in previous studies (Table 3).

The best way for decreasing the rate of inappropriate initial treatment and lessening the delay in the initiation of antibiotic treatment, while reducing the selection pressure for resistance in the ICUs, remains controversial. A clinical approach, newly named "de-escalating approach" (broad-spectrum initial therapy and de-escalate therapy once the microbiological data are available and the patient's response to therapy is evaluated) has potential theoretical advantages but requires accurate microbiological data. This has never been evaluated in terms of efficacy and risks related to exposure of ICU patients to unnecessary antimicrobial therapy. In contrast, a microbiological approach, based on the use of bronchoscopic diagnostic techniques with direct microscopic examination of BAL and/or PSB specimens, results in reduction of antibiotic use and improves patients' outcome (67).

In conclusion, the complex relationship between various risk factors for dying in patients with VAP is summarized in Fig. 1B. Besides factors related to the patient, underlying disease, and severity of pneumonia, two more appear essential and amenable to modification by physicians' behavior: avoiding the emergence and development of infection because of multiresistant pathogens by reducing the use of unnecessary antibiotics and improving the initial treatment by using a strategy of getting rapid and accurate bacteriologic information.

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8

The Clinical Diagnosis of Ventilator-Associated Pneumonia

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The diagnosis of ventilator-associated pneumonia (VAP) is an unsettled and controversial area, with no agreement about whether the decision to start antibiotic therapy, in the setting of suspected infection, should be guided by clinical criteria (the "clinical approach") or by microbiologic data from quantitative samples of lower airway secretions (the "bacteriologic approach") (1,2). This controversy exists because the clinical definition of pneumonia although sensitive, is not very specific, and many patients with the clinical findings of VAP may have a noninfectious etiology for their findings of a new lung infiltrate accompanied by fever, purulent sputum, and leukocytosis. In fact, some studies have reported that as many as two-thirds of all patients with the clinical diagnosis of VAP may not meet microbiologic criteria for infection (3).

Even though the use of a clinical definition of pneumonia may be overly inclusive, a large body of data have demonstrated that mortality (including death directly attributable to the presence of pneumonia) in VAP is reduced when patients receive prompt and accurate empiric therapy (4,5). Thus, when faced with a patient who, on clinical grounds, may have pneumonia, the clinician must often initiate broad-spectrum empiric therapy,

accounting for all pathogens that are likely to be causing infection (based on a knowledge of local patterns of predominant pathogens and their antibiotic susceptibilities), in an effort to "protect" the at-risk patient. Unfortunately, this approach has a number of adverse consequences. First, some patients will be treated with antibiotics when they are not needed, and antibiotic use has been identified as a risk factor for subsequent nosocomial pneumonia, particularly with resistant pathogens (6). Second, many patients with VAP can have other infections at the same time (sinusitis, central line infection), and if all episodes of fever and lung infiltrate are attributed to VAP, these infections may be overlooked (7,8).

For all of these reasons, some investigators have proposed that whenever VAP is suspected, the patient should have a sampling of lower respiratory tract secretions (by bronchoscopic protected brush, bronchoalveolar lavage, blind brush or lavage, or endotracheal aspirate), which is then cultured quantitatively, and the results used for several purposes (9,10). The data can be used to decide whether to start therapy, and at a later time point, or to continue it. In addition, at both time points, the information can be used to guide specific antibiotic choices, that are initially empiric and later organism directed. Although the logic for such an approach is appealing, the use of quantitative cultures also has limitations, and it is uncertain whether decisions based on these data can lead to improved pneumonia management, or it will simply mean that some patients with VAP will have either a delay in the initiation of therapy or even a lack of therapy in the setting of a progressive and potentially lethal infection. The potential impact of relying on quantitative cultures will depend on whether this approach is used to determine not only which antibiotics to use, but whether to withhold therapy in selected patients, even in the face of a potentially serious infection.

If quantitative methods are to be used in clinical practice, they must lead to better outcomes than can be achieved by other approaches. These improved end points may be reduced mortality or less use of unnecessary antibiotics. Recent data have shown that although the use of quantitative cultures can reduce the use of antibiotics in the ICU, a similar benefit can occur if clinical methods are used to guide therapy (8,11–13). There is less convincing evidence that quantitative culture data can help reduce pneumonia mortality. However, for such a claim to be credible, it must be accompanied by a mechanism explaining how such a result is possible, and a plausible mechanism is lacking. Based on many studies, the only unequivocal way to reduce mortality in VAP is to improve the accuracy of initial empiric therapy, and it is unlikely that quantitative culture methods could accomplish this end.

There are many common goals that all clinicians accept, and they can be achieved using either a clinical or a bacteriologic approach to management. These goals include: avoiding untreated or inadequately treated

patients in an effort to reduce the mortality of VAP, and avoiding the overusage of antibiotics in an effort to control the problem of antimicrobial resistance. These goals can be achieved by improving our diagnostic accuracy, focusing therapy (de-escalation) based on the patient's clinical response and the results of respiratory tract culture data, and reducing the duration of therapy to the shortest effective period (14,15). There may be no single best way to diagnose and manage VAP, and each hospital is likely to have different capabilities for applying the various diagnostic techniques, so that the key issue is to be sure that whatever management strategy is used, the clinician is able to achieve the goals stated above.

WHAT IS THE "CLINICAL APPROACH" TO EMPIRIC THERAPY OF VAP, AND IS IT ACCURATE?

Methods for Clinical Diagnosis, Including the Clinical Pulmonary Infection Score

The clinical diagnosis of VAP is made when the patient has a new or progressive lung infiltrate plus at least two of the following three criteria: fever, purulent sputum, or leukocytosis. Although this definition is sensitive, it is not specific, and some investigators have reported that as few one-third of all patients who meet these criteria have microbiologic confirmation of pneumonia using quantitative cultures (2,3). However, most clinicians use multiple criteria to diagnose pneumonia, often emphasizing certain findings over others. In fact, such a "weighted" approach to clinical diagnosis has been developed, in the form of a clinical pulmonary infection score (CPIS), and this diagnostic tool was quite accurate when it was first described (16). The original description of the scoring system assigned points to patients, each worth 0–2 points, based on six clinical assessments, including: fever, leukocyte count, quantity and purulence of tracheal secretions, oxygenation, type of radiographic abnormality, and results of sputum culture and Gram's stain. When applied prospectively, the last criterion cannot always be used, and if omitted, the score varies from 0 to 10, instead of 0 to 12; however, recently several modifications of the CPIS have been proposed and applied, as discussed below (11,17–21).

Using all six criteria, Pugin et al. (16) compared the CPIS to the quantitative diagnosis of pneumonia using bronchoscopic BAL (and calculating a bacterial index). The correlation between the CPIS and the bronchoscopic BAL bacterial index was 0.8, showing that clinical diagnosis can be as accurate as a microbiologic approach. In addition, if a CPIS > 6 was used as a clinical definition of pneumonia, then 93% of the BAL samples from such patients were diagnostic of pneumonia by microbiologic criteria. In addition, if the CPIS was ≤ 6, no patient satisfied the microbiologic definition of pneumonia. Thus, using a CPIS > 6 as the clinical definition of pneumonia,

the result was a sensitivity of 93%, and a specificity and positive predictive value of 100%. In another study, using post-mortem lung biopsy to define the presence of pneumonia, the CPIS had a sensitivity of 77% and a specificity of 42% (22). A study of 38 patients revealed a higher diagnostic accuracy with a sensitivity of 77% and a specificity of 85% (23). Although many physicians do not routinely calculate the CPIS, the aggregate score is very similar to a clinician using all available data to decide how strongly the diagnosis of pneumonia is suspected, and the findings from studies of the CPIS suggest that the clinical diagnosis of VAP may not be so inaccurate.

Continued interest in the CPIS as a diagnostic tool has led to several recent studies that suggest some utility for this clinical diagnostic tool, but the studies are all somewhat different from each other, and from earlier ones, because of methodologic variations (17–21). Most of the studies have used a "modified" clinical scoring system, finding that they could not routinely apply Pugin's method because of the unavailability of tracheal aspirate cultures at the time of initial clinical evaluation, the ICU nurses did not record sputum volume, or the lab did not measure band forms of white blood cells. In addition, some of the recent studies actually calculated the CPIS retrospectively, and it remains uncertain if this leads to the same results as when collected prospectively. Recently, one group looked at the reproducibility of the score itself by having two observers calculate the score, although some of these calculations were done retrospectively (20). The investigators found that interobserver variability was large and that it was often the result of ambiguities in the scoring system or missing data that were required to calculate the score. When all the data were available, the kappa score for level of agreement was only 0.16. In spite of these data, it is difficult to understand such variability because most of the data points are objective, and the one subjective variable, quantity of secretions, was omitted from this analysis.

Studies comparing the accuracy of CPIS to a bacteriologic diagnosis of VAP, using quantitative cultures, have shown a wide range of sensitivity and specificity, but it does appear that the accuracy of the CPIS can be improved if a reliable lower respiratory tract sample is obtained and studied carefully with a Gram's stain (17). In a study of 99 patients, of whom 69 had VAP using quantitative BAL criteria, the CPIS had a sensitivity of 83% but a specificity of only 17%. However, the modified score used did not include any microbiologic study of lower respiratory tract secretions (20). Flanagan et al. (19) compared the CPIS to nonbronchoscopic lung lavage data in a population of 145 patients. The CPIS for all 34 patients with VAP was significantly higher than the score of the nonpneumonia patients (7.6 vs. 4.1, $p < 0.0001$), and using a score of 7 to diagnose pneumonia, the sensitivity was 85%, the specificity 91%, the positive predictive value 61%, and the negative predictive value 96%. It is interesting that the CPIS

performed so well because these authors used a modified score that did not include culture data or Gram's stain of lower respiratory tract secretions. In contrast, Fartoukh et al. (17) found that the CPIS correlated poorly with a BAL diagnosis of VAP unless a Gram's stain of respiratory secretions was included in the score. In this study, 40 of 79 patients had BAL-confirmed pneumonia, and the CPIS for those with confirmed VAP was 6.5 vs. 5.9 in those without ($p = 0.07$), but this involved a scoring system without a Gram's stain of respiratory secretions. When a Gram's stain of a BAL sample was added to the CPIS scoring system (similar to Pugin's original description), then the score for confirmed VAP was 8.2 compared to 6.4 in those without VAP ($p < 0.001$). It remains to be determined if a similar degree of accuracy could be obtained with a Gram's stain of a tracheal aspirate, thus allowing an accurate diagnosis without either quantitative cultures or invasive sampling.

A group of French investigators calculated the CPIS retrospectively in 201 patients who had a bronchoscopic evaluation at the time of pneumonia suspicion, and measured the score on days 1 and 3 (21). The score on day 1 did not include any respiratory tract culture data, while this information, as well as data about radiographic progression, was incorporated into the score at day 3. The authors found that the initial CPIS score, calculated without bacteriologic information, was similar in both groups (6.4 vs. 6.2), but the values were significantly different on day 3 (8.7 vs. 7.0, $p < 0.0001$). In fact the data on day 3 were associated with a sensitivity of 89% and a negative predictive value of 84%. Thus, using a clinical approach, patients could be started on empiric therapy when there was any clinical suspicion of VAP, but therapy continued beyond day 3 only if the CPIS remains elevated. The French investigators acknowledged that using the CPIS in this fashion might allow for a clinical strategy that permitted the use of less antibiotics than with a traditional clinical strategy, but they argued that a bacteriologic approach was even better and led to a more selective application of antimicrobial therapy.

In addition to its value in diagnosing VAP, the CPIS can be used in a clinical management strategy to define whether a patient is responding to therapy. Luna et al. (18) found that the CPIS, when followed serially throughout the course of VAP management, fell in patients who survived, but not in those who did not. The most accurate indicator of adequate therapy was a rapid improvement in the PaO_2/FiO_2 ratio, and this improvement was evident in responding patients by day 3. Thus, serial measurements of the CPIS can be used to guide the modification of antibiotics during the course of therapy (discussed below), and the available data suggest that an assessment of patient response can be done accurately at day 3 of therapy. For patients who do not have a fall in score at this time point, careful reassessment is necessary, while for those with a good response, it may be possible to design an abbreviated course of therapy.

Comparison of Clinical and Bacteriologic Diagnosis

While many investigators have argued that invasive methods are more accurate than the clinical diagnosis of VAP, not all studies support that contention. For example, Marquette et al. (24) did prospective quantitative-cultures in 28 patients who subsequently died and had the diagnosis of VAP defined histologically. They reported that no quantitative method had a sensitivity >60% (24). Similarly, Kirtland et al. (25) performed autopsy studies on 39 patients, and found that no quantitative diagnostic method had a high positive predictive value for VAP, but that tracheal aspirates were 87% sensitive for defining the organisms that were present in lung tissue. This finding has generally been corroborated by other investigators, and based on these studies, it seems safe to conclude that tracheal aspirates, studied qualitatively, will rarely fail to grow an organism that can be found in lung tissue or with bronchoscopy (26–28). Thus, if clinical diagnosis is used to decide when to start therapy, and microbiologic data from tracheal aspirates are used to define the organisms present in the lung and their antibiotic susceptibilities, it is possible to treat pneumonia at its earliest time point and to target therapy to the pathogens that are present. One limitation of this approach is that not all organisms present on a tracheal aspirate culture are necessarily pathogens, as some may represent colonizing organisms. Conversely, it is unlikely that an organism causing pneumonia will not be present in a tracheal aspirate culture. Therefore, tracheal aspirates can be used, in a clinical approach to management and guide de-escalation therapy, ruling out the presence of a highly resistant pathogen if the cultures do not show such organisms.

Studies Showing the Efficacy of a Clinical Approach

Several studies have now shown that it is possible to use a clinical management approach to limit the use of antibiotics, and thereby control resistance, but still treat patients with suspected VAP in an aggressive fashion (11–13). In a study by Singh et al. (11), patients with suspected VAP were clinically evaluated with the CPIS, which included measurements of fever, leukocytosis, appearance of tracheal secretions, radiographic patterns, and oxygenation to assess the likelihood of pneumonia. If the score was greater than 6 (each of the five features was scored 0–2, for a maximum of 10 points), patients were diagnosed as having pneumonia and treated for 10–21 days. However, for those with a score of 6 or less, there was a randomization to "standard care" or 3 days of ciprofloxacin at 400 mg every 8 hr. After 3 days, for the patients treated with ciprofloxacin, the CPIS was measured again, adding the criteria of radiographic progression and the results of respiratory cultures (now giving a maximum score of 14, based on seven clinical criteria), and if the score remained 6 or lower, antibiotics were stopped. Using this approach, 42 patients with a score of 6 or less received

standard therapy, and 39 were randomized to 3 days of ciprofloxacin therapy. Only 11 of the 39 patients needed antibiotics for more than 3 days (because the CPIS had increased to >6), and the rest of the group had therapy stopped after 3 days. The entire short course therapy group had the same clinical course (CPIS at day 3) and the same mortality as the 42 patients randomized to standard therapy. However, antibiotic resistance was less frequent and withholding of therapy was more frequent in the short course therapy group. Hence, the authors demonstrated the safety and feasibility of using a clinical assessment as a method to limit the use of prolonged antibiotic therapy in patients with suspected VAP.

Ibrahim et al. (12) compared the management of 50 patients with VAP in a time period without an antibiotic protocol to 52 patients with VAP who were managed by an ICU-specific protocol. The protocol-directed therapy was based on information about ICU-specific pathogens and their susceptibilities, and required initial intravenous combination antimicrobial treatment with vancomycin, imipenem, and ciprofloxacin. The guideline also required that antibiotic treatment be modified after 48 hr based on the results of cultures, and de-escalation was commonly achieved. In fact, only 2% remained on all three drugs for a complete course of therapy. In total, 36.5% of patients had one drug discontinued and 61.5% had two antibiotics stopped within 48 hr of treatment. This high rate of de-escalation was achieved even though 25% of the pathogens were *Pseudomonas aeruginosa*, 15.4% were methicillin-resistant *Staphylococcus aureus*, and other multidrug resistant pathogens were also present. In addition to using less antibiotics, an additional feature of the protocol was an attempt to limit therapy to a 7-day course of appropriate antibiotic(s) for patients with VAP. Administration of antimicrobials beyond day 7 was only recommended for patients with persistent signs and symptoms consistent with active infection (e.g., fever >38.3°C, circulating leukocyte count >10,000 mm^{-3}, lack of improvement on the chest radiograph, continued purulent sputum). Use of the guideline was associated with a statistically significant increase in the administration of appropriate antimicrobial treatment (94% of the protocol patients got accurate therapy, compared to less than 50% in the absence of a protocol) and a decrease in the development of secondary episodes of antibiotic-resistant VAP. A significant reduction in the total duration of antimicrobial treatment to 8.1 ± 5.1 days from 14.8 ± 8.1 days ($p < 0.001$) was also achieved.

In a more recent study, Micek et al. (13) developed a policy to discontinue antibiotics when patients with suspected VAP were found to have a noninfectious cause of lung infiltrates or a resolution of clinical signs of pneumonia. Essential to effectively implementing this policy was a plan to diagnose pneumonia clinically and then use broad-spectrum empiric therapy for all patients, which included cefepime, ciprofloxacin or gentamicin, and vancomycin or linezolid. This therapy led to 93.5% of patients getting

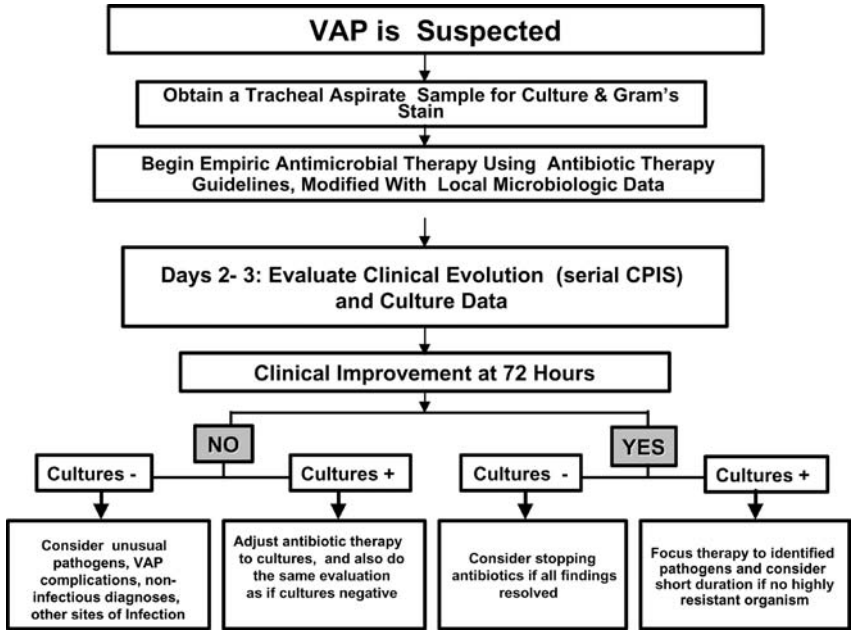

Figure 1 Summary of the clinical approach to managing suspected VAP. The key features of this approach are to provide empiric therapy as soon as there is a clinical suspicion of pneumonia, making sure to obtain a tracheal aspirate culture on all patients and to start therapy based on a knowledge of local microbiology. Equally important is an effort to re-evaluate the patient at day 3, based on serial clinical assessment and the results of tracheal aspirate cultures, focusing on de-escalation of therapy when possible. If the patient is not responding at day 3, a careful evaluation for unusual pathogens, VAP complications, noninfectious diagnoses, and a search for other sites of infection is essential.

initially effective therapy. Using this approach, compared to a group randomized not to receive this intervention, 94.7% of the discontinuation group ($n = 142$) had a recommendation to stop therapy, and this was followed in 88.7% of all patients ($n = 126$) within 48 hr of the recommendation. The duration of therapy was related to the magnitude of clinical findings initially present, as reflected by the CPIS. Duration of therapy was reduced to as low as 5.8 days in those with Gram-negative bacteria, even though resistant organisms were commonly present.

Summary of the Clinical Approach (Fig. 1)

The clinical approach to VAP management is based on the following management strategy: use all the available clinical data (including CPIS) to decide IF pneumonia is present, and make the decision WHETHER to use antibiotics

based on this assessment. Prior to starting therapy, one should collect a tracheal aspirate from an intubated patient, and start antibiotics based on existing treatment algorithms, supplemented by a knowledge of local microbiologic data. Antibiotics can be continued, pending tracheal aspirate cultures and serial assessment of clinical response, but once this information is available, one should make a decision about whether to discontinue, modify, or simplify antibiotic choices. This decision can usually be made by the third day. At this time, if the patient's clinical findings have completely resolved and the cultures are negative (in the absence of changing antibiotics within 72 hr of collecting the culture), then it may be possible to conclude that pneumonia was not present, and if the likely diagnosis is another process (atelectasis, heart failure), then therapy can be stopped. If cultures are positive, and the patient is improving, then it may be possible to narrow (to monotherapy) and to focus (to a less broad-spectrum agent) therapy, unless a highly resistant pathogen is present. If at the same time point the patient is not improving, then cultures can be used to ensure that all pathogens present are being treated. Regardless of whether cultures are positive or negative, if the patient is not improving, then diagnostic studies should be done to search for other sites of infection that could coexist with VAP (central line infection, intra-abdominal abscess, sinusitis), noninfectious processes (acute lung injury, inflammatory lung disease), unusual organisms (viruses, fungi), or complications of VAP or its therapy (empyema, antibiotic induced colitis, pulmonary embolism).

PROBLEMS WITH QUANTITATIVE CULTURES AND THEIR USE FOR THE MANAGEMENT OF SUSPECTED VAP

The reliance on quantitative cultures, by advocates of a bacteriologic approach to management, has a number of practical limitations: (1) some patients will have false-negative results and, depending on how the data are used, these patients may get no therapy even when infection is present; (2) some patients will have a delay in the initiation of therapy when relying on these methods, and such a delay may lead to some potentially salvageable patients losing their best chance to survive VAP; (3) a number of technical considerations affect the results of quantitative cultures, and these may explain why the reported accuracy of invasive methods (from one method to another and from one investigator to another) varies so widely; (4) quantitative methods rely on the idea that there is a bacteriologic "threshold," or a bacterial concentration below which infection is absent (and not treated), and this concept may be biologically implausible because infection is on a microbiologic continuum; (5) the accuracy of quantitative sampling is greatly influenced by antibiotic therapy, and many patients with suspected VAP are already on antibiotics (1,29).

The Threshold Concept

If a bacteriologic management approach is used, then a bacteriologic cutoff is used to decide whether pneumonia is present. This threshold can be 10^3 for protected specimen brushing (PSB), 10^4 or 10^5 for BAL, and 10^6 for quantitative endotracheal aspirates (9,10,21,28). However, because these data are not immediately available, some investigators have used a Gram's stain of BAL cells and started therapy if there were $>5\%$ of cells with intracellular organisms (2). The real danger with this approach comes if antibiotics are withheld until quantitative data show a threshold concentration of organisms. Although advocates of quantitative cultures have argued that it is safe to withhold therapy in many patients, in the largest prospective study of these techniques, 10% of all patients were so ill that therapy was not withheld, regardless of the results of bronchoscopic sampling (8). Another problem with this approach is that if the counts are falsely low, a patient with pneumonia will go without therapy. In addition, several studies suggest that VAP is on a histologic and bacteriologic continuum, and that low counts may not mean no pneumonia, but rather, early (and potentially treatable) pneumonia (25,30).

For example, Rouby et al. compared the post-mortem histology of VAP with quantitative cultures and found that some patients (15%) with histologic pneumonia had negative BAL cultures and that 22% of patients with confluent bronchopneumonia had negative ($<10^3$ organisms) lung tissue cultures. In addition, patients had other histologic lesions that probably preceded confluent pneumonia (and may have needed therapy), such as bronchiolitis and focal bronchopneumonia, and these lesions contained fewer organisms than were present than with more advanced pneumonia (30). These early lesions may have been treatable, but because quantitative cultures were below the threshold concentration, therapy would have been withheld. In an animal model of VAP in piglets, Wermert et al. (31) found that there was no exact bacteriologic threshold to define the presence of histologic pneumonia. This may be related to the finding in this study that the histologic lesions of pneumonia were unevenly distributed throughout the lung, and thus no sampling method could reliably sample well enough to find all patients with pneumonia.

Reproducibility of Results

If a bacteriologic threshold is to be used to define the need for antibiotic therapy, then certainly the result obtained should be reliable and reproducible. However, for both PSB and BAL, studies have shown that when multiple repeat samples are taken from the same patient, the results may vary between positive and negative. For example, when PSB was repeated 5 times in the same site, many patients had samples on both sides of the diagnostic threshold, and 25% of the organisms identified also fell on both sides of a

diagnostic threshold (32). In a similar study of BAL, only 8 of 11 patients with a positive BAL had a positive result on a second sample taken from the same area at the same sitting (33). The lack of reproducibility may be an inherent methodologic limitation of bronchoscopy, or, as suggested by the histologic data, because VAP is a patchy process, not all samples will be taken from an area involved with pneumonia.

Variability can also occur from operator to operator and from center to center. This explains why there is a wide reported range of sensitivity and specificity of invasive methods in the literature. For example, PSB has a reported sensitivity varying from 38% to 100%, and some centers that have had poor results with PSB have had excellent results with BAL and vice versa (1,9,10,34). With this type of experience reported in the literature, how can one decide which method to use and which to rely upon? One possible answer is to use multiple types of samples in any patient, but the accuracy of this effort, compared to clinical management, remains uncertain.

Other Problems

Many patients with suspected VAP are on antibiotics that can cause false-negative results, but one recent study has shown that this is less likely if the patient has been on therapy, without change, for at least 72 hr before diagnostic sampling (29). In this setting, quantitative cultures may be positive and may show a resistant organism, although it seems likely that the same data could be obtained from an endotracheal aspirate culture. If, however, the patient has had an antibiotic change within 24 hr of undergoing a quantitative sampling, then the sensitivity of invasive methods may be as low as 40%, making these methods unreliable (29).

CAN A BACTERIOLOGIC APPROACH IMPACT MORTALITY IN VAP?

A number of studies have documented that the most important determinant of mortality in patients with VAP is the adequacy of initial antibiotic therapy (4,5,35,36). If initial therapy is inadequate or delayed, then outcome is worse than if the initial (empiric) therapy is correct. Hence, if invasive methods are to have benefit, they should be able to reduce mortality and avoid the unnecessary use of antibiotics. To achieve these goals, the use of invasive methods must avoid the problem of not treating patients who have VAP (which will occur whenever there is a false-negative result), while allowing for more accurate antibiotic choices than other methods, and with the added benefit of allowing the withholding of therapy in patients who do not have VAP.

Luna et al. (4) investigated the impact of quantitative BAL on the management of 132 patients with suspected VAP. In that study, 65 patients had a positive BAL, but many (50 patients) had been started on empiric therapy

prior to the bronchoscopy. For each patient with a positive culture, the antibiotic management at three time points was examined, and related to the sensitivity of the recovered organisms to define if therapy was adequate or inadequate. These time points were: initial empiric therapy (pre-BAL), therapy after BAL was completed, and therapy after BAL results were known. The findings were that if initial empiric therapy was adequate, mortality was 38%, but if it was inadequate, mortality was 91%, and if therapy was withheld, the mortality was 60%. Hence, the outcome was most favorable if the initial therapy was adequate, but if inadequate therapy was given, or even if adequate therapy was given, but delayed, outcome remained poor. Kollef and Ward (35) studied 131 ventilated patients with mini-BAL and found organisms in 60; however, in 44 patients, initial therapy was inadequate and was changed. Overall the mortality rate for patients who had changes in therapy after BAL was 61% compared to a mortality of 33% in those with no change in antibiotics post-BAL. In another study, Rello et al. (36) found that 27 of 113 patients received initially inadequate therapy, and this group had a related mortality of 37% compared to 15% for those who got initially adequate therapy. In this last study, the overall mortality in those with inadequate therapy was 63%, a result similar to the other studies cited above.

Although proponents of a bacteriologic approach have argued that it is safe to withhold therapy in patients with suspected VAP, until the results of cultures become available, these data suggest that a delay in starting adequate therapy can be harmful, and one other study that specifically examined the impact of delays in adequate therapy also saw an increased mortality when this occurred (37). In that study, 33 of 107 patients had an initial delay in appropriate antibiotic therapy (because of a failure to write the order in a timely fashion in 75% of these patients), and this group had a mortality rate of 69.7%, compared to a rate of 28.4% without delayed therapy. In another study, Bonten et al. (38) reported the outcome in 138 patients managed by bronchoscopic data. In 72 patients, quantitative cultures were positive, but 32 initially had therapy withheld and then started when the results were known, and 14 had changes in therapy. In the group with positive results and no change in therapy, mortality was 35% compared to a mortality of 50% if therapy was changed, and 47% if therapy was first started after culture data were known. Although these differences were not statistically significant, the trends still raise a concern.

Several randomized trials have shown no benefit to the use of invasive diagnostic methods, compared to clinical management, but in all of these studies, quantitative culture data were not used to withhold or withdraw therapy, and initial empiric therapy was often adequate (39–42). Another study, which managed patients based on the results of quantitative cultures, reached different conclusions (8). In this multicenter French study, 413 patients with suspected VAP were randomized to management by either an

invasive or noninvasive approach. The population managed by the invasive, bacteriologic approach had antibiotic therapy only if bronchoscopic sampling suggested infection or if the patient had signs of severe sepsis (8), and with this approach, antibiotics were never given to 90 of 204 patients. In contrast, for the patients managed by a clinical judgment strategy, therapy was withheld in only 15 of 209 patients. Patients managed with the invasive strategy (which included the group in whom therapy was withheld) had the same 28-day mortality as patients managed by clinical judgment, but a lower 14-day mortality. However, the differences in mortality may not be related to the diagnostic approach, because patients managed by the clinical strategy, for reasons that are unexplained, had a higher frequency of inadequate empiric therapy than the patients managed by the invasive strategy. However, this study showed that if appropriate patients are identified, in this case using bronchoscopic data, therapy can be safely withheld in some patients, but importantly, the protocol did allow for therapy, regardless of the bronchoscopic findings, in the 10% of patients with suspected VAP who had signs of sepsis. Thus, as mentioned earlier, it still is controversial to withhold antibiotics while waiting for the results of quantitative cultures (as in the bacteriologic strategy), rather than to withdraw therapy once the data are known (as in the clinical strategy).

WHAT ARE THE EXISTING BENEFITS TO INVASIVE DIAGNOSTIC METHODS?

The advent of invasive methods has produced a number of well-defined studies of the natural history of VAP caused by specific pathogens (e.g., *S. aureus, P. aeruqinosa*), using quantitative cultures to define the presence of these organisms (43). Bronchoscopy and quantitative BAL may also have great diagnostic value in the immune compromised patient, but the issues in this population are different from these in traditional ventilated patients. In addition, when a patient is not responding to initial antibiotic therapy of VAP, bronchoscopy may be useful, particularly to define the presence of a resistant pathogen. But it is still uncertain if similar results could also be obtained from a simple tracheal aspirate.

In the future, studies of bronchoscopy could be focused on defining the optimal duration of therapy for VAP, by tailoring the duration of therapy to the concentration of bacteria recovered in a lower respiratory tract sample. It is possible that there are patients with VAP in whom the burden of organisms is low, or the host defenses adequate, and a short course of therapy is all that is needed. It is questions such as these that still need exploration. For the present, it seems that either a clinical or bacteriologic approach to VAP management can be successful provided that, regardless of which approach is used, the clinician achieves the goals of providing

timely and accurate therapy, while trying to reduce the exposure of patients to prolonged courses of unnecessary antibiotics.

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9

Establishing the Diagnosis of Ventilator-Associated Pneumonia: An Invasive/Microbiologic Approach Compared to a Clinical Approach

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Two diagnostic algorithms can be used in the case of ventilator-associated pneumonia (VAP) suspicion. One option is to treat every patient clinically suspected of having a pulmonary infection with new antibiotics, even when the likelihood of infection is low, arguing that several studies showed that immediate initiation of appropriate antibiotics was associated with reduced mortality (1–3). Here, the selection of appropriate empiric therapy is based on risk factors, local resistance patterns, and involves qualitative testing to identify possible pathogens, with antimicrobial therapy being adjusted according to culture results or clinical response (Fig. 1). This "clinical" approach has two potential advantages: first, no specialized microbiologic techniques are requested and, second, the risk of missing a patient who needs antimicrobial treatment is minimal, at least when all suspected patients are treated with new antibiotics. However, such a strategy leads to overestimation of the incidence of VAP because tracheobronchial colonization and noninfectious processes mimicking it are included. Qualitative endotracheal aspirate cultures contribute indisputably to the

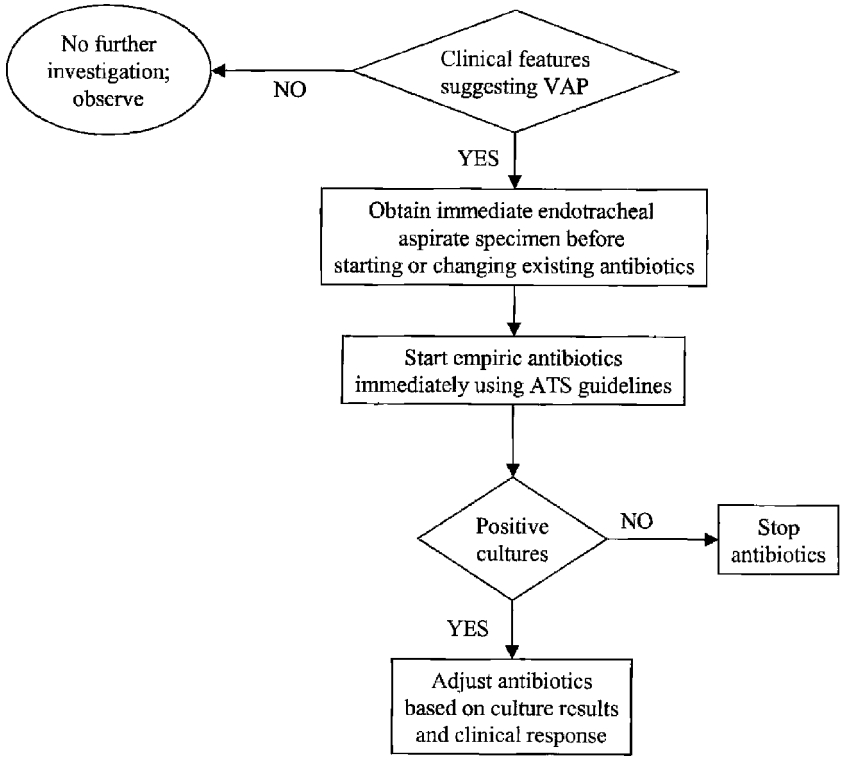

Figure 1 Diagnostic and therapeutic strategy applied to patients with a clinical suspicion of VAP managed according to the "clinical" strategy.

diagnosis of VAP only when they are completely negative for a patient with no modification of prior antimicrobial treatment. In such a case, the negative-predictive value is very high and the probability of the patient having pneumonia is close to null (4).

Concern about the inaccuracy of clinical approaches to VAP recognition and the impossibility of using such a strategy to avoid overprescription of antibodies in the intensive care unit (ICU) had led numerous investigators to postulate that "specialized" diagnostic methods, including quantitative cultures of endotracheal aspirates or specimens obtained with bronchoscopic, or nonbronchoscopic techniques including bronchoalveolar lavage (BAL) and/or protected specimen bronchial brushing (PSB), could improve identification of patients with true VAP and facilitate decisions whether or not to treat, and thus impact clinical outcome (5–7). Using such a strategy, the decision algorithm is similar to the one described in Fig. 1, except that therapeutic decisions are made based on the results of direct examination of distal pulmonary samples and the results of quantitative cultures (Fig. 2).

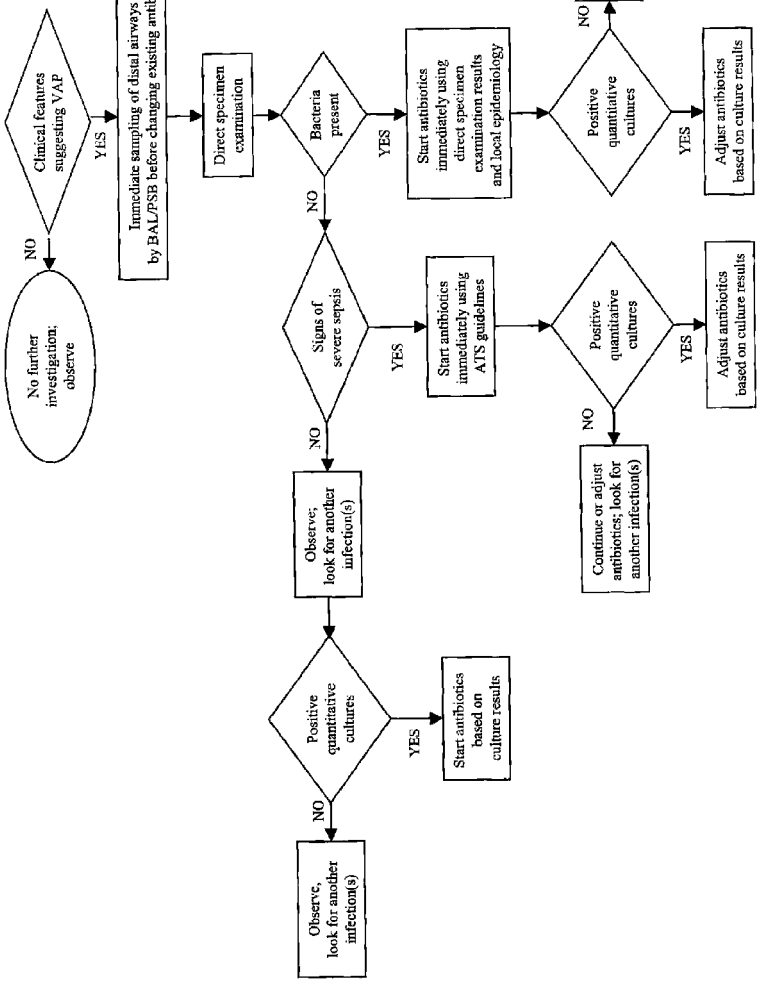

Figure 2 Diagnostic and therapeutic strategy applied to patients with a clinical suspicion of VAP managed according to the "invasive" strategy.

This chapter reviews the potential advantages and drawbacks of using bronchoscopic techniques compared with that of noninvasive modalities and/or clinical evaluation alone for the diagnosis of VAP, based on our personal experience and major additions to the literature that have appeared in recent years.

PROCEDURE

Bronchoscopy provides direct access to the lower airways for sampling bronchial and parenchymal tissues directly at the site of lung inflammation. One major technical problem with all bronchoscopic techniques is proper selection of the sampling area in the tracheobronchial tree. Almost all intubated patients have purulent-looking secretions and the secretions first seen may represent those aspirated from another site into gravity-dependent airways or from upper-airway secretions aspirated around the endotracheal tube. Usually, the sampling area is selected on the basis of the location of infiltrate on chest radiograph or the segment visualized during bronchoscopy as having purulent secretions (8). Collection of secretions in the lower trachea or mainstem bronchi, which may represent recently aspirated secretions around the endotracheal tube cuff, should be avoided. In patients with diffuse pulmonary infiltrates or minimal changes in a previously abnormal chest radiograph, determining the correct airway to sample may be difficult. In these cases, sampling should be directed to the area where endobronchial abnormalities are maximal. In case of doubt, and because autopsy studies indicate that VAP frequently involves the posterior portion of the right lower lobe, this area should probably be sampled preferentially (9). While in the immunosuppressed host with diffuse infiltrates, bilateral sampling has been advocated, there is no convincing evidence that multiple specimens are more accurate than single ones for diagnosing nosocomial bacterial pneumonia in patients requiring mechanical ventilation (10).

At least 15 studies have described a variety of nonbronchoscopic techniques for sampling lower respiratory tract secretions; results have been similar to those obtained using fiberoptic bronchoscopy (FOB) (11). Compared with conventional PSB and/or BAL, nonbronchoscopic techniques are less invasive, can be performed by clinicians not qualified to perform bronchoscopy, have lower initial costs than FOB, avoid potential contamination by the bronchoscopic channel, are associated with less compromise of gas exchange during the procedure, and can be performed even in patients intubated with small endotracheal tubes.

Disadvantages include the potential sampling errors inherent in a blind technique and the lack of airway visualization. Although autopsy studies indicate that pneumonia in ventilator-dependent patients has often spread into every pulmonary lobe and predominantly involves the posterior portion of the lower lobes, two clinical studies on ventilated patients with

pneumonia contradict those findings, as some patients had sterile cultures of PSB specimens from the noninvolved lung (10,12). Furthermore, although the authors of most studies concluded that the sensitivities of nonbronchoscopic and bronchoscopic techniques were comparable, the overall concordance was only ~80%, emphasizing that, in some patients, the diagnosis could be missed by a blind technique, especially in the case of pneumonia involving the left lung, as demonstrated by Meduri et al. (10).

COMPLICATIONS

The risk inherent in bronchoscopy appears slight, even in critically ill patients requiring mechanical ventilation, although the associated occurrence of cardiac arrhythmias, hypoxemia, or bronchospasm is not unusual. A study conducted by Trouillet et al. (10,13) in 107 ventilated patients has shown that FOB under midazolam sedation is easily done in this setting. No death or cardiac arrest occurred during or within the 2 hr immediately following the procedure. However, patients in the ICU are at risk of relative hypoxemia during FOB, even when high levels of oxygen are provided to the ventilator and gas leaks around the endoscope are minimized by a special adaptor. An average decline in mean arterial oxygen tension of 26% was observed at the end of the procedure, compared with the baseline value, and this was associated with a mild increase in $PaCO_2$. The degree of hypoxemia induced by FOB in this study was linked to the severity of pulmonary dysfunction and the decrease in alveolar ventilation. Clinical hypoxemia, as defined $PaO_2 < 60$ mmHg, was more frequent in patients with Acute Respiratory Distress Syndrome and in those who "fought" the ventilator during the procedure, as shown by multivariate analysis.

Careful attention to the anesthetic protocol, with addition of a short-acting neuromuscular blocking agent, and monitoring of patients during bronchoscopy should probably permit rapid correction and more frequent prevention of hypoxemia in this setting and, therefore, should further decrease the morbidity of this procedure. In a recent study conducted in a large series of patients with ARDS, only 5% of patients had arterial oxygen desaturation, to <90% during bronchoscopy despite severe hypoxemia in many patients prebronchoscopy (14).

Certain procedures, however, increase the risk of complications, particularly in some subsets of patients. The bleeding risk observed with the PSB technique is thus especially significant in patients with thrombocytopenia or a coagulopathy. Pneumothorax is also principally a complication of PSB, although it can occur after BAL alone in mechanically ventilated patients. In fact, the risk of FOB is paradoxically higher in nonventilated patients than in those receiving mechanical ventilation, as performance of bronchoscopy in a critically ill patient with impending respiratory failure may lead to profound hypoxemia and rapid decompensation. While bacteremia does

not appear to occur after PSB, release of the cytokine, TNF, has been documented in patients undergoing BAL (15). Transbronchial spread of infection is also an extremely remote possibility (8).

SPECIMEN TYPES AND LABORATORY METHODS

The methodology for PSB sampling was described originally by Wimberley et al. (16). This method is in fact based on the use of a combination of four different techniques: (1) FOB to directly sample the site of inflammtion in the lung; (2) a double-lumen catheter brush system with a distal occluding plug to prevent secretions from entering the catheter during passage through the bronchoscope channel; (3) a brush to calibrate the volume of secretions retrieved; and (4) quantitative culture techniques to aid in distinguishing between airway colonization and serious underlying infection, with a cut-off point of 10^3 cfu/mL for making this distinction. In an in vitro study, this system proved to be the most effective among seven different types tested. Catheters containing a protected brush were passed through an FOB heavily contaminated with saliva to reach the distal sample, i.e., a Petri dish containing a known number of organisms (16). Single-sheathed catheter brushes and telescoping plugged catheter tips with or without distal plugs are, however, also available and have been used for the diagnosis of pneumonia, even though neither has been subjected to the rigorous evaluation reported for the PSB.

Bronchoalveolar lavage requires careful wedging of the tip of the bronchoscope into an airway lumen, isolating that airway from the rest of the central airways. Infusion of at least 120 mL of saline in several (three to six) aliquots is needed to sample fluids and secretions in the distal respiratory bronchioles and alveoli (5,8,17). It is estimated that the alveolar surface area distal to the wedged bronchoscope is 100 times greater than that of the peripheral airway, and that ~1 million alveoli (1% of the lung surface) are sampled with ~1 mL of actual lung secretions retrieved in the total lavage fluid. The fluid return on BAL varies greatly and may affect the validity of results. In patients with emphysema, collapse of airways with the negative pressure needed to aspirate fluid may limit the amount of fluid retrieved. A very small return may contain only diluted material from the bronchial rather than fluid from the alveolar level and results in false-negative results.

Regardless of the technique used, rapid processing of specimens for culture is desirable to prevent loss of viability of pathogens or overgrowth of contaminants. For PSB, it is recommended that the brush be aseptically cut into a measured volume (1 mL) of sterile diluent, most commonly, nonbacteriostatic saline or lactated Ringer's solution (17). For BAL, transport in a sterile, leak-proof, nonadherent glass container is recommended to avoid loss of cells for cytologic assessment. The initial aliquot, which is usually considered as essentially representative of distal bronchi, should be

either discarded or transported separately from the remaining pooled fractions (8,17). Excessive delays in transport to the laboratory should be avoided. Quantitative cultures of freshly collected sputa vs. samples transported at room temperature over an approximately 4-hr period showed selective decreases in *Streptococcus pneumoniae* and *Haemophilus influenzae* isolation rates and fewer bacterial species overall in delayed specimens but higher counts of some other organisms, particularly Gram-negative bacilli (18). Similar results using bronchoscopic specimens were obtained by Moser et al. (19) in an experimental canine model of pneumonia caused by *S. Pneumoniae.* Although no absolute guideline exists, it is generally accepted that not more than 30 min should elapse before specimens are processed for microbiologic analysis. According to some investigators, refrigeration to prolong transport time may be used, but this technique remains controversial (20,21).

Once specimens are received in the laboratory, they should be processed according to clearly defined procedures (see Refs. 17,18 for complete description). Owing to the inevitable oropharyngeal bacterial contamination that occurs in the collection of all respiratory secretion samples, quantitative culture techniques are always needed to differentiate infecting organisms from oropharyngeal contaminants present at low concentrations. Pathogens causing pneumonia are present in lower respiratory tract inflammatory secretions at concentrations of at least 10^5–10^6 cfu/mL, whereas contaminants are generally present at $<10^4$ cfu/mL (22). The diagnostic thresholds proposed for PSB and BAL are based on this concept. As PSB collects between 0.001 and 0.01 mL of secretions, the presence of $>10^3$ bacteria in the originally diluted sample (1 mL) actually represents 10^5–10^6 cfu/mL of pulmonary secretions. Similarly, 10^4 cfu/mL for BAL, which collects 1 mL of secretions in 10–100 mL of effluent, represents 10^5–10^6 cfu/mL (18).

Although PSB samples can be subjected to direct microscopy, the optimal method for smear preparation has not yet been established. For BAL, it is recommended that a total cell count be performed to assess adequacy and a differential count be performed to assess cellularity. For quality assessment, the percentages of squamous and bronchial epithelial cells may be used to predict heavy upper respiratory contamination. Although only a few studies have directly assessed this point, it is proposed that the sample be rejected if $>1\%$ of the total cells are squamous or bronchial epithelial cells (23). Modified Giemsa staining (e.g., Diff-Quik, Scientific Products, McGraw Park, IL U.S.A.) is recommended, as it offers a number of advantages over Gram staining, including better visualization of host-cell morphology, improved detection of bacteria, particularly intracellular bacteria, and detection of some protozoan and fungal pathogens (e.g., *Histoplasma, Pneumocystis, Toxoplasma*, and *Candida* spp.) (18).

Because BAL harvest cells and secretions from a large area of the lung and specimens can be microscopically examined immediately after the procedure to detect the presence or absence of intracellular or extracellular bacteria in the lower respiratory tract, it is particularly well suited to provide rapid identification of patients with pneumonia. In one study in which the diagnostic accuracy of direct microscopic examination of BAL cells could be directly assessed with both histologic and microbiologic postmortem lung features in the same segment, Chastre et al. (24) demonstrated a very high correlation between the percentage of BAL cells containing intracellular bacteria and the total number of bacteria recovered from the corresponding lung samples and the histologic grades of pneumonia. In 10 of 11 lung segments with $\geq 10^4$ bacteria per gram of lung tissue cultured, $\geq 5\%$ of the cells recovered by lavage contained intracellular organisms. In contrast, $< 1\%$ of cells recovered by lavage contained intracellular bacteria of eight of nine noninfected lung segments, and $> 5\%$ of the cells contained intracellular organisms in only one lung segment in which the diagnosis of infection in the same lung segment was excluded. In this study, the morphology of intra- and extracellular bacteria observed in BAL fluid preparations obtained from infected lung segments was consistent with the types of organisms ultimately cultured at high concentrations from lung tissue samples, confirming the potential usefulness of this technique for selecting an effective antimicrobial treatment before culture results are available. Several other studies have confirmed the diagnostic value of this approach (24–30). However, assessment of the degree of qualitative agreement between Gram stains of BAL fluid and PSB quantitative cultures for a series of 51 patients with VAP showed the correspondence to be complete for 51%, partial for 39%, and nonexistent for 10% of the cases (27).

USEFULNESS OF PSB AND BAL TECHNIQUES

The potential contribution of the PSB technique to evaluating ICU patients suspected of having developed VAP has been extensively investigated in both human and animal studies, including eight investigations in which the accuracy of this culture technique was determined by comparison of both histologic features and quantitative cultures from the same area of the lung (19,24,31–36). Despite the need for cautious interpretation, the results of those studies indicate that the PSB technique offers a sensitive and specific approach in identifying the micro-organisms involved in pneumonia in critically ill patients and can differentiate between colonization of the upper respiratory tract and distal lung infection. Pooling the results of the 18 studies evaluating the PSB technique in a total of 795 critically ill patients shows that the overall accuracy of this technique for diagnosing pneumonia is high; sensitivity is 89% (95% CI, 87–93%) and specificity is 94% (95% CI, 92–97%) (37,38).

Despite providing a larger sample of lung secretions than PSB, BAL is subject to the same risk of contamination as protected bronchial brushings. Many groups have now investigated the value of quantitative BAL culture for the diagnosis of pneumonia in ICU patients (24,37,39). Although some investigators have concluded that BAL provides the best reflection of lung's bacterial burden, both quantitatively and qualitatively, others have reported mixed results with poor specificity of BAL fluid cultures for patients with high rates of tracheobronchial colonization. When the results of the 11 studies evaluating BAL fluids from a total of 435 ICU patients suspected of having developed nosocomial pneumonia were pooled, the overall accuracy of this technique was found to be very close to that of PSB; the Q value was 0.84 [Q represents the intersection between the summary receiver operating characteristics (ROC) curve and a diagonal from the upper left corner to the lower right corner of ROC space] (37). Similar conclusions were drawn in another meta-analysis when the results of 23 studies were pooled. These data indicate that the sensitivity and specificity of BAL are $73 \pm 18\%$ and $82 \pm 19\%$, respectively (39).

PATIENTS ALREADY RECEIVING ANTIMICROBIAL THERAPY

Performing microbiologic cultures of pulmonary secretions for diagnostic purposes after initiation of new antibiotic therapy in patients suspected of having developed nosocomial pneumonia can clearly lead to a high number of false-negative results, regardless of the way in which these secretions are obtained. In fact, all microbiological techniques are probably of little value in patients with a recent pulmonary infiltrate who have received new antibiotics for that reason, even for <24 hr. In this case, a negative finding could indicate either that the patient has been successfully treated for pneumonia and the bacteria eradicated or that he had no lung infection to begin with.

In one study, in which follow-up cultures of protected bronchoscopic specimens were obtained in 43 cases of proven nosocomial pneumonia, 24 and 48 hr after the onset of antimicrobial treatment, nearly 40% of cultures were negative after only 24 hr of treatment and 65% after 48 hr (40). Similar results were obtained by Montravers et al. (41) in a series of 76 consecutive patients with VAP evaluated by FOB after 3 days of treatment (41). In this study, using follow-up PSB sample cultures to directly assess the infection site in the lung, 88% of patients had negative cultures after the onset of treatment. Using both PSB and BAL, Souweine et al. (42) prospectively investigated 63 episodes of suspected VAP. On the basis of prior antibiotic treatment, three groups were defined: no previous antibiotic treatments, $n = 12$; antibiotic treatment initiated >72 hr earlier, $n = 31$; and new antibiotic treatment started within the last 24 hr, $n = 20$. Results were entirely consistent with the studies referenced earlier. If patients had been treated with antibiotics but did not have a recent change in antibiotic class, then

the sensitivity of PSB and BAL culture (83% and 77%, respectively) was similar to the that of these methods when applied to patients not being treated with antibiotics. In other words, prior therapy did not reduce the yield of diagnostic testing among those receiving antibiotics given to treat a prior infection. On the other hand, if therapy was recent, the sensitivity of invasive diagnostic methods using traditional thresholds was only 38% with BAL and 40% with PSB. These two clinical situations should be clearly distinguished before interpreting pulmonary secretion culture results however they were obtained. In the second situation, when the patient had received new antibiotics after the appearance of the signs suggesting the presence of pulmonary infection, no conclusion concerning the presence or absence of pneumonia can be drawn if the culture results are negative. Pulmonary secretions, therefore, need to be obtained before new antibiotics are administered, as is the case for all types of microbiologic samples.

POTENTIAL DRAWBACKS OF BRONCHOSCOPIC TECHNIQUES

Four recent studies using a protocol based on postmortem lung biopsies have suggested that, in the presence of prior antibiotic treatment, many patients with histopathologic signs of pneumonia have no or only minimal growth from lung and bronchoscopic specimen cultures (4,9,36,43). In one study, lesions of bronchopneumonia were characterized by bacterial concentrations $>10^3$ cfu/mL of lung tissue in only 55% of lobes and one-third of lung segments with histologic bronchopneumonia even remained negative when cultured. Similarly, in a study of 30 patients who died under mechanical ventilation after having received prior antibiotic treatment, Torres et al. (44) found that quantitative bacterial cultures of lung biopsies using 10^3 cfu/g of tissue as a cut-off point had low sensitivity (40%) and low specificity (45%) and could not differentiate the histologic absence or presence of pneumonia. Interestingly, in this study, the operating characteristics of the PSB technique were very similar to those obtained with lung cultures.

However, it should be remembered that several constraints specific to the evaluation of any procedure used in the diagnosis of bacterial pneumonia must be respected even when using a model in which the gold standard includes both histologic features and quantitative cultures of lung tissue. First, diagnostic methods based on microbiologic techniques can only document, both qualitatively and quantitatively, the bacterial burden present in lung tissue. In no case can these techniques retrospectively identify a resolving pneumonia, at a time when antimicrobial treatment and lung antibacterial defenses might have been successful in suppressing microbial growth in lung tissue. Second, although several studies have shown that once bacterial infection of the lung is clinically apparent, there are at least 10^4 micro-organisms per gram of tissue, this assumption is valid only when patients have not received appropriate antimicrobial treatment after the onset of lung infection

before obtaining lung cultures. Therefore, to evaluate the accuracy of any microbiologic technique using lung cultures as the "gold standard," it is absolutely imperative that no new antibiotics have been introduced during this time interval. Third, using histologic criteria as a reference implies that the patient had not developed a lung infection prior to the episode to be evaluated; otherwise, it would be difficult if not impossible to distinguish a recent infection from the sequelae of the previous one and thus to correctly interpret the results of the diagnostic tool(s) that are being evaluated. Finally, lesions of bronchopneumonia in patients with VAP may be limited to scattered foci of infection in the lungs (9,43). Therefore, if postmortem tissue samples are too small, the histologic diagnosis of pneumonia can be underestimated using technique. However, as a diagnostic technique based on peripheral samplings can provide information only on the lung segment from which specimens had been taken, the so-called "false-negative" results of PSB or BAL, as defined by entire examination of the lung, can be explained by the absence of pneumonia at the very level of the sampling area.

Interestingly, when analysis in these studies was limited to patients with no prior antibiotics or when only lung-tissue cultures were used as the gold standard, results obtained using bronchoscopic techniques for diagnosing nosocomial pneumonia were much better, with a sensitivity always $>80\%$.

Other studies have confirmed the accuracy of bronchoscopic techniques for diagnosing nosocomial pneumonia. In a study evaluating spontaneous lung infections occurring in baboons with permeability pulmonary edema and undergoing mechanical ventilation, Johanson et al. (31) found an excellent correlation between the bacterial content of lung tissue and results of quantitative culture of lavage fluid and PSB specimens. Bronchoalveolar lavage recovered 74% of all species present in lung tissue, including 100% of those present at a concentration $\geq 10^4$ cfu/g of tissue. In this study, PSB specimens identified only 41% of all species recovered from lung tissue. But it must be noted that only micro-organisms present at low concentrations in the lung were missed, as 78% of species present at concentrations $>10^4$ cfu/g of tissue were correctly isolated. Similarly, in a study of 20 ventilated patients who had not developed pneumonia before the terminal phase of their disease and who had no recent changes in antimicrobial therapy, Chastre et al. (24) found that bronchoscopic PSB specimens obtained just after death were able to identify 80% of all species present in the lung, with a strong correlation between the results of quantitative cultures of both specimens (24). Using a discriminative value of $\geq 10^3$ cfu/mL to define positive PSB cultures, this technique identified lung segments yielding $\geq 10^4$ bacteria per gram of tissue with a sensitivity of 82% and a specificity of 89%. These findings confirm that bronchoscopic PSB and/or BAL samples very reliably identify, both qualitatively and quantitatively, micro-organisms

present in lung segments with bacterial pneumonia, even when the infection develops as a superinfection in a patient already receiving antimicrobial treatment for several days.

Values within $1 \log_{10}$ of the cut-off must, however, be interpreted cautiously, and FOB should be repeated in symptomatic patients with a negative ($<10^3$ cfu/mL) result (45). Many technical factors, including medium and adequacy of incubation and antibiotic or other toxic components, may influence the results. The reproducibility of PSB sampling has been recently evaluated. Three groups have concluded that although in vitro repeatability is excellent and in vivo qualitative recovery is 100%, quantitative results are more variable. In 14–17% of patients, results of replicate samples fell on both sides of the 10^3-cfu/mL threshold, and results varied by more than $1 \log_{10}$ in 59–67% of samples (46–48). This variability is presumably related to both irregular distribution of organisms in secretions and the very small volume actually sampled by PSB. The conclusion is that as with all diagnostic tests, borderline PSB and/or BAL quantitative culture results should be interpreted cautiously and the clinical circumstances considered before drawing any therapeutic conclusion.

ARGUMENT FOR BRONCHOSCOPY IN THE DIAGNOSIS OF VAP

The use of invasive techniques, such as FOB, coupled with quantitative cultures of PSB or BAL specimens helps direct the initial antibiotic therapy in addition to confirming the actual diagnosis of nosocomial pneumonia. When culture results are available, they allow for the precise identification of the offending organisms and their susceptibility patterns. Such data are invaluable for optimal antibiotic selection. They also increase the confidence and comfort level of health-care workers in managing patients with suspected nosocomial pneumonia (49). Rello et al. (3) found that 43% of patients required a change in their initial antibiotic regimen based on the results of bronchoscopic evaluation: 27% of patients were receiving ineffective antibiotic therapy, 9% less than optimal antibiotic therapy, and 7% unnecessary antibiotic therapy. Similar results were found by Alvarez-Lerma et al. (1) in a large series of 499 patients with proven VAP. Therefore, antibiotic therapy that is directed by quantitative culture results may be more effective than empiric treatment. It is clear that the inadequate initial management of VAP is associated with increased mortality, and there is evidence that the clinical recognition of treatment failure may be delayed.

The second most compelling argument for invasive bronchoscopic techniques is that they can reduce excessive antibiotic use. There is little disagreement that the clinical diagnosis of nosocomial pneumonia is overly sensitive and leads to the unnecessary use of broad-spectrum antibiotics.

Because bronchoscopic techniques may be more specific, their use would reduce antibiotic pressure in the ICU, thereby limiting the emergence of drug-resistant strains and the attendant increased risks of superinfection (50,51). Most epidemiologic investigations have clearly demonstrated that the indiscriminate use of antimicrobial agents in ICU patients may have immediate and long-term consequences that contribute to the emergence of multiresistant pathogens and increasing the risk of serious superinfections (52). This increased risk is not limited to one patient but may raise the risk of colonization or infection by multidrug-resistant bacterial strains in patients throughout the ICU and even the entire hospital. Virtually, all reports emphasize that better antibiotic control programs to limit bacterial resistance are urgently needed in the ICUs and that patients without true infection should not receive antimicrobial treatment (52).

The more targeted use of antibiotics could also reduce overall costs, despite the expense of bronchoscopy and quantitative cultures, and minimize antibiotic-related toxicity. This is particularly true in the case of patients who have late-onset VAP, in whom expensive combination therapy is recommended by most authorities in the field. A conservative cost analysis performed in a trauma ICU suggested that the discontinuation of antibiotics upon the return of negative bronchoscopic quantitative culture results could lead to a savings of more than $1700 U.S. per patient suspected of VAP (53).

Finally, probably the most important risk of not performing bronchoscopy for the patient is that another site of infection may be missed. The major benefit of a negative bronchoscopy may in fact be to direct the attention away from the lungs as the source of fever. Many hospitalized patients with negative bronchoscopic cultures have other potential sites of infection that can be identified via a simple diagnostic protocol. In a study of 50 patients with suspected VAP who underwent a systematic diagnostic protocol designed to identify all potential causes of fever and pulmonary densities, Meduri et al. (54) confirmed that lung infection was present in only 42% of cases and that the frequent occurrence of multiple infectious and noninfectious processes justifies a systematic search for the source of fever in this setting. Delay in the diagnosis or definitive treatment of the true site of infection may lead to prolonged antibiotic therapy, more antibiotic-associated complications, and induction of further organ dysfunction.

Other than decision-analysis studies (55–57) and one retrospective study (49), only four trials have so far assessed the impact of a diagnostic strategy on antibiotic use and outcome of patients suspected of having HAP using a randomized scheme (7,58–60).

One of the first studies to clearly demonstrate a benefit in favor of the bacteriological strategy was a prospective cohort study conducted in 10 Canadian ICUs (49). The authors compared 92 patients suspected of having developed pneumonia who underwent FOB and 49 patients who did not. Mortality among bronchoscopy patients was 19% vs. 35% for controls

($p = 0.03$). Furthermore, patients managed with a bacteriological strategy received fewer antibiotics and more patients had all their antibiotics discontinued compared with the clinical strategy group, thereby confirming that the two strategies actually differed.

No differences in mortality and morbidity were found when either invasive (PSB and/or BAL) or noninvasive (quantitative endotracheal aspirate cultures) techniques were used to diagnose VAP in three Spanish randomized studies (58–60). However, those studies were based on a relatively few numbers of patients (51, 76, and 88) and antibiotics were continued in all patients despite negative cultures, thereby neutralizing one of the potential advantages of any diagnostic test in patients clinically suspected of having VAP. Concerning the latter, several prospective studies have concluded that antibiotics can indeed be stopped in patients with negative quantitative cultures with no adverse effects on the recurrence of HAP and mortality (6,25).

A large, prospective, randomized trial compared clinical vs. bacteriological strategy for the management of 413 patients suspected of having VAP (7). The clinical strategy included empiric antimicrobial therapy, based on clinical evaluation and the presence of bacteria on direct examination of tracheal aspirates, and possible subsequent adjustment or discontinuation according to the results of qualitative cultures of endotracheal aspirates (Fig. 1). The bacteriological strategy consisted of FOB with direct examination of BAL and/or PSB samples and empiric therapy initiated only when results were positive; a definitive diagnosis based on quantitative culture results of samples obtained with PSB or BAL was achieved before adjusting, discontinuing, or, for some patients with negative direct examination (no bacteria identified on cytocentrifuge preparation of BAL fluid, or PSB samples) and positive quantitative cultures ($>10^3$ cfu/mL for the PSB and $>10^4$ cfu/mL for BAL), starting therapy (Fig. 2). Empiric antimicrobial therapy was initiated in 91% of the patients in the clinical strategy group and in only 52% of those in the bacteriological strategy group. Compared with patients managed clinically, those receiving bacteriologic management had a lower mortality rate on day 14 (25% and 16%; $p = 0.02$), lower sepsis-related organ failure assessment scores on days 3 and 7 ($p = 0.04$), and less antibiotic use (mean number of antibiotic-free days, 2 ± 3 and 5 ± 5; $p < 0.01$). Multivariate analysis showed a significant difference in mortality on day 28 in favor of bacteriologic management, associated with a significant reduction of antibiotic consumption. Pertinently, 22 nonpulmonary infections were diagnosed in the bacteriological strategy group and only five in the clinical strategy group, suggesting that overestimation of VAP may lead to missed nonpulmonary infections. The possible consequences of delayed treatment or definite diagnosis because of antibiotic interference are prolonged antibiotic therapy, more antibiotic-associated complications, and induction of additional organ dysfunctions.

Therefore, our personal judgment is that the use of bronchoscopic techniques to obtain PSB and BAL specimens from the affected area in the lung in ventilated patients with signs suggestive of pneumonia allows a definition of a therapeutic strategy superior to that based exclusively on clinical evaluation. These bronchoscopic techniques, when performed before introduction of new antibiotics, enable physicians to identify most patients who need immediate treatment and help to select optimal therapy, in a manner that is safe and well tolerated by patients. On the other hand, these techniques prevent resorting to broad-spectrum drug coverage in all patients who develop a clinical suspicion of infection. Although the true impact of this approach on patient outcome remains controversial, being able to withhold antimicrobial treatment from some patients without infection may constitute a distinct advantage in the long term by minimizing the emergence of resistant micro-organisms in the ICU and redirecting the search for another (the true) infection site.

In patients with clinical evidence of severe sepsis with rapid worsening organ dysfunction, hypoperfusion, or hypotension, or in patients with a very high pretest probability of the disease, the initiation of antibiotic therapy should not, however, be delayed while awaiting bronchoscopy, and patients should be given immediate treatment with antibiotics. It is probable, in this latter situation, that simplified nonbronchoscopic diagnostic procedures could find their best justification, allowing distal pulmonary secretions to be obtained on a 24-hr basis, just before starting a new antimicrobial therapy.

Despite broad clinical experience with the PSB and BAL techniques, it remains, nonetheless, unclear which one should be used in clinical practice. Most investigators prefer to use BAL rather than PSB to diagnose bacterial pneumonia, because BAL (1) has a slightly higher sensitivity to identify VAP-causative micro-organisms, (2) enables better selection of an empiric antimicrobial treatment before culture results are available, (3) is less dangerous for many critically ill patients, (4) is less costly, and (5) may provide useful clues for the diagnosis of other types of infections. However, it must be acknowledged that a very small return on BAL may contain only diluted material from the bronchial rather than alveolar level and thus may give rise to false-negative results, particularly for patients with very severe COPD. In these patients, the diagnostic value of BAL techniques is greatly diminished and the PSB technique should be preferred (17).

CONCLUSION

The rapid emergence and dissemination of antimicrobial-resistant micro-organisms in hospitals worldwide is a problem of crisis dimensions. The root causes of this problem are multifactorial, but the core issues are clear. The emergence of antimicrobial resistance is highly correlated with selective pressure that results from inappropriate use of antimicrobial agents. Appro-

priate antimicrobial stewardship not only includes the limitation of use of inappropriate agents in patients with VAP, but also improves our ability to diagnose and exclude infection in the ICU setting to avoid administering unnecessary antibiotics in patients without infection.

KEY POINTS

1. Bronchoalveolar lavage and/or PSB permit collection of distal pulmonary secretions with minimal or no upper airway contamination, either through an FOB or, blindly, using an endobronchial catheter wedged in the tracheobronchial tree.
2. Owing to the inevitable oropharyngeal bacterial contamination, which occurs in the collection of all respiratory secretion samples, quantitative culture techniques are always needed to differentiate oropharyngeal contaminants present at low concentration from higher-concentration infecting organisms.
3. Because even a few doses of a new antimicrobial agent can negate the results of microbiologic cultures, pulmonary secretions in patients suspected of having developed pneumonia should always be obtained before new antibiotics are administered.
4. Although appropriate antibodies may improve survival in patients with bacterial pneumonia, use of empirical broad-spectrum antibiotics in patients without infection is potentially harmful, facilitating colonization and superinfection with multiresistant micro-organisms.
5. Bronchoalveolar lavage may also provide useful clues for the diagnosis of other forms of respiratory failure such as pulmonary hemorrhage or other types of infections, especially in immunocompromised patients.
6. Invasive diagnostic methods, including BAL and/or PSB, could improve identification of patients with true bacterial pneumonia and facilitate decisions whether or not to treat, and thus improve clinical outcome.

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10

Mechanisms of Antimicrobial Resistance in the Intensive Care Unit

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INTRODUCTION

Bacteria have evolved myriad mechanisms to protect themselves from antibiotics (1–4). Antimicrobial resistance can be acquired from diverse genetic events ranging from chromosomal mutation to acquisition of exogenous DNA (e.g., plasmids, transposons, integrins, etc.) (3). Antimicrobial resistance occurs by four general mechanisms: enzymatic inactivation or

modification of the antibiotic, alteration in the bacterial target site, permeability barriers to antibiotic influx, and active and efflux pumps (whereby antibiotics are extruded from the bacterial cells) (1–4). Once genetic mutations conferring resistance emerge, they typically increase over time. Endemic and epidemic outbreaks of resistance clones facilitate spread of these difficult-to-treat organisms from hospitals, geographic regions, and countries (5,6). Over the past two decades, resistance rates to a variety of antibiotics have escalated dramatically both globally and within the United States (U.S.A.) (7–10). Clonal spread of organisms carrying antimicrobial resistance determinants between patients, hospitals, cities, states, and countries has fueled the explosive rise in resistance rates globally (7,9,11). Selection pressure from antibiotic use amplifies and perpetuates resistant clones (12). Antimicrobial resistance rates are highest in intensive care units (ICUs), because of the debilitated state of patients, prolonged hospital stays, comorbidities, and liberal use of antimicrobials (13,14). Ventilator-associated pneumonia (VAP) is associated with high rates of multidrug-resistant (MDR) organisms (12,15). Inadequate antimicrobial therapy, as a result of MDR, is an independent risk factor for mortality (16–18). For serious nosocomial infections, broad-spectrum therapy is essential to cover potentially resistant organisms (12,19). Resistance to antibiotics also has been noted in patients with specific risk factors [e.g., bronchiectasis or structural lung disease, immunosuppressive illness or drug therapy, human immunodeficiency virus (HIV) infection, prior antibiotic therapy, cystic fibrosis (CF)]. As patients with CF survive into adulthood, infections with pan-resistant *Pseudomonas aeruginosa, Burkholderia cepacia*, and *Stenotrophomonas maltophilia* may emerge (20). In addition, resistance to a variety of classes of antibiotics has emerged among common community pathogens such as *Streptococcus pneumoniae* (pneumococcus) (7,21) and *Haemophilus influenzae*, important causes of pneumonia, bronchitis, and sinusitis (22). Importantly, a few dominant clones of MDR *Str. pneumoniae* spread rapidly between countries and continents, limiting therapeutic options. In addition, methicillin-resistant *Staphylococcus aureus* (MRSA), formerly encountered only in hospitals or long-term care facilities (LTCFs), has now emerged in community settings (23). Recently, strains of vancomycin-resistant *Sta. aureus* (VRSA) were identified as a result of genetic transfer of resistance determinants from vancomycin-resistant *Enterococcus faecium* (VREF) (24).

In this chapter, we first discuss the dominant mechanisms of resistance among Gram-negative bacteria (GNB), that account for a majority of cases of hospital-acquired pneumonia (HAP) (13–15,25). We next discuss some of the key pathogens responsible for HAP such as *P. aeruginosa*, Enterobacteriaceae, and *Acinetobacter* spp., as well as the rare opportunistic organisms *B. cepacia* and *Ste. maltophilia*. Finally, we review trends in antimicrobial resistance among Gram-positive cocci and discuss implications for future therapy.

ENTEROBACTERIACEAE

Epidemiology and Prevalence

Bacteria within the family Enterobacteriaceae (which include *Enterobacter* spp., *Klebsiella pneumoniae, Escherichia coli, Proteus* spp., *Serratia marcescens*, *Citrobacter* spp.) comprise ~80% of GNB and 50% of clinical isolates identified in hospital laboratories in the U.S.A. (26). *Enterobacteriaceae* account for 20–30% of HAPs and are important causes of nosocomial bacteremias and infections at diverse sites (27). Data from the National Nosocomial Infection Surveillance (NNIS) study noted an increase in the prevalence of HAP due to *Enterobacter* spp. over the past two decades. *Enterobacter* spp. were implicated in 7% of cases of HAP between 1981 and 1986, 11% between 1986 and 1989, and 11% between 1990 and 1996 (28,29). During these same time frames, the prevalence of *K. pneumoniae* as a cause of HAP decreased slightly (from 12% to 7% to 8%) (28,29). Data from 112 medical ICUs in the NNIS system from 1992 to 1997 implicated *Enterobacter* spp. in 9% of pneumonias, 7% of ear–nose–throat (ENT) infections, 5% of urinary tract infections (UTIs), 5% of cardiovascular infections, and 3% of bacteremias (25). In that survey, *K. pneumoniae* accounted for 8% of pneumonias, 4% of ENT infections, 6% of UTIs, 2% of cardiovascular infections, and 4% of bacteremias (25). *Escherichia coli* were implicated in 4% of pneumonias, 3% of ENT infections, 14% of UTIs, 1% of cardiovascular infections, and 3% of bacteremias (25). Other Enterobacteriaceae are less common causes of infections. In Europe, *E. coli* was the most common organism implicated in bacteremias in the SENTRY study, accounting for 20% of episodes, whereas *K. pneumoniae* and *Enterobacter* spp. accounted for 4.7% and 3.9% of episodes, respectively (27). *Enterobacteriaceae* rarely cause community-acquired pneumonia (CAP) in previously healthy patients but may cause CAP in patients with specific risk factors (e.g., advanced age, immunosuppression, alcoholism, residence in LTCFs, structural lung disease, etc.) (30–34).

Antimicrobial Resistance

Antimicrobial resistance is increasing in many species of *Enterobacteriaceae* as well as other GNB (26,35). Antibiotic resistance among *Enterobacteriaceae* (and other GNB) can occur via multiple mechanisms, including target site modifications, changes in porin channels (resulting in impermeability), active efflux pumps, and enzymatic modification (36,37). Production of β-lactamases that inactive penicillins (Pes), cephalosporins (CEPHs), monobactams, and/or carbapenems is the most common mechanism by which GNB acquire resistance to β-lactam antibiotics (36,37) (discussed in detail in what follows).

Gram-Negative β-Lactamases

Chromosomal β-lactamases are almost universally present in GNB (36,38). These enzymes, found in the periplasmic space of GNB, hydrolyze the β-lactam ring, thereby inactivating it before it can bind to penicillin-binding proteins (PBPs) on the cell membrane. Several different types of β-lactamases confer resistance among *Enterobacteriaceae*, including AmpC cephalosporinases; TEM, sulfhydryl variable (SHV), or OXA enzymes; extended spectrum β-lactamases (particularly among *K. pneumoniae*) (36,37,39).

Group I (Type 1) AmpC β-Lactamases

The AmpC (type 1)β-lactamase (Ambler molecular class C) enzymes mediate broad-spectrum β-lactam resistance, including extended-spectrum Pcs and CEPHs, aztreonam, and β-lactam/β-lactamase inhibitor combinations; carbapenems and fourth-generation CEPHs are not affected (40). AmpC β-lactamases are produced by many *Enterobacteriaceae* (e.g., *E. coli, Enterobacter* spp., *Citrobacter freundii, Ser. marcescens, Shigella* spp. *Morganella morganii, Providencia* spp.) as well as by *Acinetobacter* spp. and *P. aeruginosa* (40). The AmpC enzyme is usually not found in other *Enterobacteriaceae* such as *C. diversus, Klebsiella* spp., *Salmonella* spp., or *Proteus mirabilis* (40). Most AmpC enzymes are encoded on the chromosome, but in recent years, numerous plasmid-mediated AmpC enzymes have been reported. Plasmid-mediated class C β-lactamases are detected most frequently in *K. pneumoniae* but may also be found in *K. oxytoca, Salmonella,* and *P. mirabilis* (41). The regulation of AmpC enzyme production is complex and is mediated by the *ampR* gene product, AmpR (42). The expression of AmpR varies by species and explains different rates of resistance to β-lactam agents between species (42). For instance, *E. coli* and *Shigella* spp. contain the *ampC* gene, but the production of AmpC β-lactamase is not induced by β-lactam antibiotics. Only a small amount of β-lactamase is produced, and extended-spectrum cephalosporins (ESCs) are not hydrolyzed (42). In contrast, among nosocomial GNB such as *Enterobacter* spp., *C. freundii, M. morganii, Serratia* spp., and *P. aeruginosa*, AmpC β-lactamase is inducible by β-lactam antibiotics, conferring resistance to ESCs (40). Carbapenems and cefepime are less susceptible to hydrolysis by AmpC than other β-lactams and remain active against these strains (40,43). The carbapenems are strong inducers of AmpC, but the rapid bactericidal action of these agents typically kills the pathogen before a significant quantity of enzyme is produced (44).

Stable derepression (i.e., stably enhanced expression of AmpC β-lactamases) is facilitated by prior clinical use of ESCs (particularly third-generation CEPHs) (36,45,46). Selection of mutants with derepressed AmpC production may occur when CEPHs are used to treat infections with AmpC β-lactamases (40,45). This phenomenon of *inducible* β-lactamase expression is clinically significant. It should be emphasized that strains with inducible

AmpC production *appear susceptible* to third-generation CEPHs in vitro. However, during treatment with CEPHs, mutants that produce the AmpC enzyme constitutively, or at high levels, are selected and become the predominant population. These derepressed mutants are *highly resistant* to third-generation CEPHs (44). This was the mechanism responsible for the significant increase in resistance to third-generation CEPHs noted among *Enterobacter* spp. during the 1980s (45). By the mid-1990s, 35–50% of nosocomial isolates of *Enterobacter* and *Citrobacter* expressed derepressed *amp*C phenotype (47). Treatment of these organisms with third-generation CEPHs may lead to clinical failures and breakthrough bacteremias (48,49). Some strains of *Enterobacter* acquire additional mutations in a gene known as *amp*D, which results in constitutive high-level expression of AmpC β-lactamase (50). Carbapenems (27,35,51,52) or fourth-generation CEPHs (cefepime or cefpirome) (35,44,53) are the preferred agents for serious infections because of AmpC β-lactamase-producing strains. Combining one of these agents with an aminoglycoside may confer synergy in some cases. The newer carbapenem, ertapenem, usually covers AmpC-producing strains of *Enterobacteriaceae* (54,55), but is not active against *P. aeruginosa*. Resistance to carbapenems is rare among *Enterobacteriaceae* (26,35,54), but can occur when dual mutations are present (i.e., high-level AmpC expression and loss of outer membrane porin proteins) (50,56).

Common Group 2 (Molecular Class A) β-Lactamases

In addition to chromosomal β-lactamases, plasmids (extrachromosomal genetic elements) containing diverse β-lactamases are important causes of antibiotic resistance in ICUs. TEM-1 is the most common β-lactamase found in *E. coli* and is also found in *K. pneumoniae, Enterobacter* spp., *H. influenzae,* and *Neiserria gonorrheae,* among others (57,58). The TEM-1 enzyme is plasmid -mediated and can also be transferred to the chromosome by smaller genetic elements, transposons (54). TEM-1 confers resistance to ampicillin, ticarcillin, and CEPHs but does not affect ESCs, cephamycins, or monobactams (57,58). Additional plasmids, termed SHV, were subsequently described in *K. pneumoniae* and other *Enterobacteriaceae*, especially *E. coli* (58). Plasmids within the SHV-1 family have also been translocated to chromosomes via transposons (58). Unlike TEM-1, SHV-1 enzymes can hydrolyze third-generation CEPHs when produced in large amounts and may be resistant to some β-lactam/β-lactamase inhibitor combinations (59,60). Additional families of β-lactamases were subsequently described (e.g., OXA and PER) (61–64).

Treatment of Infections caused by *Enterobacteriaceae*

The carbapenems are the most active agents against β-lactamase-producing *Enterobacteriaceae* (>99% susceptibility) (26,27,35,54). A recent survey in

the U.S.A. of >235,000 isolates of *Enterobacteriaceae* detected only three strains resistant to carbapenems (0.001%) (26). Cefepime is active against >98% of isolates of *Enterobacteriaceae* in most studies (26,27,35). Data from NNIS in medical ICUs in the USA in 1998 noted that ~90% of strains of K. *pneumo*niae were susceptible to ceftazidime; only 66% of *Enterobacter* spp. were susceptible (25). Piperacillin/tazobactam is the most active of the Pcs, with susceptibility rates exceeding 85–90% (26,27). Ampicillin/sulbactam has limited activity against *Enterobacteriaceae* (45–57% susceptibility) (26,27). Coresistance to multiple antibiotics is common. In the SENTRY study in the USA from 1997 to 2000, 80% of ceftazidime-resistant *Enterobacter* spp. strains were also resistant to piperacillin/tazobactam (35). Further fluoroquinolone (FQ) resistance was far more common among ceftazidime-resistant strains.

During the period of study (1997–2000), resistance rates to β-lactam antibiotics remained relatively stable (35). Among *Enterobacter* spp., resistance to aztreonam, ceftazidime, and ceftriaxone ranged from 12.3% to 21.2%; and in *K. pneumoniae* from 5.9% to 6.8% (35). Other investigators cited stable rates of resistance in the USA from 1998 to 2001 to β-lactams, but noted significance increases in FQ-resistant rates (26). Among non-β-lactam antibiotics, aminoglycosides (particularly amikacin) have excellent activity against *Enterobacteriaceae*, with >95% susceptibility (26,27). Among *Enterobacter* spp., resistance to aztreonam, ceftazidime, and ceftriaxone ranged from 12.3% to 21.2%, whereas that in *Klebsiella* ranged from 5.9% to 6.8%. Activity of FQs is generally good (85–97%) (26,27), but resistance to these agents can emerge (26,65,66). Interestingly, rates of FQ resistance among *Enterobacteriaceae* were higher in non-ICU patients or outpatients compared with ICU patients in one recent study of 23 hospitals in the USA (67), likely reflecting excessive use of FQs in outpatient settings. Unfortunately, strains of MDR *Enterobacteriaceae* have been isolated with increasing frequency (68,69) and limit therapeutic options.

Extended-Spectrum β-lactamases

Since the 1980s, diverse mutations of one or more amino acids around the active site of TEM, SHV, or OXA genes have led to myriad β-lactamases capable of hydrolyzing ESCs, including ceftazidime (46,70–72). These extended-spectrum β-lactamases, termed ESBLs, are most often associated with *K. pneumoniae* and *E. coli* but are carried on plasmids and are transferable to other genera of enteric bacilli, including *P. mirabilis*, *Citrobacter, Serratia,* and others (70,73,74). There are at least 115 TEM ESBLs, 42 SHV ESBLs, and 14 ESBLs in the OXA family; the number of identified ESBLs is growing so rapidly that a web site tracks the number and properties delineating these enzymes (61). Extended-spectrum β-lactamases ESBLs hydrolyze ESCs with an oxyimino side chain. These include ceftazidime, ceftriaxone, cefotaxime, and the oxyimino-monobactam aztreonam. While

most enzymes have greater hydrolytic activity against ceftazidime and aztreonam than cefotaxime, the reverse is true for SHV ESBLs and for certain TEM mutants with different amino acid substitutions (72). Risk factors for colonization or infection with ESBL-producing *K. pneumoniae* include prior use of antimicrobials, residence in an ICU, indwelling devices, and increased severity of illness (75,76). Use of ESCs (particularly ceftazidime) promotes the emergence of ESBLs (69,77).

Since the initial detection of ESBLs among *K. pneumoniae* in Western Europe in the early 1980s, ESBLs spread rapidly worldwide. Endemic and epidemic spread of ESBLs within hospitals or within regions can be devastating (75,76,78,79). In one ICU outbreak, 72 patients (38%) acquired ESBL-producing *K. pneumoniae* after admission to the ICU (often within the first week) (80). Risk factors for acquisition of ESBL were the presence of arterial and urinary catheters and duration of mechanical ventilation (MV) or urinary catheterization (80). In another outbreak of MDR-*K. pneumoniae*, prior receipt of third-generation CEPHs or aminoglycosides was an independent risk factor for colonization or infection (79).

The prevalent type of enzyme varies by geographic location (36,39,77,81–83). The ESBL-producing organisms should be considered resistant to all Pcs, CEPHs, and aztreonam (84). Some isolates are susceptible to β-lactamase inhibitor combinations, but these compounds are not consistently reliable.

Estimates of ESBL-producing isolates among *K. pneumoniae* range from 12% in ICU patients in the U.S.A., 25% of isolates surveyed in the Western Pacific region, 45% of isolates surveyed in Latin America, to 19% among bloodstream isolates in a global surveillance program (85–88). Ceftazidime resistance rates among *K. pneumoniae* in the U.S.A. climbed from <3% in the 1980s to 14% by the mid-1990s (89–92); in some hospitals, >40% of *K. pneumoniae* are resistant to ceftazidime (59). Some ESBLs, encoded on large 80–300 k plasmids, also carry resistance genes to aminoglycosides, tetracyclines, trimethoprim/sulfamethoxazole (T/S), and aminoglycosides (39,50), resulting in MDR (39,72,85,86,93). TEM and SHV ESBLs do not effectively hydrolyze the cephamycins—cefoxitin and cefotetan—because these are not oxyimino CEPHs. However, some ESBL-producing strains have acquired a plasmid-mediated *amp*C, gene, which hydrolyzes the cephamycins and also confers resistance to β-lactam/β-lactamase inhibitor combinations (e.g., piperacillin/tazobactam, ampicillin/sulbactam, and ticarcillin/clavulanate) (81,94,95). Subsequent to initial reports of this occurrence, there have been numerous others from many countries, including Europe, Asia, and the U.S.A. (56,95,96). Recently, PER-1, an ESBL initially found in a *P. aeruginosa* strain in France (63), was subsequently detected in *Acinetobacter* spp. and *P. aeruginosa* in Turkey (62) and Italy (63). Lately, PER-1 was detected in *Acinetobacter* spp. in Korea (64). In addition, porin-deficient mutations conferring resistance to cephamycins

have been described (97). This mutant strain also exhibited higher MICs to FQs, probably because of the porin deficiency.

Treatment of Infections caused by ESBL-Producing Organisms

Cephalosporins should not be used to treat infections caused by ESBL-producing organisms, irrespective of in vitro susceptibility tests (87,98). Detecting in vitro resistance to CEPHs with ESBL-producing organisms is problematic, because of the "inoculum effect" (99,100). The ESBL-producing organisms appear susceptible at a standard inoculum of 10^5 but have highly elevated MICs at higher inoculums of 10^7 or 10^8 (71,99). This "inoculum effect" is noted with third-generation CEPHs and the "fourth-" generation CEPH, cefepime (71), and is clinically significant. Clinical failures are common when CEPHs are used to treat infections caused by ESBL-producing organisms (59,87,98,101–104). Further, β-lactam/β-lactamase inhibitor combinations are not reliable against ESBL when an AmpC-enzyme coexists (81,94).

Fluoroquinolones are active against some ESBL-producing organisms, but FQ resistance and ESBL production often coexist (85,93,94,98). The prevalence of FQ resistance among ESBL-producing GNB ranges from 10% to 40%. Initial reports of FQ resistance were chromosomally mediated, but plasmid-mediated FQ resistance was recently noted in *K. pneumoniae* (105). The association of FQ resistance in ESBL-producing GNB is probably multifactorial and is likely related to exposure of these organisms to antibiotic selection pressures in hospitals (72). A survey of a group of ESBL isolates showed that 40% were resistant to both gentamicin and ciprofloxacin (CIP); the authors suggest that this may be related to a selected decrease in membrane permeability (93). In a global study of *K. pneumoniae* bacteremias, 60% of CIP-resistant isolates produced ESBLs compared to only 16% of CIP-susceptible strains (106). As previously noted, the emergence of a porin deficient mutant with elevated MICs to FQs was described (97). In summary, FQs should be effective against isolates displaying in vitro susceptibility, but they cannot be considered reliable agents for empirical treatment of many ESBL-producing or MDR strains (93,102).

The carbapenems (imipenem/cilastatin or meropenem) are the best agents to treat serious infections caused by ESBL-producing *Enterobacteriacae* (26,87,102). They are highly stable to β-lactamase hydrolysis and penetrate porins easily because of their small molecular size and zwitterionic structure.

Endemic and epidemic spread of ESBLs within hospitals can be devastating (75,76,79). When ESBLs are endemic within hospitals, limiting the use of ESCs (particularly ceftazidime) and switching to carbapenems or β-lactam/β-lactamase inhibitor combinations may curtail outbreaks (76,78,107,108). In another study, reducing the use of ESCs and aminoglycosides curtailed an epidemic of ESBL-producing *K. pneumoniae* (79). Some

ESBL-producing *K. pneumoniae* remain susceptible to β-lactams (77,78,108). Alterations in the active enzyme site in ESBLs facilitate entry of β-lactamase inhibitors through the cell wall, making ESBLs more susceptible to inhibition than the parent compounds (52). In this context, β-lactam/β-lactamase inhibitor combinations may be efficacious. However, excessive use of single antibiotic classes may promote emergence of resistance (69). For example, a rise in use of piperacillin/tazobactam was associated with increased rates of *Acinetobacter* resistance to piperacillin/tazobactam and cefotaxime (107). Overuse of imipenem/cilastatin for ceftazidime-resistant ESBL-producing *K. pneumoniae* was associated with imipenem resistance in *P. aeruginosa* and *Acinetobacter baumannii* (59,69). Stepwise increases in resistance among *K. pneumoniae* during treatment with imipenem has also been noted (38,64).

Other Mechanisms of Antimicrobial Resistance Among GNB

Diverse enzymes inactivate other antibiotic classes [(e.g., aminoglycoside modifying enzymes, chloramphenicol acetyltransferase, alterations in dihydrofolate reductase (confers resistance to trimethoprim); DNA gyrase and topoisomerase IV (confers resistance to FQs) (4,66,109)]. Alterations in porin proteins on the outer membrane of GNB reduce permeability to β-lactam, carbapenem, or FQ antibiotics (66,109). Energy-dependent efflux pumps encoded in plasmids or chromosomes confer resistance to multiple antibiotic classes (e.g., β-lactams, FQs, chloramphenicol, macrolides, tetracyclines) (4,66,109). (A detailed discussion of these myriad mechanisms is beyond the scope of this chapter.) Because resistance to FQs is escalating dramatically, we next discuss the issue of FQ resistance.

Resistance to FQs

Fluoroquinolone use has been widely accepted in both hospital and community setting because of ease of administration and antibacterial spectrum. These agents have a novel mechanism of action among antibiotics, by inhibiting DNA synthesis (65,66). This inhibition occurs by interaction of the FQ with DNA complexes and one of two target enzymes: DNA gyrase and topoisomerase IV (66). Subunits GyrA and GyrB of DNA gyrase are analogous to the ParC and ParE subunits of topoisomerase IV. Fluoroquinolones block these enzymes and cause a physical barrier to replication, RNA polymerase, and DNA helicase, leading to cell death.

Resistance to FQs can also occur by changes by decreased permeability or active efflux of the drug. DNA gyrase is the main drug target for GNB; topoisomerase IV is the primary target in Gram-positive bacteria (65,66). Spontaneous mutations of the genes mediating these enzymes occur at low frequency in large bacterial populations. The first step in Gram-negative FQ resistance most often occurs via alterations in DNA

gyrase. Additional mutations that alter the secondary target enzyme, topoisomerase IV, produce higher levels of resistance. Fluoroquinolones that achieve concentrations exceeding the MIC of the first-step mutants at the site of infection are not likely to select spontaneous mutants because the mutants are killed. However, first-step mutations in *P. aeruginosa* yield CIP MICs above the achievable concentration, and FQ resistance can easily emerge with this agent (or other FQs) (65,110).

To reach the drug target in Gram-negative organisms, FQs must transgress the outer membrane and the cytoplasmic membrane. The molecular size of FQs is small and the charge characteristics are favorable, so that they penetrate the outer membrane through porin channels by diffusion. Fluoroquinolones then diffuse through the cytoplasmic membrane. Decreases in porin permeability may increase MICs (97), but this mechanism *alone* does not cause high-level resistance. More important is the reduced accumulation of drug caused by efflux systems that actively remove the drug from the cell (111). Most efflux pumps can extrude other antimicrobials besides FQs and confer MDR. Expression of the efflux system is regulated, and a chromosomal mutation causes an increase in the pump components, resulting in resistance (65,66).

Resistance to FQ usually results from two types of chromosomal mutations described earlier: reduced affinity for DNA gyrase and increased efflux pumps. Plasmid-mediated resistance to FQ was recently described in *K. pneumoniae* (105). An AmpC-type β-lactamase was coexpressed on this plasmid. The mechanism appears to be novel and involves production of a protein, which protects DNA gyrase from inhibition by FQs (112). Currently, plasmid-mediated resistance is rare (113).

A survey of global patterns of susceptibility against 48,440 Enterobacteriaceae clinical isolates shows high-susceptibility rates to FQs (>90%) (114). However, a survey of antimicrobial susceptibilities of *Enterobacteriaceae* in the U.S.A. from 1998 to 2001 showed that resistance to FQs was increasing more rapidly than all antibiotics studied (115). The increase in resistance was most pronounced in *E. coli, P. mirabilis,* and *Enterobacter cloacae*. Importantly, ~30% of isolates of *P. aeruginosa* in the U.S.A. have acquired resistance to FQs (10,11,115). In addition, FQ resistance among other GNB (including *Enterobacteriaceae*) has increased globally over the past decade, particularly in countries outside of North America (10,27,44). The rapid emergence of resistance in developing countries may reflect widespread use of FQ antibiotics (116). The rapid emergence of FQ resistance in *P. aeruginosa* is predictable, as a single mutation in this pathogen increases the MIC above the peak serum concentrations, allowing the resistant spontaneous mutants to become the predominant population in an infection. Resistance among other bacteria is facilitated by selection pressure (e.g., prophylactic use of FQ in oncology patients with chemotherapy-induced neutropenia (117–119) and increasing use of FQs in the

community) (120,121) and clonal spread of resistant organisms (122). In Barcelona, Spain, rates of CIP resistance in *E. coli* are sufficiently high so that CIP prophylaxis is no longer effective during episodes of neutropenia in cancer patients (119). In fact, bacteremia due to GNB was more common in patients receiving CIP prophylaxis!

The increased use of FQs with less antipseudomonal activity may also play a role in *P. aeruginosa* resistance (123). Susceptibilities to CIP among *P. aeruginosa* isolates at a tertiary-care hospital in Chicago decreased following substitution of ofloxacin for CIP (123). The expanding use of FQs with less antipseudomonal activity in the community may contribute to increasing *P. aeruginosa* resistance. In a recent case–control study, recent FQ use, residence in an LTCF, recent aminoglycoside use, and older age were the independent risk factors for FQ-resistant *E. coli* and *K. pneumoniae* (124). Selecting the FQ with the best activity against the targeted organism and maximizing concentration-dependent pharmacodynamic properties are important to retain the effectiveness of this class of antibiotics (125).

Fluoroquinolone resistance has also become prevalent in other GNB that require multiple mutations for resistance to occur. Among the pathogens, best studied include *Campylobacter jejuni* and *E. coli*. Resistance in *C. jejuni* emerged in animal and human populations concurrently in Europe when FQs began to be used for animal husbandry (126–129). In the 1990s, FQ resistance in *E. coli* emerged in Europe (38,130). In Spain, healthy children and adults were found to have FQ-resistant *E. coli* fecal carriage during the 1990s, and FQ resistance in poultry was documented (38,131). Together with the emergence of FQ resistance in *Campylobacter* spp. (128), these data suggest that food sources may be a reservoir of resistance in humans.

PSEUDOMONAS AERUGINOSA

Epidemiology and Prevalence

Pseudomonas aeruginosa, an aerobic Gram-negative rod, is a common cause of opportunistic infections in debilitated or critically ill patients in ICUs (132). It is endowed with a formidable array of virulence factors that facilitate attachment to host cells, tissue invasion, and systemic disease (132). The pathogen primarily colonizes or infects patients with impaired host defenses (e.g., immunosuppressive medications, burns, neutropenia, organ transplant recipients, need for MV) (15,132,133). In the normal host, invasive infections occur when there is disruption of normal skin or mucous membranes, or insertion of medical devices such as urinary or intravascular catheters, or endotracheal tubes (132). *Pseudomonas aeruginosa* accounts for 16–20% of HAPs and even higher rates [20–50%] in mechanically ventilated

patients in ICUs (12,25,133–140) and in patients with acute respiratory distress syndrome (141–143). The bacteria is a common cause of late-onset (>4 days) HAP but rarely causes "early onset" (<4 days) HAP in the absence of other risk factors (12,18,135,137,140,144).

Mortality associated with *Pseudomonas* HAP is 40–70%, which partly reflects the debilitated state of patients infected with this pathogen; attributable mortality is lower from 14% to 38% (133,135–138). Further, *P. aeruginosa* is the second most common GNB causing nosocomial infections. A survey of clinical isolates of Gram-negative aerobes [35,790 organisms] from 396 ICUs in the U.S.A. from 1990 to 2000 noted that *P. aeruginosa* constituted 19.7% of isolates (145). Data from 112 medical ICUs in the NNIS system from 1992 to 1997 implicated *P. aeruginosa* in 21% of pneumonias, 13% of ENT infections, 10% of UTIs, 5% of cardiovascular infections, and 3% of bacteremias (25). Although primarily a *nosocomial* pathogen, *P. aeruginosa* has been implicated in community-acquired infections (e.g., otitis externa in swimmers and diabetic patients) (146), skin infections following the use of whirlpools and hot tubs (147), puncture wounds of the feet (148), respiratory infections in patients with CF (128), bronchiectasis (149), severe chronic obstructive pulmonary disease (COPD) (132,150), or HIV infection (151). In the absence of specific risk factors, it rarely causes CAP (152).

Pseudomonas aeruginosa is ubiquitous in nature and can be isolated from soil, water, plants, vegetables, and the hospital environment (132,153). Owing to its minimal nutritional requirements, the pathogen can grow in diverse environments and at widely different temperatures, making it an effective opportunistic pathogen (132). In hospitals, it has numerous reservoirs that include sinks, respiratory equipment, cleaning solutions, flowers, uncooked vegetables, and the hands of medical personnel (132,133,154). Outbreaks of nosocomial *P. aeruginosa* infections have been linked to contaminated environmental sources or cross-infection from colonized patients or health-care workers (155,156). Evidence does not support airborne transmission (153).

Pseudomonas aeruginosa is a classic example of an organism that forms a biofilm (132,157). Biofilms develop preferentially on inert surfaces such as endotracheal tubes or on dead tissue such as sequestra of bone and lung tissue (158). They constitute a protected mode of growth, which allows for survival in a hostile environment. Like other biofilms, *P. aeruginosa* biofilms are developed communities with individual bacterial cells embedded in an extracellular polysaccharide matrix that are inherently resistant to antimicrobial treatment (132). Chronic bacterial infections often involve biofilm formation (158). Mucoid strains of *P. aeruginosa* are commonly isolated from the sputum of patients with CF (158,159). An interplay between biofilm formation and antibiotic resistance has been noted. A specific gene, PvrR, in *P. aeruginosa* isolates from CF patients, regulates conversion

between antibiotic susceptible and resistant forms, and also affects biofilm formation (157).

Hospitalization increases the carriage rates, particularly among severely burned patients, those receiving MV, and those on broad-spectrum antibiotics (135,160,161). Colonization may proceed to invasive infection, including pneumonia, UTI, burn-wound infections, and septicemia (133,153,154). Oropharyngeal or tracheal colonization rises with increased length of hospitalization and severity of illness and is an important risk factor for pseudomonal HAP (144,153,155). Prior use of antibiotics increases the risk of colonization or infection with *P. aeruginosa* (12,18,137,153).

Antimicrobial Susceptibility

Pseudomonas aeruginosa is intrinsically resistant to most antibiotics and may acquire resistance during therapy (132,160,161). The most active antibiotics (>75% susceptible) are carbapenems, amikacin, piperacillin, cefepime, ceftazidime, and tobramycin (90,109,115,162,163). Rates of resistance are higher in larger, teaching hospitals and are strongly influenced by prior antibiotic use in ICUs (12,90,109,135). In addition, initially susceptible strains may acquire drug resistance during treatment (134,164). This has been reported with virtually all classes of drugs. A recent large surveillance study in the U.S.A. from 1998 to 2001 of >70,000 isolates of *P. aeruginosa* cited the following susceptibility rates among hospitalized ICU and non-ICU patients: piperacillin/tazobactam (>90%), amikacin (91–94%), meropenem or imipenem (74–87%), ceftazidime (80–89%), cefepime (80–82%), CIP or levofloxacin (69–79%) (115). During this period (1998–2001), rates of resistance to ceftazidime and FQs increased (by 5–6%), whereas susceptibility rates to other agents remained relatively stable (115). A survey of 396 ICUs in the U.S.A. from 1990 to 2000 noted stable rates of resistance to β-lactams among *P. aeruginosa* (~15% of isolates were resistant to ceftazidime) (91,145). Similar trends (i.e., stable rates of resistance to β-lactams) were noted from NNIS data over the past decade. In contrast, resistance to FQs has increased rapidly among *P. aeruginosa* (11,67,115,145,165). The NNIS data from 2001 revealed that 27.3% of *P. aeruginosa* isolates in ICUs were resistant to FQs (a 55% increase compared with 1995–1999); 17.7% of isolates were resistant to imipenem (165). A separate study analyzed 8244 isolates of *P. aeruginosa* collected in ICUs in the U.S.A. between 1990 and 2000; resistance to FQs rose 3-fold to ~30% nationwide (145). Among FQ-resistant strains, cross-resistance to structurally unrelated compounds is common (11,115). A study of >5000 isolates from North America found a direct correlation between FQ susceptibility and susceptibility patterns to other agents such as piperacillin/tazobactam, ceftazidime, and tobramycin (11).

Antimicrobial resistance develops in 20–50% of patients with *Pseudomonas* HAP, even with appropriate therapy (2,134,138,160). Resistance develops by multiple mechanisms, including production of chromosomal type 1 β-lactamases, ESBLs, metallo-β-lactamases (carbapenemases), aminoglycoside-modifying enzymes, changes in outer membrane permeability, and active efflux (2,109,160). Multidrug-resistant *P. aeruginosa* may emerge in a stepwise fashion after exposure to antibiotics (109,164). Prior exposure to broad-spectrum β-lactams is a risk factor for β-lactam resistance. In one medical center, a significant correlation was noted between antecedent use of ceftriaxone, cefotaxime, ceftazidime, and piperacillin and resistance to these compounds among bacterial strains (including 155 isolates of *P. aeruginosa*) (92). Similarly, Manian et al. (102) analyzed resistance rates among 594 initial and repeat Gram-negative isolates from 287 patients in ICUs. Sixty-one percent of isolates were *Enterobacter* or *P. aeruginosa*. Resistance rates to CEPHs and Pcs were higher among repeat isolates; this resistance was linked to prior treatment with third-generation CEPHs (102).

A review of 19 patients infected with MDR-*P. aeruginosa* isolates from a tertiary-care hospital in Boston documented extensive antibiotic exposure in all cases (160). Ceftazidime, CIP, imipenem, and piperacillin/tazobactam were the agents most often prescribed prior to isolation of pan-resistant strains. These investigators also examined the relative risk of emergence of resistance in *P. aeruginosa* isolates exposed to four different antimicrobial agents: ceftazidime, CIP, piperacillin, and imipenem (166). Overall, resistance emerged during treatment in 10% of 271 patients with *P. aeruginosa* infections. Pulsed field gel electrophoresis typing confirmed that these resistant organisms evolved from initially susceptible populations. Imipenem had the highest overall risk of emergence for resistance, ceftazidime, the lowest, while CIP and piperacillin were the intermediate in this regard. Although this was an observational study with a relatively small number of patients (e.g., 37 patients received imipenem), previous randomized trials of HAP noted higher risk of emergence of resistance in patients receiving imipenem compared with piperacillin/tazobactam (167) or CIP (134). European investigators confirmed the strong relationship between antecedent antibiotic use and development of antibiotic-resistant *P. aeruginosa* (135,168). In one study of pseudomonal VAP, independent risk factors for piperacillin resistance (by multivariate analysis) included underlying medical condition, which is rapidly or ultimately fatal and previous exposure to FQs (135). Not surprisingly, piperacillin-resistant strains were more likely to be resistant to multiple antibiotic classes compared with piperacillin-susceptible strains. Interestingly, prior receipt of FQs has previously been shown to be an independent risk factor for carriage and persistent colonization with MRSA (169–171), as well as for *A. baumannii* (172) infections.

Mechanisms of Resistance

Resistance to β-lactam antibiotics is usually mediated by overproduction of ampC chromosomal β-lactamases, that are universally present in *P. aeruginosa* (173). This results in clinically significant resistance to all third-generation CEPHs. The so-called fourth-generation CEPHs, cefepime and cefpirome, are more active than the third-generation compounds because of their higher outer membrane permeability, lower affinity for β-lactamase, and higher avidity for PBPs (2). These CEPH-resistant isolates often remain susceptible to extended-spectrum Pcs or carbapenems (40,167). However, strains of *P. aeruginosa* may acquire clinically significant resistance to these agents by a combination of outer-membrane impermeability and hyperproduction of β-lactamase (2,160). Plasmid-mediated β-lactamases (typically PSE-1 and PSE-2) also confer resistance but are more common in *Enterobacteriaceae* (40,174). Within the past decade, ceftazidime-resistant *P. aeruginosa* because of a variety of ESBLs (e.g., SHV, TEM, PER, VEB) have been reported (62,63,175–177). A recent study in Thailand documented spread of an integron conferring multiple antimicrobial resistance determinants to ESBL-producing strains of *P. aeruginosa* (177).

For the carbapenems, imipenem, and meropenem, the major resistance mechanism is a loss of the specific porin OprD (2,132,178). This may occur in up to 50% of patients treated with imipenem for >1 week (2). Studies of organisms overexpressing OprD show that it is relatively specific for carbapenems and does not mediate passage of other β-lactams and quinolones. Kohler et al. (178) examined the respective contributions of OprD and efflux on carbapenem resistance in *P. aeruginosa* (178). Previous work had demonstrated that the MexAB–OprM efflux system includes most β-lactams in its spectrum (179). By constructing mutants with varying combinations of OprD and MexAB-OprM expression, these workers showed that meropenem MICs were strongly influenced by efflux while imipenem was unaffected (178).

Plasmid-mediated metallocarbapenemases, initially described in Japan (40,174,180), remain rare in the U.S.A. (132). These metallocarbapenemases hydrolyze carbapenems and a variety of Pcs and CEPHs and are not inhibited by clavulanic acid, sulbactam, or tazobactam (181). The predominant carbapenemase in Japan, termed IMP-1, has also been found in Europe (182,183); other novel ones within that family (i.e., IMP-2–IMP-7) have been described in Asia (184) and Canada (173). The genes responsible for IMP-1 production are termed bla_{IMP} and are mediated by integrons carried by large plasmids (174). In one study of 69 clinical isolates of *P. aeruginosa* harboring bla_{IMP} (174), risk factors for bla_{IMP}-positive *P. aeruginosa* strains included prolonged hospitalization, antineoplastic chemotherapy, corticosteroid therapy, and indwelling urinary catheters. A second family of metallo-β-lactamases, the VIM types, has been detected in several countries

and has been associated with clonal spread and hospital outbreaks (175,185). Selection pressure is a strong risk factor for emergence of imipenem resistance (12,59,89,186,187). Other factors associated with carbapenem-resistance include residence in ICUs or large teaching hospitals, respiratory source, and organ transplantation (134,186). Imipenem-resistant *P. aeruginosa* among residents of nursing homes and LTCFs reflects prior antibiotic usage patterns (89).

The high-intrinsic antibiotic resistance observed among *P. aeruginosa* historically was attributed to impermeability across the outer membrane. However, it has become increasingly clear that this is largely attributable to the activity of several efflux pump (37,188). At least five appear to be present on the basis of genomic data (189).

Resistance to aminoglycosides is conferred by enzymatic modification by plasmid-mediated acetylating, adenylating, or phosphorylating enzymes (132,190). Less commonly, low-level resistance to aminoglycosides occurs because of reduced penetration across the outer membrane (132). Resistance to FQs can occur via mutations in DNA gyrase, decreased permeability, or active efflux of the antibiotic (66). Quinolone-resistant strains of *P. aeruginosa* are relatively common. Factors associated with FQ resistance include monotherapy for HAP (134), prior use of FQs (66), CF (191), sequestered sites, and residence in ICUs (89). The most common mutations affect DNA gyrase (192) or efflux pumps (193). Quinolones may also select for mutants that are resistant to other classes of antibiotics, called multiple antibiotic resistance mutants. At least three related efflux mutations (*nalB-nfxB-* and *nfxC*) have been observed in the laboratory. These affect regulatory genes that lead to overexpression of efflux pumps (178,194). These mutants are cross-resistant to FQs, chloramphenicol, tetracyclines, and carbapenems (178).

Treatment

Mortality associated with *P. aeruginosa* is high (>40%), which in part reflects the debilitated state of patients infected with this organism (16,136,137). Clinical failure rates, persistent of the organism(s), and relapse rates are high, even with appropriate therapy (133,134,138). Although randomized, controlled therapeutic trials have not been performed, retrospective studies (195) suggest that combination therapy may lessen mortality for serious pseudomonal infections. We agree with other experts (15,115,133,196) that combination therapy with two active agents is warranted for serious infections caused by *P. aeruginosa*. In this context, an antipseudomonal β-lactam (e.g., piperacillin, cefepime, ceftazidime, or a carbapenem) plus an aminoglycoside is preferred, as this combination may achieve synergy. Alternatively, an antipseudomonal β-lactam plus

CIP (dose 400 mg IV q8 hr) (134) or levofloxacin (dose 750 mg/day) (197) can be administered. The role of inhaled or nebulized antibiotics is not known. Aerosolized tobramycin has been shown to reduce colony counts and improve lung function in patients with CF (128,198) or bronchiectasis (149) chronically infected with *P. aeruginosa*, but data assessing its role in other patient populations are lacking.

ACINETOBACTER SPP.

Epidemiology and Prevalence

Bacteria within the genus *Acinetobacter* are encapsulated, aerobic Gram-negative coccobacilli that cause opportunistic infections in critically ill patients (172,199–203). There are 19 *Acinetobacter* genospecies, but *A. calcoaceticus–A. baumannii* complex accounts for the vast majority of infections (172,201,203). *Acinetobacter* spp. are 3 to 10-fold less common than *P. aeruginosa* as causes of nosocomial infections (204). Data from 112 medical ICUs in the NNIS system from 1992 to 1997 implicated *Acinetobacter* spp. in 6% of pneumonias, 2% of ENT infections, 1% of UTIs, 2% of cardiovascular infections, and 2% of bacteremias (25). *Acinetobacter* spp. are implicated in 4–6% of VAPs in ICUs in the U.S.A. (25,145), but higher rates have been cited in some regions in Europe and South America (12,15,136,139,205). *Acinetobacter* spp. rarely cause CAP in temperate climates but may cause CAP in subtropical regions (206,207). Less common sites of *Acinetobacter* infections include soft tissue and wound infections, catheter-related infections, and urinary tract infections (172,201,203). Mortality with bacteremias or pneumonias caused by *Acinetobacter* spp. is high (crude mortality rates of 30–75%) (136,137,172,201,203).

Risk Factors for Colonization and Infection

Resistant *Acinetobacter* spp. arise by selection pressure in debilitated ICU patients (12,172,201,208,209). Risk factors for acquisition of *Acinetobacter* spp. include prior antibiotic use, tracheostomy or endotracheal intubation, residence in an ICU, prolonged MV, and invasive devices (12,199,200,203,208,210). Colonization or infection with *Acinetobacter* spp. may follow use of antibiotics, which selects out these highly resistant organisms (12,137,199,203). In critically ill patients, The pathogen may colonize the gastrointestinal tract, skin, and respiratory tract and may be a precursor of infections (202,211). *Acinetobacter* spp. are common commensals of the skin and throat of normal hosts (203) and are ubiquitous in the environment. The bacteria are commonly isolated from water, soil, hospital equipment (e.g., tap water, wash basins, ventilator equipment, dialysis baths, mattresses, etc.) (203), and the hands of caregivers (5,203). Clonal outbreaks in hospitals may reflect transmission from

medical personnel or contaminated environmental surfaces or equipment (5,6,172,205,212–217).

Antimicrobial Resistance

Nosocomial *Acinetobacter* spp. are often resistant to multiple antibiotics, including CEPHs (except ceftazidime and cefepime), Pcs, aminoglycosides, FQs, tetracyclines, macrolides, rifampin, and chloramphenicol (6,115,201,204,209,218–221). Carbapenems are the preferred agents (>90% activity); susceptibility to other β-lactam antibiotics is variable among centers and geographic regions (85,115,204). Cefepime, ceftazimde, ticarcillin/clavulanate, and piperacillin are the most active noncarbapenem β-lactams (50–80% susceptibility rates) (115,201,218–220). A recent survey of 65 hospitals in the U.S.A. examined antimicrobial susceptibility rates among >7300 isolates of *Acinetobacter* spp. from 1998 to 2001 (115). Cumulative 1998–2001 antimicrobial susceptibility rates for non-ICU and ICU inpatients were as follows: imipenem (97%), meropenem (92%), only ceftazidime (49–55%), amikacin (79–82%), ticarcillin/clavulanate (71%), piperacillin/tazobactam (61%), CIP (41–49%), levofloxacin (48–55%) (115). Importantly, MDR, defined as resistance to at least three agents (ceftazidime, CIP, gentamicin, imipenem), was noted in 32.5% of isolates from non-ICU inpatients and 24.2% of isolates from ICU patients in 2001 (115).

Others have noted high rates of MDR among *Acinetobacter* spp. [32%] in recent surveys (204) and resistance rates continue to escalate. In two recent surveys of nosocomial isolates of *Acinetobacter* spp., susceptibility to piperacillin/tazobactam declined from 72% to 59% from 1999 to 2000 (221) and from 73% to 57% from 1998 to 2001 (115). Similarly, activity of FQs declined from 70–80% in surveys in the U.S.A. conducted in 1997 (85) to ~50% in more recent surveys (115). Resistance to FQs is usually attributable to chromosomal mutations affecting *gyr*A and *par*C genes (65,222), but plasmids containing quinolone-resistance determinants have been described (105). Activity of other antibiotic classes against *Acinetobacter* spp. is variable. In many centers, 30–80% of *Acinetobacter* isolates are resistant to aminoglycosides (25,219,223) (primarily because of aminoglycoside modifying enzymes) (224). Activity of the tetracyclines against *Acinetobacter* spp. is variable; minocycline and doxycycline are the most active agents within this class (219,220).

Resistance to β-lactam antibiotics is mediated primarily by β-lactamase production, but alterations in PBPs or reduced permeability may contribute (203). All *Acinetobacter* spp. possess a chromosomal (*amp*C) β-lactamase capable of hydrolyzing CEPHs and Pcs (201,225). High-grade resistance to β-lactams (but not carbapenems) may occur via hyperproduction of *amp*C β-lactamases and altered porin proteins (199,203). In addition, a variety of ESBLs, including those of the TEM, SHV, and OXA families, have been detected (176,203,226). Recently, PER-1, an ESBL pre-

viously reported only in Europe, was detected in 53 of 97 *Acinetobacter* spp. isolates in Korea (64). Pulsed field gel electrophoresis suggested clonal spread (64).

Carbapenem resistance occurs sporadically because of a variety of mechanisms including porin loss (227), mutations in PBPs, carbapenemases (176), and ESBLs (226,228). Several members of the OXA family of ESBLs (e.g., OXA 25–27 and 37) hydrolyze carbapenems in clinical isolates of *Acinetobacter* spp. (228). Prior use of carbapenem and CEPH antibiotics is a risk factor associated with carbapenem resistance (5,6). Clonal spread of carbapenem-resistant *Acinetobacter* has been noted (59,215). A recent survey of 15 hospitals in Brooklyn, New York, U.S.A., noted that 53% of isolates of *Acinetobacter* were resistant to carbapenems; 12% to *all* standard antibiotics (5). Only polymyxin retained consistent activity. A single clone accounted for 62% of isolates (5). Interhospital spread of MDR-*Acinetobacter* in Brooklyn likely reflected spread from colonized patients or health-care workers (6).

Multidrug-resistant strains often remain susceptible to sulbactam (215,218–220,229,230). Several studies cited excellent results with ampicillin/sulbactam for treatment of serious nosocomial infections including VAP, bacteremias, or meningitis (229,231–234). The efficacy of ampicillin/sulbactam is entirely because of the sulbactam component (215). Some isolates of *Acinetobacter* are resistant to *all* antibiotics (235). Colistin (polymyxin E) has good in vitro activity against MDR-*Acinetobacter* spp. (220,236), but clinical success rates have been disappointing (234,237). In one series, 60 patients with nosocomial infections caused by MDR strains of *Acinetobacter* or *P. aeruginosa* were treated with colistin; favorable responses were noted in 35 patients [58%]. However, only five of 20 (25%) with pneumonia responded (237). These data are consistent with murine models, in which colistin had weak bactericidal activity compared with imipenem and sulbactam (236).

For serious infections caused by *Acinetobacter* spp., we favor combination therapy with two active agents. Awareness of local antimicrobial susceptibility patterns is important. For initial empirical therapy, a carbapenem plus an aminoglycoside should be administered. Ampicillin/sulbactam is reserved for carbapenem-resistant strains (5,229). Colistin is reserved for isolates resistant to all other antibiotic classes (215). For MDR strains, combinations of two or more agents may be used to achieve synergy. Synergistic killing may be achieved with combinations of colistin, rifampin, imipenem, or ampicillin/sulbactam (238,239).

BURKHOLDERIA CEPACIA COMPLEX

Members of the *B. cepacia* complex are Gram-negative organisms that cause pulmonary infection in immunocompromised hosts, particularly those with

CF, chronic granulomatous disease (CGD), or sickle cell hemoglobinopathies (20,240,241). The taxonomy of the *B. cepacia* complex has been revised recently. Organisms previously identified as "*B. cepacia*" are divided genotypically and, in some cases, phenotypically into nine distinct genomic species or genomovars (242–244). The nine genomovars make up what is known as the *B. cepacia* complex (242,244). Ninety percent of *B. cepacia* complex isolates identified in patients from North America are either genomovar III or *B. multivorans*, but all nine genomovars have been isolated from sputum samples of CF patients (242–246).

Epidemiology and Pathogenesis

Burkholderia cepacia complex are found in the environment (e.g., soil, water, and plants) (240,244,247,248) and may contaminate equipment in the hospital (e.g., nebulizers, water sources) (240,242). Patients can acquire *B. cepacia* complex either from the environment or from other infected patients. Spread occurs through direct contact or droplet transmission; there is no clear evidence of airborne transmission (242). *Burkholderia cepacia* complex infections can occur in patients without CGD or CF, usually in the setting of common source nosocomial outbreaks (249). Outbreaks have been linked to contamination of antiseptic products, hand lotion, and multidose albuterol vials (242).

The incidence of *B. cepacia* complex infections has increased over the last two decades (250). Currently, the prevalence of pulmonary infection by *B. cepacia* complex among CF patients in the USA and United Kingdom (UK) ranges from 3% to 5% (251), but rates vary widely depending on the center and geographic location. Some CF centers cite infection rates as high as 40% (252). In Canada, prevalence rates ranged from 5% in Quebec to 25% in the eastern Canadian provinces, with an overall rate of 15% (253). Infection by *B. cepacia* complex often occurs in CF patients *after* colonization with *P. aeruginosa* (254). It is believed that *P. aeruginosa* may facilitate *B. cepacia* attachment; both organisms may exist as a biofilm in the lungs of CF patients (254). Treatment of infections caused by *B. cepacia* is difficult, as these organisms are intrinsically resistant to multiple antibiotics (241,255,256).

Burkholderia cepacia organisms have the capacity for person-to-person spread, within both hospital and community settings (250,257–259). In a recent prospective study, risk factors for acquisition of *B. cepacia* complex among patients with CF included hospitalization for pulmonary exacerbations, CF summer camp attendance, and direct contact with CF patients colonized with *B. cepacia* complex (250). Receipt of aerosolized antimicrobials was protective against infection by *B. cepacia* complex (250). The factors necessary for transmission are incompletely understood and may be specific to certain strains (253). Certain genetic elements are associated with

transmissibility: *cblA*, which encodes the protein for cable pilus production, was found in a genomovar III strain and appears to be highly transmissible (253,260). In addition, *B. cepacia* epidemic strain marker (BCESM), which encodes a protein of unknown function, has been found in multiple genomovar III strains that cluster in certain CF centers (253,261). However, patient-to-patient transmission of strains lacking cable pili or BCESM may also occur, suggesting that additional virulence factors are important for spread (242).

The transmissibility of *B. cepacia* complex has led to the development of infection-control practices both in hospital settings and within the community (242). Infection-control guidelines were recently released for care of patients with CF (242). Separation of *B. cepacia*-colonized patients with CF from noncolonized patients is recommended (242,250). The emphasis on limiting spread, however, may be socially isolating and stigmatizing for infected patients (240). What constitutes appropriate infection-control policies for patients with *B. cepacia* complex is controversial. Whether all strains of *B. cepacia* complex are capable of spread from person-to-person has not been clarified. In a recent study, 905 isolates of *B. cepacia* complex collected from 459 patients with CF throughout Canada were examined to identify strain differences in transmissibility (253). Eighty percent of patients were infected with genomovar III; importantly, all clustered isolates from individual centers were from genomovar III. Within genomovar III, there was also clustering of strain types according to province, suggesting patient-to-patient spread (253). In contrast, *B. multivorans* (genomovar II), which comprised 9% of isolates among infected patients, was never associated with clustered isolates. Another study evaluated transmission of infection by *specific genomovars* among 62 CF patients infected with *B. cepacia* complex (251). Infections were caused by genomovar III strains in 46 of 62 patients (74%); *B. multivorans* was next most common, present in 19 of 62 patients (31%). No spread of *B. multivorans* was seen during the 17-year study, whereas that of genomovar III strains among patients was common and could replace infection by *B. multivorans*. Therefore, strains of genomovar III appear to have a propensity for person-to-person spread. Further investigation is needed to identify the factors unique to the highly transmissible strains.

Clinical Characteristics of Infections caused by *B. cepacia* Complex

Burkholderia cepacia complex is most commonly isolated from the lung (241) but may cause bloodstream infections (240). In patients with CF, respiratory colonization with *B. cepacia* complex often occurs late in the course of disease (241) and is often associated with a progressive decline in respiratory function (262) and a worse survival (253) compared with uninfected CF patients. However, the course is heterogeneous, and asymptomatic

colonization may persist for prolonged periods in some patients (242). Some patients present with a fulminant life-threatening pneumonia (termed "cepacia syndrome") (263). Cepacia syndrome is typically accompanied by high fever, bacteremia, and death in 62–100% of patients (242). The reasons for the variable natural history of *B. cepacia* complex infections are unclear but may reflect differences in virulence among strains or host factors. Specific genomovars may influence the course of disease (253,264). In one study, mortality was higher among CF patients with genomovar III infection (20 of 46 died) compared with infections caused by *B. multivorans* (three of 19 died) (251). Data examining the effect of infection by *B. cepacia* complex on outcome following lung transplantation are conflicting. In some centers, infection with *B. cepacia* complex conferred a reduced survival (66,265,266), but genomovar status and/or strain type of the infecting organisms may influence outcome (251,267). In one study, mortality after lung transplantation was higher among CF patients infected with genomovar III compared with infection by other genomovars (251).

Treatment

Treatment of infections caused by *B. cepacia* complex is difficult for several reasons including intrinsic resistance to many antibiotic agents, phenotypic properties of the organism(s) conferring intracellular survival, resistance to neutrophil killing, and biofilm formation, which assist in evading host defenses (241). Most strains are resistant to aminoglycosides and polymyxin antibiotics because of an unusual lipopolysaccharide component of the cellular membrane (268). The most active agents against *B. cepacia* complex include carbapenems (particularly meropenem), FQs, ceftazidime, T/S and chloramphenicol (240,241,269). Choice of agent depends upon in vitro susceptibility tests. Susceptibility among the various *B. cepacia* genomovars differs (243). Resistance to antimicrobials can occur via multiple mechanisms (intrinsic or acquired), including β-lactamase production (241), alteration of intracellular drug targets or enzymatic degradation (270,271), decreased permeability of the cell wall (268), and multidrug efflux pumps (268,270,272). A homolog of the MexAB–OprM efflux system found in *P. aeruginosa* was described in *B. cepacia* complex (268). Additionally, a novel multidrug efflux protein called BcrA, which is specific for tetracycline and nalidixic acid, has been described (273). Efflux pumps confer broad cross-resistance to FQs, including newer agents (272,274). Development of novel efflux pump inhibitors may eventually counteract such resistance (275).

Some strains of *B. cepacia* complex are resistant to all antibiotics tested. In such cases, the use of combinations of antibiotics may achieve bactericidal activity in vitro (269). In one study of >100 MDR isolates of *B. cepacia* complex, the most active triple combinations included high-dose

(inhaled) tobramycin plus meropenem plus a second intravenous agent (ceftazidime, chloramphenicol, T/S, or aztreonam) (269).

STENOTROPHOMONAS MALTOPHILIA

Prevalence, Epidemiology, and Risk Factors

Stenotrophomonas maltophilia, a nonfermenting Gram-negative rod, is a rare cause of infections in critically ill, debilitated patients (88,209,255,276). The pathogen has also emerged as a cause of pulmonary infections in patients with CF (241,277). The most common sites of infections in non-CF patients are intravascular catheters and the lung (209,255,276,278). Predisposing risk factors for colonization or infection with *Ste. maltophilia* include antibiotic therapy (particularly broad-spectrum agents), MV, tracheostomies, residence in ICUs, serious comorbidities, organ transplantation, hematological malignancies, neutropenia, cytotoxic chemotherapy or corticosteroids, and central venous catheters (88,255,276,278–280). Prior treatment with imipenem (particularly in non-CF patients) is a risk factor for colonization or infection with *Ste. maltophilia* (276,280,281). Among patients with CF, risk factors for acquisition include corticosteroids, antipseudomonal antibiotics, FQs, and inhaled aminoglycosides (241,282). The bacteria can be isolated from environmental sources in the ICU, including water, ventilator tubing and suction equipment, disinfectant solutions, nebulizers, and spirometers (255,278). Infections with *Ste. maltophilia* are associated with crude mortality rates ranging from 10% to 60% (255,279,280). These high mortality rates, in part, reflect the frequent presence of comorbidities and debilitating illnesses among infected patients.

Antimicrobial Susceptibility

Stenotrophomonas maltophilia is intrinsically resistant to most β-lactam antibiotics (including carbapenems) (278,283), but 40–90% of isolates are susceptible to ticarcillin/clavulanate (209,255,283). Trimethoprim/sulfamethoxazole is the most active antibiotic (>90% susceptibility in vitro); minocycline is active against 45–97% of strains (209,280,283). Both these agents are bacteriostatic. Aminoglycosides have poor activity (<25% susceptible) (209,283). Activity of FQs is modest [15–55% of isolates are susceptible] (209,278,283). Multidrug-resistant *Ste. maltophilia* may emerge via selection pressure. The drug of choice for infections caused by *Ste. maltophilia* is T/S (209,278,280). For serious or refractory infections, T/S can be combined with other antibiotics to which the organism is susceptible to achieve synergy (278).

GRAM-POSITIVE COCCI

Staphylococcus aureus

Prevalence, Epidemiology, and Risk Factors

Staphylococcus aureus is the leading cause of bacterial infections worldwide (284). It accounts for ~20% of nosocomial bacteremias (25,285), 39% of skin and soft-tissue infections (284), and 20% of HAPs (18,25,284–287). Over the past two decades, its prevalence as a cause of HAP has increased. Data from the NNIS system from 1981 to 1986 implicated *Sta. aureus* in 13% of cases of HAP (28) compared to 15% from 1986 to 1989 (29), 19% from 1990 to 1996 (28), and 20% from 1992 to 1997 (25). Rates are even higher (>30%) in comatose patients in neurosurgical ICUs (288,289). Data from 112 medical ICUs in the NNIS system from 1992 to 1997 implicated staphylococci (both coagulase negative and positive) in 31% of ENT infections, 4% of UTIs, 57% of cardiovascular infections, and 49% of bacteremias (25). The major risk factor for bloodstream infections with staphylococci is intravascular devices (290). Risk factors for infection or pneumonia with *Sta. aureus* include neurosurgery, head trauma, corticosteroids, HIV infection, burns, diabetes mellitus, prolonged ICU stay, and nasal carriage (288,291–293).

Antimicrobial Resistance

Antimicrobial resistance has escalated dramatically among *Sta. aureus* (291,292). The vast majority (>95%) of staphylococci produce β-lactamase and are resistant to Pc (291). Antistaphylococcal Pcs or cefazolin is an optimal therapy for infections caused by *methicillin-susceptible* strains of *Sta. aureus* (MSSA) (292). Unfortunately, up to 55% of nosocomial isolates of *Sta. aureus* are *Staph. aureus* MRSA (290,292). Resistance to methicillin is conferred by the *mec*A gene, which is carried on a transposon and integrates into the chromosome; the mecA gene results in alterations in Pc-binding protein-2a and confers resistance to all β-lactam antibiotics (292). Importantly, most strains of MRSA exhibit resistance to multiple antibiotic classes (e.g., tetracyclines, macrolides, sulfonamides, aminoglycosides, FQs, etc.) (284,294). The prevalence of MRSA increased dramatically within the past two decades, via dissemination of a few dominant "epidemic" clones (23,260,294,295). In 1975, only 2.4% of nosocomial isolates of *Sta. aureus* in the U.S.A. were MRSA; by 1992, it was 35% (296). The NNIS data from US hospitals from 1998 to 2001 cited an incidence of MRSA of 50.5% in ICUs and 40% in non-ICU inpatients (40%) (165). Additionally, MRSA is endemic in many long-term care facilities (LTCFs) (prevalence rates ranging from 8% to 53%) (165,297). Transfer of MRSA clones within and between hospitals and LTCFs contribute to the spread of MRSA. More ominously,

community sources of MRSA have been identified within the past several years (298–300).

The epidemiology of MRSA worldwide is dominated by a small number of clones, some of which are MDR (301–303). The so-called "epidemic" clones have been reported in virtually every continent (260,302,304–306). In some hospitals, cities (295), or even countries (307), a limited number of clones are responsible for the preponderance of MRSA isolates. For example, in a New York hospital burn center, the majority of MRSA isolates were derived from an "Iberian" clone (308), which had previously been reported in both Spain (307) and Portugal (309). A survey of 12 New York hospitals in 1996 noted that a single clone was responsible for 42% of MRSA; further, 79% of MRSA among HIV-infected patients were derived from a single clone (295). In Zurich, Switzerland, an outbreak of MRSA infections among injection drug users (IDUs) resulted from dissemination of a single clone from a hospice for IDUs (310). An epidemiology study of 174 isolates of community-acquired MRSA (CA-MRSA) in Minnesota noted that 150 [86%] belong to a single clonal group (23). A survey of 17 tertiary-care hospitals in Canada found that six clones accounted for 87% of all MRSA isolates (260).

In addition to MRSA clones with the *mec*A gene, widespread dissemination of other resistance determinants has also occurred. For example, FQ resistance has increased among *Sta. aureus* (particularly MRSA) because of spread of a few international clones. Shortly after the introduction of CIP, emergence of resistance to FQs in MRSA was dramatic (294). In one study, FQ resistance increased from 0% to 79% among MRSA and from 0% to 14% among MSSA (311). Ribotyping confirmed that FQ resistance was almost entirely caused by a single MSSA clone and four MRSA clones (312). Subsequent studies confirmed clonal spread of FQ-resistant MRSA in Europe (313) and Latin America (302). An analysis of 499 MRSA isolates from 22 hospitals in five hospitals in Latin America found that a single clone (the Brazilian clone) constituted 97% of strains from Brazil, 100% of those from Uruguay, 86% from Argentina, and 53% from Chile (302). The MDR isolates may spread rapidly within and between countries and continents and pose a threat to future therapeutic options.

Risk Factors for MRSA Colonization or Infection

Risk factors associated with MRSA colonization and infection include previous hospitalization, ICU stay, presence of indwelling catheters, prior or prolonged antibiotic therapy, chronic underlying conditions, dialysis, surgical wounds, exposure to patients colonized or infected with MRSA, residence in LTCFs, and advanced age (292,297,314). Prior antibiotic exposure is a strong risk factor for colonization or infection with MRSA (12,289,315). Exposure to antibiotics (even prophylactic regimens) facilitates change in flora from MSSA to MRSA (315). Subpopulations of *mec*A

Sta. aureus may be amplified via selection pressure (315). The importance of prior antibiotic use as a risk factor for MRSA pneumonia is underscored in several studies (12,289,316). In another study, risk factors for VAP because of MRSA included use of corticosteroids, prolonged MV (>6 days), and COPD (289). French investigators cited prolonged MV (>6 days) and prior antimicrobial use (within 15 days) as independent risk factors for antibiotic-resistant organisms (including MRSA) (12). Pujol et al. (287) prospectively evaluated 139 cases of VAP caused by *Sta. aureus* from 1990 to 1994. Among 98 cases caused by MSSA, 55 [56%] were early-onset VAP and 43 [44%] were late-onset (>6 days) (287). In sharp contrast, all 41 cases of MRSA pneumonia were late-onset VAP. Logistic regression analysis of all patients with *Sta. aureus* pneumonia revealed that intubation for >3 days days and prior bronchoscopy were independent risk factors for MRSA pneumonia (287).

Colonization of the nasopharynx, skin, or surgical wounds is associated with an increased risk for infections caused by MRSA (317–319). Surgical wounds (318,319) or breaks in the skin (320) are risk factors for persistent MRSA carriage. Nasopharyngeal carriage of MRSA may persist for months or even years (297,320,321) and is a risk factor for subsequent infections with this organism (321,322). Intranasal mupirocin is generally effective in eradicating *Sta. aureus* nasal carriage in the short term but has had minimal or no impact in reducing the rate of infections (323). Current data do not support routine use of prophylactic mupirocin, although it is possible that subsets of patients (e.g., carriers at increased risk for surgical or line infections) (323) or residents of LTCFs may benefit (324).

Guidelines to limit and control MRSA focus on preventing colonization and cross-transmission on the hands of medical personnel (325). Changes or restriction in hospital formularies can reduce the prevalence of MRSA (107). In one hospital, the prevalence of MRSA decreased after restricting CEPHs, imipenem, clindamycin, and vancomycin (107). Reducing risk factors may also decrease MRSA infections (325). The use of antiseptic or antimicrobial impregnated catheters significantly decreased catheter-related infections (290,326).

Infections caused by MRSA

Infections caused by MRSA are associated with increased mortality rates, length of hospital stay, and costs compared with MSSA (14,303,314,327–331). Mortality rates are higher in patients with pneumonia caused by MRSA compared with those of MSSA (289,316,332). This heightened mortality associated with MRSA infections likely reflects host and demographic factors (e.g., comorbidities) and/or differences in efficacy of therapy (e.g., vancomycin) rather than differences in the virulence of the organisms. Clinical cure rates with nosocomial MRSA pneumonia are higher with single-lobe involvement, absence of VAP, and absence of oncologic or renal

comorbidities (333). Historically, vancomycin has been the drug of choice for MRSA infections (292,316). However, vancomycin is not bactericidal and penetrates poorly into lung parenchyma (292,334). In one recent study, MRSA infection was the most significant predictor of delayed treatment for staphylococcal bacteremias (335). Delay in appropriate therapy is an independent predictor of infection-related mortality among patients with nosocomial *Sta. aureus* bacteremias (335).

Community-Acquired MRSA Infections

Recently, serious MRSA infections arising in the community were observed (336–339). Some cases of CA-MRSA occurred in patients with known risk factors (e.g., injection drug abusers, HIV infection, serious underlying conditions, prior hospitalization, antimicrobial use, etc.) (322,340), but more ominously, severe staphylococcal infections were noted in previously healthy children or adults with no apparent risk factors (23,242,300,339,341–343). In most studies, strains of CA-MRSA display different antimicrobial susceptibilities and genetic profiles compared to nosocomial strains (23,339,341,342,344), suggesting these isolates arose independently in the community. The prototype CA-MRSA strain, originally described from a pediatric patient in North Dakota in 1998 (345), has since spread to the northeastern states (242). This clone, termed MW2, harbors a unique staphylococcal chromosomal cassette *mec*type IV and contains several virulence factors including the Panton Valentine Leukocidin (PVL) gene and enterotoxins involved in toxic shock syndrome (242). This MW2 strain has a more-rapid doubling time than hospital-acquired clones of MRSA (346). This property may allow the strain to survive in the community and compete with normal, colonizing flora in healthy hosts. The prevalence of CA-MRSA in the U.S.A. is rare in surveillance studies (0.2–2.5%) (338,347), but in certain geographic locales, one-third to one-half of isolates of *Sta. aureus* in children are MRSA (341,348). Risk factors for colonization with CA-MRSA include hospitalization within the prior 24 months, an outpatient visit within 12 months; LTCF admission within 12 months; antibiotic use (prior 1–12 months), chronic illness, IV drug use, and household contact with MRSA carriers (322). In one comprehensive review of 57 studies, the prevalence of MRSA carriage was 17.8% among household contacts of MRSA carriers and only 0.2% among individuals with no identifiable risk factors (322). Secondary spread of CA-MRSA to children in day-care centers (298,349), infants via infected breast milk (342), and among family members of index cases (350) has been reported.

Community-acquired MRSA remains relatively rare worldwide, but epidemic (351) and clonal spread (242,260,342,352) has been documented. In France, 14 previously healthy individuals developed infections caused by CA-MRSA (*mec*A positive) (342). All 14 isolates contained the PVL gene, which encodes a potent toxin involved in skin and soft-tissue infections and necrotizing pneumonia. The PVL gene was never detected among

nosocomial MRSA infections (342). Recently, an outbreak of CA-MRSA carrying the PVL gene was described among postpartum women in the U.S.A. (242). Recent large outbreaks of CA-MRSA among incarcerated persons in Mississippi (353), Los Angeles (353), and San Francisco (352) were described. In the San Francisco jail, the prevalence of MRSA increased from 29% in 1997 to 74% in 2002 (352). This rise was largely attributable to two clonal groups, accounting for 64% of MRSA isolates (352). These clones were not genetically related to the MW2 clone originally described in North Dakota (345), but were similar to a clonal outbreak reported in Los Angeles in 2002 (353). Hence, a few distinct clones of CA-MRSA have been responsible for endemic and epidemic spread and pose a threat for future dissemination into other communities.

Treatment of Infections Caused by *Sta. aureus*

Antistaphylococcal Pcs or cefazolin remains an optimal treatment for infections caused by MSSA (291,316). For patients intolerant of β-lactams, clindamycin, T/S, FQs, or minocycline can be used (depending upon antimicrobial susceptibility results) (291). Vancomycin is less effective than β-lactam antibiotics against MSSA. In one study of bacteremic staphylococcal pneumonia, the use of vancomycin was an independent risk factor for mortality (316). However, vancomycin or linezolid should be used to treat documented infections caused by MRSA. Further, when risk factors for MRSA are present in patients with HAP, vancomycin or linezolid should be incorporated into the initial empirical therapy (while awaiting results of cultures) (19,333). Methicillin-resistant *Sta. aureus* are often resistant to multiple antibiotic classes (e.g., FQs, tetracyclines, macrolides, gentamicin, and rifampin) (66,354,355). Fortunately, MRSA isolates are almost uniformly susceptible to vancomycin, linezolid, and quinupristin/dalfopristin (Q/D) (292)(333,356). Randomized clinical trials demonstrated that Q/D and linezolid were as effective as comparators (e.g., vancomycin or antistaphylococcal β-lactams) for the treatment of skin and soft-tissue infections (357–359) or pneumonia (359–362). One recent retrospective study of 160 patients with MRSA pneumonia showed superior clinical cure rates [59% vs. 36%] and survival rates [80% vs. 63.5%] with linezolid compared with vancomycin (333). The advantage of linezolid remained significant after adjusting for baseline variables. Although these observations need to be confirmed in prospective, randomized trials, these data suggest that linezolid may be superior to vancomycin for nosocomial MRSA pneumonia. Recent reports of resistance to glycopeptides (363–365) or linezolid have been described (366,367).

Glycopeptide Intermediate-Susceptible *Sta. aureus*

From 1995 to 1997, strains of MRSA displaying reduced susceptibility to glycopeptides [glycopeptide intermediate-susceptible *Sta. aureus* (GISA)] were detected in Japan (368), France (369), and the U.S.A. (365,370,371).

The National Committee for Clinical Laboratory Standards (NCCLS) defines the following MIC breakpoints for vancomycin: $\leq 4\,\mu g/mL$ "susceptible"; 8–16 μg/mL "intermediate"; $\geq 32\,\mu g/mL$ "resistant" (364). These isolates displayed intermediate susceptibility to vancomycin (termed VISA), with MICs ~8 μg/mL (370,371). Prolonged exposure to vancomycin and prior MRSA infections were the dominant risk factors for GISA (369,371–373). A thickened bacterial cell wall was responsible for reduced susceptibility to vancomycin; none of the isolates in these sentinel studies contained known vancomycin-resistance genes (e.g., *van*A, *van*B, etc.) from enterococci (371). Importantly, most GISA strains also have the *mec*A gene and are resistant to multiple antibiotic classes (364,365). However, these strains usually remain susceptible to teicoplanin, T/S, tetracycline, linezolid, and Q/D. Fortunately, those of *Sta. aureus* exhibiting reduced susceptibility to vancomycin (MIC $\geq 4\,\mu g/mL$) remain rare in the U.S.A. and worldwide (284,364,365,374). More ominously, two clinical isolates displaying high-grade resistance to vancomycin (MICs of 32 and $>128\,\mu g/mL$) were described in 2002 in Michigan (375) and Pennsylvania (376). Both isolates contained the *vanA* gene, suggesting that the resistance determinant was acquired via exchange of genetic material from VREF (377). *Staphylococcus aureus* and VREF often coexist in the intestinal tract, providing a potential reservoir for emergence of VRSA (378). While VRSA is exceptionally rare, aggressive infection-control efforts are critical to control and limit the spread of VRE and MRSA (325). Guidelines for the prevention and control of VISA and VRSA have been published. The role of vaccines is uncertain. However, a single dose of a conjugate vaccine with *Sta. aureus* types 5 and 8 capsular polysaccharides conferred partial immunity against *Sta. aureus* bacteremia among patients receiving chronic hemodialysis (380).

Treatment of VISA or VRSA

Quinupristin/dalfopristin and linezolid are highly active against MRSA and VRSA (>99% susceptibility) (356,381,382), but resistance (although rare) to these agents has been described (383–386). Resistance to dalfopristin in staphylococci may develop by *erm* genes, which results in decreased binding of macrolides, lincosamides, and streptogramin B (MLS_B resistance) (387). However, Q/D is a combination of a streptogramin A (quinupristin) and a streptogramin B (dalfopristin); hence, Q/D remains active even against isolates with only the MLS_B mutation (387). Resistance to streptogramin A antibiotics can emerge via mutations in acetyltransferase genes (*vat*A, *vat*B, *vat*C) or genes encoding effux pumps (*vga*A and *vga*B) (386,387). Data from the European SENTRY study cited Q/D resistance in 35 of 3052 *Sta. aureus* isolates; all but two Q/D-resistant strains were MRSA (386). A cluster of MRSA strains expressing *vat*B and *vga*B genes from two hospitals in France suggested clonal spread (386). Initial studies in North America (>18,000 isolates of Gram-positive cocci) found uniform susceptibility to linezolid

(100%) (382). Subsequent reports cited resistance to linezolid among a few isolates of VREF via mutations in domain V of 23S rRNA (249,385). Indwelling prosthetic devices and prolonged therapy with linezolid are risk factors for development of resistance among VREF (388). Nosocomial spread of linezolid-resistant VREF has also been documented (385,389). Isolates of MRSA resistant to linezolid emerged in the laboratory during serial passages in vitro (367). To our knowledge, only a single clinical isolate of linezolid-resistant MRSA has been cited (366) because of a mutation in the domain V of 23S (G2576U) (383). Minocycline, T/S, and chloramphenicol may be active against MRSA or VRSA (377).

Coagulase-Negative Staphylococci

Coagulase-negative staphylococci (CoNS) (e.g., *Sta. epidermidis, Sta. saprophyticus, Sta. hemolyticus* etc.) rarely cause pneumonia but are common causes of nosocomial bacteremias and skin and soft-tissue infections (290,390). In the U.S.A., CoNS account for 36% of ICU bacteremias (25). Patients with indwelling medical devices (e.g., central venous catheters, neurosurgical shunts, prosthetic heart values, artificial joints) are at greatest risk for infections caused by CoNS (25,290).

In the U.S.A. >75% of CoNS contain the *mec*A gene and are resistant to β-lactam antibiotics (391). Prior receipt of β-lactam antibiotics is a risk factor for colonization or infection with methicillin-resistant CoNS (392,393). Vancomycin is the drug of choice for infections caused by CoNS, but strains of *Sta. epidermidis* and *Sta. hemolyticus* exhibiting tolerance or high-level resistance to vancomycin and teicoplanin have been reported (393,394). European surveys in the 1990s documented resistance to teicoplanin in 3–19% of isolates of CoNS (393,395,396). Most of these teicoplanin-resistant strains remain susceptible to vancomycin (397). Italian investigators prospectively examined 535 episodes of CoNS bacteremias; 20 strains [4%] were resistant to teicoplanin; only one solate was resistant to vancomycin. Risk factors for glycopeptide resistance included previous exposure to β-lactams or glycopeptides, multiple hospitalization in the previous year, or concomitant pneumonia (393).

"Heteroresistance" to vancomycin (i.e., subpopulations of staphylococci that exhibit elevated MICs to vancomycin) has been described (398). Prior use of vancomycin and admission to the ICU were independent risk factors for heteroresistance. Although the clinical significance of heteroresistance to vancomycin is uncertain (399), it is likely that this may herald its appearance among *Sta. aureus.* Limiting the use of vancomycin is critical to preventing or delaying emergence of resistant clones. Importantly, vancomycin and other glycopeptide antibiotics may be ineffective against catheter infections caused by *Sta. epidermidis* because of poor antibiotic penetration through the biofilm matrix (290). Removal of infected catheters (in addition to appropriate antimicrobial therapy) is required to eradicate catheter

infections (290,399). Glycopeptide strains of CoNS are often susceptible to T/S, tetracyclines, Q/D, and linezolid (399).

Streptococcus pneumoniae

Streptococcus pneumoniae (pneumococcus) is the most common cause of otitis media in children (400), and CAP (401) and meningitis (400,402–404) in adults. Pneumococcus is a rare cause of endocarditis (405), peritonitis (406), arthritis, or infections at miscellaneous sites (400). *Streptococcus pneumoniae* is an uncommon cause of nosocomial infections (400,406), implicated in 2–4% of nosocomial bacteremias (406–408). Epidemics of pneumococcal infections may occur in closed communities such as jails (409), shelters (410), nursing homes (411), and day-care centers (412). The incidence of pneumococcal disease is greatest among patients with underlying conditions such as HIV infection (413); hematological malignancy (401,414); chronic pulmonary, cardiac, renal, or hepatic disease; advanced age (415,416); and immunosuppression (400,406,415–418). The incidence is greatest at the extremes of life, but pneumococcus can affect all age groups (416). Mortality from invasive pneumococcal infections has not changed significantly in the past 30 years [10–20% for bacteremic pneumonia; 21–28% for meningitis (400,402,415–419)].

Evolution of Antimicrobial Resistance

Resistance to Pcs CEPHs, macrolides, and other antibiotic classes has escalated dramatically worldwide and within the U.S.A. in the past two decades (420–422). Multidrug resistance, defined as resistance to three or more classes of antibiotics, is now endemic among pneumococci in many countries (423). Currently, in the U.S.A., 9–25% of pneumococci are MDR (420,424–426). Fortunately, even MDR isolates are nearly universally susceptible to the newer FQs and vancomycin (294,426). Despite dramatic increases in in vitro resistance, fatality rates have not increased, casting doubt on the clinical significance of these susceptibility reports. Before discussing the clinical relevance of these resistance patterns, we first discuss the trends in antimicrobial resistance among various antibiotic classes.

Mechanisms of Resistance of Pc

Pneumococcal susceptibilities to Pc are defined as follows: MIC ≤ 0.06 mg/mL, susceptible (S); MIC of 0.12–1.0 mg/mL, intermediate (I); MIC ≥ 2 mg/mL, resistant (R) (426). Penicillin resistance (Pc-R) is caused by mutations in chromosomal genes that alter PBPs (421). Alteration of PBPs decreases binding of Pcs and other β-lactam antibiotics, including CEPHs, to the cell wall (421). Resistance is a stepwise process, with successive genetic mutations resulting in increasing resistance (421). Rates of resistance to

non-β-lactam antimicrobials are also higher in Pc-resistant isolates, even though mechanisms of resistance differ (424,425). Resistance to non-β-lactam antibiotics may reflect transfer of DNA from other streptococcal species, transposons, or diverse mutations from selection pressure (421,427).

Prevalence and Epidemiology of Pc-R

Penicillin-resistant *Str. pneumoniae* (PRSP) arose from a few clones in a few geographic locations (e.g., South Africa, Australia) in the late 1960s and then spread throughout the world (7,21,421,428). More than 80% of Pc-resistant isolates worldwide are derived from six serotypes (6A, 6B, 9V, 14, 19F, 23F) (7,21,425). A majority of PRSP in Europe, the U.S.A., South America, and Asia are derived from three dominant clones (serotypes 23F, 6B, 14), likely introduced from Spain and France (421,424,428–430). The prevalence of PRSP varies markedly among regions (11), countries, and states (21,424,426–428). Rates of Pc-R are very high in some areas (e.g., Spain, eastern Europe, France, Israel, and some Asian countries), ranging from 25% to 86% (400,401,416,427,428,430–435). In contrast, PRSP remain uncommon in Sweden, Finland, The Netherlands, Switzerland, Canada, and other selected countries (421,432,436–438).

Once resistant strains are introduced into a geographic locale, subsequent spread may escalate rapidly by selection pressure (432). In Iceland, following introduction of an MDR clone (serotype 6B) from Spain, the prevalence of MDR rose to 17% within 5 years (439). The incidence of PRSP in Japan increased from $<1\%$ during 1974–1982 to 28% by 1991 (432). In one prospective study in Barcelona, Spain, the incidence of PRSP increased from 4.3% (none high grade) in 1979 to 40% in 1990 (13% high grade); erythromycin-resistant strains increased from 0% to 9.4% during that time [434]. In France, the incidence of PRSP climbed from 0.3% in 1980–1986 to 12.5% in 1990 [432]. In Korea, PRSP increased from 1.7% during 1985–1986 to 25% by 1990 (440).

In the U.S.A., Pc-R was rare prior to 1992. In a nationwide survey of pneumococci from 1979 to 1986 by the CDC, only 0.02% of pneumococci exhibited high-grade resistance ($\text{MIC} \geq 2\,\mu\text{g/mL}$) to Pc (i.e., Pc-R) (441). The prevalence of PRSP in the U.S.A. escalated dramatically in the 1990s (11,424,426). Large surveillance studies in the U.S.A. documented Pc-R ($\text{MIC} \geq 2\,\mu\text{g/mL}$) in 1.3–2.6% of isolates during 1991–1992 (442,443), 9.5% from 1994 to 1995 (444), and 14–18% in later surveillance studies (7,11,21,426,427). Although resistance rates to Pc climbed steadily in the mid-1990s, recent studies suggest the rise has slowed or stabilized (426). In fact, in some regions, resistance rates have declined, likely reflecting lower usage of β-lactam drugs. A recent study from Memphis, Tennessee, U.S.A., cited declining rates of β-lactam resistance among pneumococci from 1996 to 2001 (445). High-level Pc-R ($\text{MIC} \geq 4\,\mu\text{g/mL}$) decreased from 39.7% in 1997 to 10.3% in 2001 (445). During that same time period, erythromycin

resistance increased (from 57% to 73%); resistance to levofloxacin did not change (from 3.2% to 3.0%).

Risk Factors

Prior antibiotic use is the dominant risk factor associated with antimicrobial-resistant pneumococci (416,424,425,446). Use of β-lactams, macrolides, or sulfonamides within 1–6 months has been associated with an increased risk of colonization or infection with PRSP (401,446,447). Other risk factors include age <6 years (448,449), isolates from the middle ear or sinus source (420,450), hematological malignancies or other serious comorbid conditions (401,408,416), underlying immunosuppressive disease (401,451), HIV infections (447), residence in nursing homes (411), recent hospitalization (415,416), and age >65 years (401). Transmission of Pc-R strains may occur within day-care centers (448,449), hospitals (452), nursing homes (411), homeless shelters (410), and correctional facilities (409).

Resistance to CEPHs

In vitro breakpoints for CEPH susceptibility: Pneumococcal susceptibilities to cefotaxime/ceftriaxone were recently revised in January 2002 by the NCCLS. For nonmeningeal infections, breakpoints were as follows: susceptible, MIC $\leq 1\,\mu g/mL$; intermediate, MIC $= 2\,\mu g/mL$; and resistant, MIC $\geq 4\,\mu g/mL$ (453). For meningeal infections, the breakpoints are MICn $\leq 0.5\,\mu g/mL$ for susceptible, MIC $= 1\,\mu g/mL$ for intermediate, and MIC $\geq 2\,\mu g/mL$ for resistant (453).

Mechanisms for CEPH resistance: Resistance to CEPHs is caused by alterations in PBPs 2x, 2b, and 1a, which result in reduced affinity for CEPHs (454). It increases in parallel with Pc-R (21,426). Approximately one-third of pneumococci with intermediate susceptibility to Pc (MIC $= 0.12$–$1\,\mu g/mL$) are also resistant to first or second generation CEPHs; >95% of these isolates remain susceptible to cefotaxime/ceftriaxone (21,426). Isolates with high-grade Pc-R (MIC $\geq 2\,\mu g/mL$) are nearly invariably resistant to first or second generation CEPHs, but 67–78% of these isolates remain susceptible to cefotaxime and ceftriaxone (21,426).

As with Pc-R, the prevalence of CEPH resistance varies considerably among different countries and geographic regions (11,427). Resistance rates to CEPHs generally parallel Pc-R. A recent international survey cited high-grade resistance to ceftriaxone/cefotaxime (MIC $\geq 2\,\mu g/mL$) among 5% of pneumococcal isolates in Spain and France (countries with high rates of Pc-R) (427). In contrast, ceftriaxone resistance was absent in China, the U.K., and Germany (427). In the U.S.A., surveys in the mid-1990s cited high-grade resistance rates to cefotaxime/ceftriaxone of 1–4% (21,425,426,455), which appear to have stabilized. By 2001–2002, only 1.7% of pneumococcal isolates in the TRUST surveillance study were resistant

to cefotaxime (426). As with Pc-R, pneumococci displaying resistance to CEPHs are often resistant to multiple antibiotic classes (21,418,426). Prior treatment with antibiotics is an independent risk factor CEPH resistance among pneumococci (401,418). The clinical significance of CEPH resistance is controversial.

Clinical Impact of Pc or CEPH Resistance

The clinical impact of in vitro resistance to antibiotics is controversial. Treatment failures because of Pc or CEPH resistance have been reported for meningitis (456,457) or otitis media (450,458,459), but the relationship between drug resistance and clinical failure for pneumococcal pneumonia or bacteremias is not clear (401,416,422). Despite dramatic escalation in antimicrobial resistance over the past two decades, mortality rates from invasive pneumococcal infections have not changed significantly (419). Host factors (e.g., age, comorbidities) (401,415,416,460) and virulence intrinsic to the organism (461) influence mortality, irrespective of antimicrobial susceptibility profiles. Several retrospective (447,462) and prospective (416,417,463) studies cited no increase in mortality in patients with invasive pneumococcal infections caused by Pc-R strains. Several studies of pneumococcal bacteremias cited similar mortality rates among patients with Pc-R or Pc-susceptible (Pc-S) strains when other risk factors (e.g., comorbidities) were taken into account (415–417,431,461,463). Pallares et al. (416) prospectively studied 504 adults with pneumococcal pneumonia seen over 10 years. Resistance rates to Pc and cefotaxime were 29% and 6%, respectively. Factors independently associated with increased mortality included multilobar involvement, shock, leukopenia ($<5000\,\text{cells/mm}^3$), heart failure, nosocomial pneumonia, and age ≥ 70 years (416). Mortality was higher in Pc-R strains (38%) compared with that in Pc-S strains (24%) ($p = 0.001$). However, this difference was no longer statistically significant after adjusting for other predictors of mortality ($p = 0.04$, OR of 1.0). Among patients treated with CEPHs, mortality was similar in resistant and susceptible strains (26% vs. 28%, $p = 0.89$).

Another prospective study of 460 episodes of pneumococcal bacteremia identified the following risk factors for death: age >65 years, residence in a nursing home, presence of COPD, high acute physiology (APACHE) scores, and need for MV (463). Neither the antibiotic regimen nor the frequency of antibiotic changes influenced prognosis. A multicenter international study of invasive pneumococcal infections found no correlation between fatality rates and antimicrobial nonsusceptibility; however, certain serotypes (e.g., serotype 3) were associated with increased mortality even when isolates were fully susceptible to penicillin (461). A prospective study of 101 patients with pneumococcal pneumonia (47 patients had bacteremia) cited mortality rates of 15% (eight of 52) in patients with Pc-R or cephalosporin resistance vs. 6% (3 of 49) with Pc or CEPH-susceptible

isolates; this difference was not statistically significant (401). More importantly, discordant antibiotic therapy was not associated with mortality [3 of 17 deaths (18%) with discordant therapy vs. 8 of 84 deaths (10%) with concordant therapy]. A recent international prospective study analyzed 844 patients with pneumococcal bacteremia; overall mortality rate was 17% (417). High-grade PRSP (MIC $\geq 2\,\mu g/mL$) was noted in 9.6% of isolates. Multivariate analysis identified the following risk factors for mortality: age >65 years, severity of illness, and underlying disease with immunosuppression. Penicillin resistance did not independently influence mortality. Further, discordant therapy with Pcs, cefotaxime, or ceftriaxone did not increase mortality or suppurative complications. In contrast, discordant therapy with cefuroxime was associated with a higher mortality ($p = 0.01$). A retrospective analysis of 63 patients with pneumococcal endocarditis in Spain cited a mortality rate of 35% (405). Left-heart failure, but not Pc-R, was independently associated with increased mortality.

Several series found no heightened mortality among patients with pneumococcal infections caused by cefotaxime-resistant organisms even when CEPHs were used as therapy (401,418,464–466). A recent study of 522 nonmeningeal infections caused by *Str. pneumoniae* found similar mortality rates between patients with CEPH-resistant or CEPH-susceptible isolates (418). Among 185 patients treated with ceftriaxone or cefotaxime, 30-day mortality with CEPH-susceptible organisms was 18% (26 of 148) vs. 13% (3 of 24) with intermediate and 15% (2 of 13) with resistant isolates ($p = 0.81$). In the 159 patients treated with amoxicillin-clavulanic acid ($n = 137$) or Pcs ($n = 22$), 30-day mortality rates were 11% with Pc-S strains and 22% in Pc-nonsusceptible strains ($p = 0.07$). No strain in this study had an MIC $> 2\,\mu g/ml$ (418).

For meningeal infections, treatment failures have been cited with Pc- or CEPH-resistant pneumococci, but data are conflicting. In two retrospective studies, nonsusceptibility to Pc was not associated with a worse outcome among patients with pneumococcal meningitis (402,404). In one study, thrombocytopenia (<100,000), arterial pH > 7.47, or the need for MV was associated with heightened mortality (402).

In contrast to the foregoing observations, some studies suggest that high-level Pc-R may adversely influence mortality. In one retrospective study of >5000 patients with bacteremic pneumococcal pneumonia, mortality rates were higher when isolates displayed high-grade resistance to cefotaxime (MIC ≥ 2) or Pc (MIC ≥ 4) (467). Others cited an increased incidence of suppurative complications with PRSP (either Pc-I or Pc-R) (460). Further, in a retrospective review of 421 cases of pneumococcal bacteremia, Pc-R (MIC $\geq 2\,\mu g/ml$) was independently associated with mortality by multivariate analysis (413). Other risk factors associated with increased mortality included older age, severe disease, multilobar infiltrates on chest radiographs, and Hispanic ethnicity. Interestingly,

survival was not correlated with the in vitro activity of antibiotics used (413).

In summary, the clinical impact of resistance to Pc or CEPHs remains controversial but is certainly less impressive than in vitro data. Current breakpoints for Pc (MIC $\geq 2\,\mu g/ml$) do not appear to be clinically relevant for nonmeningeal pneumococcal infections. We agree with other experts that Pcs, cefotaxime, or ceftriaxone are excellent agents for severe nonmeningeal pneumococcal infections, even for isolates displaying MICs up to $2\,\mu g/mL$ (415–418). However, the efficacy of β-lactams for isolates with higher MICs ($\geq 4\,\mu g/mL$) has not been established (467). Finally, β-lactams cannot be considered adequate for meningeal infections due to nonsusceptible isolates, as treatment failures have been reported (457,468,469).

Resistance to Macrolide Antibiotics

Resistance to macrolides has risen in tandem with Pc-R (21,423,424,426). In 1996, the NCCLS defined a new in vitro breakpoint for erythromycin for *Str. pneumoniae*: MIC $= 0.5\,\mu g/mL$ (intermediate); MIC $\geq 1\,\mu g/mL$, (resistant) (470). Breakpoints for clarithromycin and azithromycin were defined as MIC $\geq 1\,\mu g/mL$ and MIC $\geq 2\,\mu g/mL$, respectively (471).

Mechanisms of macrolide resistance: Macrolides inhibit protein synthesis by binding ribosomal target sites in bacteria, causing premature dissociation of the peptidyl-tRNA from the 50S ribosome (472). Resistance to macrolides occurs primarily through two mechanisms: target site (ribosomal) modification (473) or active drug efflux (474). Pneumococci resistant to erythromycin by either mechanism are also resistant to azithromycin, clarithromycin, and roxithromycin (422,472,475,476). The most common ribosomal mutation is encoded by the *erm*AM (erythromycin ribosome methylation) gene (422,477,478), but several additional mutations in ribosomal proteins or nucleotides have been described (422,473,479–481). These various ribosomal modifications (MLS_B phenotype) confer high-grade resistance (i.e., erythromycin MIC $> 64\mu/mL$) (422,477). Mutations affecting the ribosomal target also confer resistance to lincosamides (e.g., clindamycin) and streptogramins (MLS_B phenotype) (473). The second major mechanism of macrolide resistance is active (proton-dependent) efflux, which is encoded by the *mef*E (macrolide efflux) gene (477), which was renamed *mef*A (478). Compared with ribosomal modification(s), efflux mutations result in much lower erythromycin MICs [1–32 μg/mL] (422,477). In addition, efflux mutants affect *only* 14- and 15-membered-ring macrolides (M phenotype) (474,478).

The prevalence of *erm*AB and *mef*E mechanisms varies according to countries or geographic regions. Efflux accounts for 61–85% of macrolide resistance among pneumococci in North America (21,436,480,482) and Japan (483), and <30% of macrolide resistance in Europe (477,479,484–486)

and South Africa (487). In addition to *erm* and *mef* mutants, additional mechanisms account for 1–3% of macrolide resistance among pneumococci (21,479,480,482). Fortunately, >99% of macrolide-resistant pneumococci are susceptible to ketolides (novel agents within the macrolide class) (21,422,478,488,489), streptogramins (e.g., Q/D) (356,490), and oxazolidinones (e.g., linezolid) (490,491). All strains are susceptible to vancomycin (21,422,489).

Epidemiology and global trends: Macrolide resistance has escalated dramatically worldwide and in the U.S.A. since the early 1990s (422,492). Rates of macrolide resistance are highly variable among countries (422,427,430,492). The Alexander Project, an international surveillance program, cited macrolide-resistance rates among pneumococci ranging from 3.2% in Brazil to 68% in Hong Kong (492). In Asia, they range from 3% in Malaysia to 89% in Taiwan (430). Two large surveillance studies in Europe cited rates of erythromycin resistance ranging from 0% to 48% (492,493). Recent large surveillance studies in the U.S.A. from 1997 to 2002 cited rates of macrolide resistance ranging from 15% to 31% (84,422,426,494). In Canada, rates of macrolide resistance from 1993 to 1998 were lower (ranging from 2.5% to 9.3%) (424,436,495). The dominant risk factor for macrolide resistance is previous antibiotic use (446,477,496,497). In Finland (498) and Spain (499), resistance to macrolides correlated with regional macrolide use.

The prevalence of macrolide-resistant pneumococcci is higher in pediatric populations (e.g., age <5 years) (400,485); day-care centers (480,500,501); children with recurrent otitis media (502); isolates from middle ear, nasopharynx, or respiratory tract (426,449,492); nosocomial acquisition (400,449,503). In adults, antimicrobial resistance among pneumococci is higher in insured (460,494) or affluent populations (487), or in elderly patients receiving multiple antibiotics for exacerbations of bronchitis (120,504). These relationships reflect previous antibiotic use in these populations. The incidence of macrolide resistance is higher among Pc-R strains (21,427,492). Typically, <5% of Pc-S pneumococci are resistant to macrolides, whereas 50–70% of Pc-R strains are resistant to macrolides (21,426,427,436). Macrolide resistance is also increasing independent of Pc-R (422,478,492). In China, 72% of pneumococci isolated during 1997–1998 were resistant to macrolides, even though <4% were resistant to Pc (427). Several European studies also cited high rates of macrolide resistance even among Pc-S pneumococci (434,500,502). These high rates of macrolide resistance may reflect selection pressure from liberal use of macrolides (499).

Transmission from children harboring drug-resistant *Str. pneumoniae* (DRSP) in the nasopharynx is a critical mechanism, whereby resistant strains are disseminated into the community (both children and adults) (422,500). Previous antimicrobial use is a strong risk factor for nasopharyngeal

carriage of erythromycin-resistant *Str. pneumoniae* (449,505). Macrolide-resistant pneumococci may persist for prolonged periods even after a single dose of azithromycin (506). Crowding, as may be observed in day-care centers (480), hospitals (449), correctional facilities (409), homeless shelters (410,507), or chronic care facilities (508), facilitates transmission of DRSP.

Clonal spread: Clonal spread is an important mechanism for transmission of macrolide-resistant pneumococci among hospitals, day-care centers, geographic regions, or even between countries (294,429,480,485). In numerous studies, Pc, macrolide, or MDR was linked to specific serotypes (423). In central Italy, serotypes 6 and 19 had far higher rates of erythromycin resistance than others (502). Nosocomial spread of serotype 14 strain was implicated as a cause of invasive pneumococcal infections in rural Slovakia (449). Travel amplifies spread of resistance clones within or between geographic regions, countries, or even continents (7,427,429,449,485). Strains of MDR pneumococci (serotype 6) observed in Italy (502) were previously described in Greece (448), suggesting clonal spread. Typically, once resistance clones are introduced into a country/region, rates of resistance increase, often dramatically, over a few years (437,478,486,509). The pace of transmission is accelerated via selection pressure from antibiotic use. In Spain, erythromycin resistance rates increased from 10% in 1989 to 34% in 1997 (486). In Belgium, macrolide resistance increased from 1% in 1983 to 21.5% in 1994 (509). Three serotypes (19, 14, and 6) accounted for 80% of macrolide resistance, consistent with clonal spread (509). In Germany, the rate of macrolide resistance in children of age <5years increased from 9.2% in 1998–1999 to 17.4% by 2000–2001 (478). In Hong Kong, erythromycin resistance rose from 0% in 1983 to 42% in 1993 (437). In the U.S.A., large surveillance studies cited rates of macrolide resistance of 0.2% in 1988 (22), 5.0% by 1992–1993 (443), and 21% by 1997–1998 (426). By 2001–2002, 28% of pneumococci were resistant to macrolides (426). Rates of resistance varied markedly among states (ranging from 3.5% to 47%) (21,426).

Clinical impact of macrolide resistance: Despite dramatic escalation in levels of in vitro macrolide resistance among pneumococci, the clinical impact of these in vitro trends remains uncertain (422). Macrolide and β-lactam antibiotics have been the cornerstones of therapy for community-acquired respiratory infections (including pneumonia) for more than four decades (30,510–513). Clinical success rates were high when macrolides were used to treat acute exacerbations of chronic bronchitis or CAP, even as monotherapy (510,514). In a retrospective review 175 patients with CAP who were older than the age of 60 years or had at least one comorbidity were treated with macrolides as monotherapy, only two patients (1.1%) died (510). Two large retrospective studies found that mortality rates for CAP were lower when patients were treated with a macrolide antibiotic plus a β-lactam, compared with either agent alone (511,515). Favorable pharmacokinetic

and pharmacodynamic (PK/PD) parameters (516) and high concentrations of antimicrobials at sites of infections (517) may explain the good clinical outcomes achieved despite MIC values in vitro that appear to be "resistant" (516). Macrolides achieve high concentration (well above serum concentrations) at bronchopulmonary sites and within phagocytes at sites of infection (422,517). Further, macrolides exhibit immunomodulatory effects (422) that may enhance efficacy in respiratory infections. Despite these favorable properties, anecdotal cases of treatment failures (including fatalities) with macrolides for pneumococcal infections have been reported (503,518–522). Lonks et al. (520) recently reported 86 patients with bacteremic pneumococcal infections displaying nonsusceptibility to erythromycin. Excluding patients with meningitis, 18 of 76 case patients (24%) and none of 136 matched controls were taking a macrolide when blood cultures were obtained ($p < 0.0001$). Fortunately, all 18 patients failing macrolides responded to alternative therapy (β-lactam antibiotics in 17; vancomycin in 1).

As macrolide resistance becomes endemic in some regions, treatment failures can be expected. Nonetheless, macrolide antibiotics remain as viable alternatives for treating CAP or pneumococcal infections in patients *with no risk factors* for macrolide resistance. When local rates of macrolide resistance are high, or when patients have specific risk factors for macrolide resistance, alternative agents should be used. For severe, life-threatening CAP or pneumococcal infections, we recommend combining ceftotaxime, ceftriaxone, or β-lactam/β-lactamase inhibitor with an antipneumococcal FQ.

Resistance to Other Antibiotic Classes

Resistance to antibiotic classes unrelated to β-lactams (e.g., tetracyclines, T/S, chloramphenicol) has risen in tandem with Pc-R (21,423,424,426). Resistance to tetracycline (as well as doxycycline and minocycline) occurs via alterations in the *tet*M gene, which is carried on the same transposon as genes encoding resistance to T/S and chloramphenicol (73,423). The prevalence of tetracycline resistance worldwide is highly variable (3–>80%) (423,448). In the U.S.A., levels of tetracycline resistance ranged from 2% to 10% from 1979 to 1994 (444,455); more recent data suggest resistance rates of 20–60% (21,426). Similarly, resistance to T/S escalated dramatically within the past decade. In several countries, rates of resistance to T/S exceed those of tetracycline or macrolide antibiotics (400,427,523). A multicenter study in Europe and Asia during 1997–1998 cited marked variability in the prevalence of resistance to T/S among pneumococci (427). Resistance to T/S was observed in both Pc-S and Pc-R strains. Rates of resistance to T/S for some countries were as follows: China (27%), U.K. (2%), Germany (4%), Spain (22%) and France (14%) (427). Recent studies in the USA cited T/S resistance rates of 20–60% among pneumococci (21,425,426). Importantly, Pc-R pneumococci are usually resistant to T/S (resistance rates of 75–92%) (21,425,435). Strains of MDR pneumococci are endemic in many

countries (423). In the U.S.A., 9–25% of pneumococci were MDR in recent studies (426,444,480,494). Fortunately, >99% of pneumococci remain susceptible to the newer FQs (426,427). All strains are susceptible to vancomycin (426,427,444,480,494).

Resistance to FQs

Mechanisms of FQ resistance: Fluoroquinolones inhibit bacterial enzymes that hinder DNA supercoiling, resulting in cell death (423). The target-sites for FQs are topoisomerase IV (ParC, ParE enzymes) and DNA gyrase (GyrA2, GyrB2) (524,525). Resistance to FQs may develop by target-site modification or active efflux (423). Ciprofloxacin is the least-active FQ against pneumococci (524). In vitro activity of the FQs against *Str. pneumoniae* is as follows: gemifloxacin > moxifloxacin > gatifloxacin > levofloxacin > CIP (526,527). Sequential chromosomal mutations in the quinolone-resistance determining regions of *par*C, *par*E, *gyr*A, or *gyr*B confer high-level resistance to FQs (42,528,529). The first step mutation in *par*C results in intermediate resistance to CIP (MIC = 4–8 μg/mL) (423,530). The second-step mutation in *gyr*A results in high-level resistance to CIP (MIC, 16–64 μg/mL) (423,530). Mutations in *par*E and *gyr*B also mediate resistance (423). Some isolates resistant to CIP exhibit cross-resistance to levofloxacin and other newer respiratory FQs (e.g., moxifloxacin, gatifloxacin, gemifloxacin) (120,527). The newer FQs have enhanced activity against topoisomerase IV and DNA gyrase compared with that of CIP, so that even organisms with a mutation in the *par*C subunit remain susceptible to these agents (423,526). Prior FQ use (particularly with CIP) is a risk factor for selecting FQ-resistant strains (528). The rate of selection of FQ-resistant mutants is lower with the newer respiratory FQs (524,531–533). Gemifloxacin and moxifloxacin have lower MICs than levofloxacin or gatifloxacin and may be less likely to select for resistant mutants than other FQs (527,529,533). Active efflux (mediated by an efflux protein, PmrA) (534) is a less common mechanism that may cause low-level resistance to FQs (2 to 4-fold rise in MICs) (423).

Prevalence and epidemiology: Rates of resistance to the newer FQs remain low (<1.0%) globally (294,427) and in the U.S.A. (42,426). However, as with other antibiotics, the prevalence of FQ resistance varies among regions and is influenced by antibiotic usage patterns. Higher levels of FQ-resistance have been noted in some locales (445,535,536), hospitals (504,529), and LTCFs (537,538). Resistance to CIP has increased in Canada (120,539), Northern Ireland (540), Spain (528,541,542), and Hong Kong (535,536). Recently, isolates of *Str. pneumoniae* displaying resistance to levofloxacin were detected in Canada (504,539), the U.S.A. (445,529), and Hong Kong (536,543–545). One recent study cited levofloxacin-resistance rates approximating 3% in Memphis, Tennessee, U.S.A., but rates remained

stable from 1996 to 2001 (445). A nosocomial outbreak of FQ-resistant *Str. pneumoniae* among 16 patients in Canada with chronic bronchitis reflected clonal dissemination (serotype 23F) containing both *par*C and *gyr*A mutations (504). All patients had previously received CIP for lower respiratory tract infections. The link between COPD and FQ resistance is consistent with previous studies identifying COPD as a major risk factor for acquisition of MDR pneumococci (294,452). Molecular evaluation of 26 CIP-resistant isolates from a Canadian surveillance study noted considerable genetic heterogeneity, whereas PRSP were derived from a limited number of clones (546). In addition, considerable genetic diversity was noted among CIP-resistant pneumococci in Spain (542). Clonal dissemination is the dominant mechanism of spread of Pc-R but is not likely the main factor for FQ resistance. However, clonal spread has been noted in some studies. Clinical isolates from six Hong Kong hospitals documented an increase in levofloxacin-resistant *S. pneumoniae* (LRSP) from 5.5% to 13.3% from 1998 to 2000 (536). A case–control study of 27 patients with LRSP cited the following risk factors for LRSP: presence of COPD, residence in a nursing home, and exposure to FQs (543). Genetic analysis of 10 isolates of LRSP from Hong Kong indicated clonal dissemination from the Spanish 23F clone (547). All 10 isolates were MDR but remained susceptible to telithromycin, Q/D, and linezolid (547). This clone has also been described in Europe and the U.S.A. (294,537). Two pandemic MDR clones displaying FQ resistance ($Spain^{23F}$-1 and $Spain^{9V}$-3) were isolated in France and Spain as early as 1992 (548). However, FQ resistance has remained low in Europe (294) and in the U.S.A. (42,426,549).

Clinical impact of resistance: Treatment failures among FQ-resistant *Str. pneumoniae* have been described (529,535,539,550) but remain rare. The low failure rate may also reflect the fact that newer FQs achieve high concentrations in lung tissue (several fold above serum levels) and have favorable PK/PD parameters (125,527,551,552). Nonetheless, there are sentinel reports of four treatment failures in Canada (539) and two in the U.S.A. (529) because of *S. pneumoniae* LRSP. In addition, LRSP emerged in four immunocompromised patients following treatment of 15 episodes of CAP (550). Initial episodes of CAP ($n = 15$) were caused by levofloxacin-S strains. One of four reinfections and five of six relapses were because of LRSP. All strains had mutations in *par*C and *gyr*A. Although current rates of resistance to newer FQs are low (<1%) globally and in North America (42,420,426,427,549), indiscriminate use of FQs may limit the future utility of this class of antimicrobials (533). During 1993–1998, prescriptions per 100 persons per year for FQs in the U.S.A. increased from 3.1 to 4.6, whereas the overall number of antimicrobial prescriptions decreased from 53.5 to 51.5 (549). The frequency of FQ prescriptions was highest for patients aged ≥65 years. Resistance to levofloxacin (defined as MIC ≥ 4 mg/mL) was

noted in only 15 of 6,529 (0.2%) clinical isolates in the U.S.A. collected from 1998 to 1999 (549). However, eight of 15 LRSP isolates came from Connecticut (these eight isolates were not genetically related) (549). Selection pressure in some locales may be the major contributor to resistance. Judicious use of FQs is warranted to preserve efficacy and curtail emergence of resistant organisms (125,533). Further, agents other than FQs should be considered to treat respiratory tract infections among patients who have recently received FQ antibiotics (533,550).

Vancomycin Resistance

Vancomycin, a glycopeptide that inhibits bacterial cell wall synthesis, is uniformly active against DRSP (including MDR strains) (21,420,426,427). However, a few strains of *Str. pneumoniae* display "tolerance" to vancomycin (i.e., lysis and killing does not occur) (553–555). Antibiotics bind normally to these "tolerant" isolates and MIC is not altered. However, killing is dramatically reduced because autolysis is not triggered (553). Thus, bacteria survive and regrow following removal of vancomycin. One recent study of 116 clinical isolates of pneumococci detected tolerance to vancomycin or Pc in 3% or 8% of isolates, respectively (555). All three vancomycin-tolerant isolates were of serotype 9V and had similar molecular fingerprinting patterns, suggesting they were highly related (555). Tolerance may lead to treatment failures (particularly in the setting of meningitis, where bactericidal activity is necessary for eradication) (554) and may be a precursor of resistance (553).

Treatment of Pneumococcal Pneumonia

Cefotaxime or ceftriaxone is the cornerstone of therapy for invasive infections caused by *Str. pneumoniae*, as these agents typically have excellent activity against both Pc-S and Pc-R strains. However, recent studies suggest that adding a second agent (particularly a macrolide) may improve outcomes (even when isolates are susceptible to Pc or CEPHs). Retrospective studies found that combining a macrolide with a β-lactam antibiotic improves outcomes (survival) for CAP (511,515) or bacteremic pneumococcal pneumonia (419,556,557). In a recent study, Spanish investigators retrospectively analyzed 409 patients with pneumococcal bacteremia seen over a 10-year period (556). By multivariate analysis, four variables were independently associated with death: age >65 years, shock, concurrent resistance to both β-lactam and macrolide antibiotics, and no inclusion of a macrolide in the initial antibiotic regiment. Similarly, in a 20-year longitudinal study of bacteremic pneumococcal pneumonia in the U.S.A., mortality was lowest among patients treated with a macrolide combined with a β-lactam (419). The basis for improved outcome with combination therapy is not obvious, particularly because the combination of Pc and erythromycin was antagonistic in vitro and in animal models of invasive pneumococcal infections

(558). Although prospective, randomized trials are lacking, these various retrospective studies suggest that the combination of β-lactam and macrolide (or FQ) antibiotic is optimal for severe pneumococcal infections. Optimal treatment of pneumococci displaying high grade resistance to both Pc and CEPHs is not clear. However, for nonmeningeal infections, newer FQs should be effective (559). For pneumococcal meningitis, vancomycin is warranted for strains displaying even intermediate susceptibility to Pc or CEPHs.

Pneumococcal Vaccination

Vaccination of high-risk patients may reduce the incidence of invasive pneumococcal infections and nasopharyngeal carriage. The 23-valent vaccine used in adults reduces the frequency of invasive pneumococcal infections (560,561), and encompasses most serotypes responsible for Pc-R or macrolide- or multidrug resistance. The seven-valent conjugate vaccine for use in children contains serotypes 4, 6B, 9V, 14, 18C, 19F, and 23F (562) that include most strains carrying antibiotic resistance determinants, and reduces nasopharyngeal carriage (562) and invasive pneumococcal infections (563). Importantly, data from the CDC cited a reduction in the incidence of antibiotic-resistant invasive pneumococcal disease among children and adults since the introduction of the conjugate vaccine (564). Thus, even unvaccinated adults may benefit from the use of this vaccine in children. Recently, a nine-valent conjugate vaccine (not yet available) reduced the incidence of vaccine-serotype and antibiotic-resistant invasive pneumococcal infections in children with and without HIV infection (565).

PREVENTION OF RESISTANCE (ALL PATHOGENS)

Judicious use of antibiotics (566) and aggressive infection-control measures (1,567) are essential to minimize spread of antimicrobial resistance. Screening for colonization in the ICU and strict isolation procedures may limit the spread of MRSA (568,569) but are expensive and cost effective only in outbreak settings. In hospital settings, restricting certain classes of antimicrobials and avoiding monotherapy are sometimes, but not consistently, effective in curtailing epidemics of antibiotic-resistant organisms (67,374). In ICUs, rotating antibiotics (“crop rotation”) may curtail antibiotic resistance (570,571), but optimal agents, length of cycles, and long-term impact have not been elucidated. A recent study of VAP suggests that shortening the duration of antibiotic therapy from 15 to 8 days did not adversely affect mortality and reduced the emergence of resistance (572). However, for VAP caused by *P. aeruginosa* and nonfermenters, relapse rates were higher with 8 days (41%) when compared with 15 days (26%) of therapy.

Awareness of local resistance patterns and prior antibiotic exposure (among individual patients) are essential to guide appropriate empirical

therapy (19,141). In a recent prospective study of HAP in ICUs, risk factors for antimicrobial resistance were identified (573). Absence of prior antibiotic therapy, neurological disturbances on ICU admission, early-onset pneumonia, and aspiration on ICU admission were associated with antimicrobial-susceptible HAP (573). Not surprisingly, prior antibiotic therapy, >8 days duration of ICU stay, and >6 days of MV were strongly associated with antimicrobial-resistant pathogens (573). Previous investigators noted a strong association between duration of MV (>6 days) and prior antimicrobial therapy and the risk for antimicrobial resistant pathogens (141). Therefore, empirical choice of antibiotics for patients with pneumonia should take into account the antibiotic history of the patient, local resistance patterns, host, and demographic factors that influence bacteriology. For severe VAP in patients with risk factors for antimicrobial-resistant pathogens, we initiate therapy with broad-spectrum antibiotics to include coverage for *P. aeruginosa* and MRSA (13,19,574). When possible, therapy should be "de-escalated" once a causative agent has been found (13). Finally, in community and hospital settings, reducing the frequency and duration of antibiotic use may limit the selection pressure driving resistance.

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11

What Are the Optimal Regimens for Adequate Empiric Therapy of Ventilator-Associated Pneumonia and How Can De-Escalation Therapy Be Achieved?

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In his valedictory address entitled *Aequanimitas*, Sir William Osler wrote, "In seeking absolute truth we aim at the unattainable, and must be content with finding broken portions" (1). This philosophical point has applicability in the empiric therapy of ventilator-associated pneumonia (VAP). In attempting to understand the complexities of VAP, the clinician encounters some sobering facts. In their review of VAP, Chastre and Fagon (2) note that mortality rates of ICU patients with this infection ranged from 24% to 76%. The medical literature is replete with reports noting that inadequate therapy for serious infections leads to increased mortality (3–12). Such data can be daunting for the clinician, whose goal of preventing mortality may not be attainable in all patients with VAP. Further complicating the matter is that there does not presently exist a definitive body of medical literature, which has established a gold standard regimen for treating VAP. The absence of such data in the presence of such outcome statistics creates an important broken portion in the practice of critical care medicine.

In recent years, there have been several reviews that have summarized clinical trials and offered options for the empiric treatment of this infection (2,13–16). The goal of this chapter is not to offer yet another opinion of what the empiric regimen should be but instead to focus on some of the issues and unresolved questions that influence the clinical judgment that leads to empiric therapy for VAP.

APPROPRIATENESS OF EMPIRIC ANTIBIOTIC THERAPY

In some of the initial discussions dealing with the influence of antibiotics on mortality in serious infections, the term *inadequate* was used to describe those situations in which the organism causing the infection was not covered by the antibiotic regimen initially ordered (9,10). This concept was adapted over time in recognition of the fact that variables other than susceptibility of the organism to the prescribed antibiotic(s) were important. In an analysis based on 107 consecutive patients receiving mechanical ventilation and antibiotic treatment for VAP, Iregui et al. (10) noted that 30.8% (33 of 107) received antibiotic treatment that was delayed for 24 hr or more after initially meeting diagnostic criteria for VAP and were classified as having initially delayed appropriate antibiotic therapy (IDAAT). Two major variables were identified in these patients with IDAAT: (1) a delay in writing an antibiotic order (in 75.8%); and (2) the presence of a bacterial species resistant to the initially prescribed antibiotic regimen (in 18.2%). The investigators found that hospital mortality was 69.7% in the patients with IDAAT in contrast to only 28.4% in those without IDAAT ($P < 0.01$). An earlier study noted that even when patients with VAP were changed to a regimen that covered the pathogen based on a susceptibility report, the increase in mortality with inadequate therapy was not eliminated (5). Acknowledgment of this finding was the basis for the statement that secondary modifications of an initially failing antibiotic regimen do not substantially improve the outcome for critically ill patients (11). These results challenge the clinician to order antibiotics that cover the involved pathogens even before culture results are obtainable. In the empiric approach to VAP, the more easily modifiable major factor contributing to IDAAT is the prevention of delay in writing the antibiotic order. More challenging than promptly writing the order is the crafting of a regimen that covers the involved organisms, including those with resistance mechanisms. To accomplish this, the clinician must have knowledge of the involved organisms, the evolving patterns of resistance, and the unintended consequences of antibiotic therapy in contributing to resistance.

Table 1 Pathogen Distribution in HAP. Data from CDC NNIS System

	1984[a] (%)	1986–1989[b] (%)	1990–1992[c] (%)	1990–1996[d] (%)	1990–1999[e] (%)	1995–2001[f] (%)
S. aureus	13	16	20	19	18	21.4
P. aeruginosa	17	17	16	17	17	16.3
Enterobacter	9	11	11	11	11	10.3
Klebsiella	12	7	7	8	7	6.7
E. coli	6	6	5	4	4	4.0
H. influenzae				5	4	3.7
Acinetobacter				4	NR	5.0

[a]Ref. 17.
[b]Ref. 18.
[c]*Clin Micro Rev* 1993; 6: 428.
[d]*Am J Infect Control* 1996; 24: 380.
[e]*Am J Infect Control* 1999; 27:520 (reported data from ICUs).
[f]CDC unpubished data, The NNIS System, 2001.
NR=not recorded. Data presented in this table were obtained prior to the CDC's March 2002 change in the criteria for defining nosocomial pneumonia (http://www.cdc.gov/ncidod/hip/NNIS/members/pneumonia/pneumonia_final.htm).

PATHOGENS IN VAP

Over the past two decades, data collected through the Centers for Disease Control and Prevention's (CDC) National Nosocomial Infections Surveillance (NNIS) System have provided a glimpse into the pathogens commonly encountered in hospital-acquired pneumonia (HAP) (17–21). Those data, which include but do not specifically identify cases of VAP, are summarized in Table 1. After 1999, the CDC altered their system to report the risk-adjusted infection rates and not pathogen-specific rates. This change was in part influenced by the increasing problem of antimicrobial resistance occurring globally. Twenty-four studies of VAP diagnosed by bronchoscopic techniques have been reviewed, representing 1689 episodes and 2490 pathogens (2). The pathogen distribution was *Pseudomonas aeruginosa*—24.4%, *Staphylococcus aureus*—20.4%, Enterobacteriaceae—14.1%, *Haemophilus* species—9.8%, *Streptococcus* species—8.0%, and *Acinetobacter* species—7.9%.

STAPHYLOCOCCUS AUREUS

A major pathogen in the consideration of empiric therapy for VAP is *S. aureus*. According to data from the CDC in 2000 reflected in Fig. 1, more than 55% of the *S. aureus* isolates associated with hospital-acquired infections in patients in the ICU were resistant to nafcillin or oxacillin (22). One of the most fundamental issues is how empiric therapy for VAP should

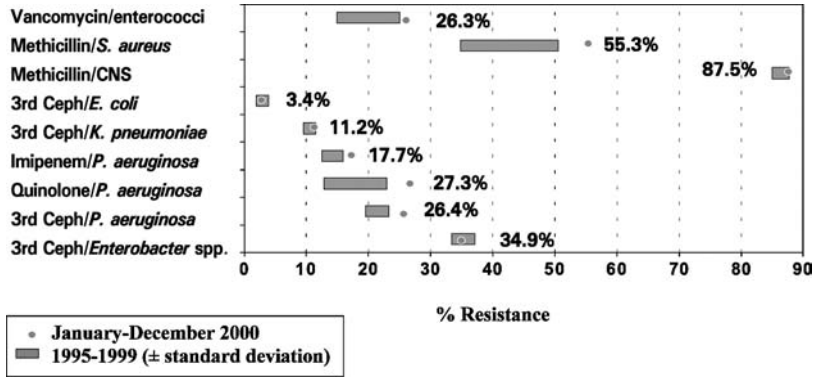

Figure 1 Proportion of isolates of select pathogens associated with hospital-acquired infections that are resistant to the specified antimicrobial agent (percentage of resistant isolates) among patients in the ICU, NNIS system (Am J Infect Control 2001; 29:404–421). For each antimicrobial/pathogen pair, the pooled mean percentage of isolates resistant is determined for January–December 2000 (·). Next to or overlapping this point is the average percentage of resistant isolates (±2 SD) during the previous 5 years (*bars*). Finally, the increase in the resistance rate in 2000 compared with the previous 5 years is shown in the column to the right of the graphed point (difference in the percentage of resistant isolates between 2000 and the historical mean, divided by historical mean (Am J Infect Control 2001; 29:404–421). CNS, coagulase-negative staphylococci; *E. coli*, *Escherichia coli*; *K. pneumoniae*, *Klebsiella pneumoniae*; *P. aeruginosa*, *Pseudomonas aeruginosa*; *S. aureus*, *Staphylococcus aureus*; 3rd Ceph, third-generation cephalosporins. (Reprinted with permission: From Ref. 22.

be administered when considering the prevalence of *S. aureus*, including methicillin-resistant *S. aureus* (MRSA). As depicted in Fig. 2, the prevalence of MRSA is more likely with late-onset infections than in those that occur early. Acknowledging that even late-onset VAP in patients not previously on antibiotics is rarely caused by MRSA, an international conference of experts offered the opinion that those with VAP who had not previously received antibiotics should not be treated with vancomycin empirically (14).

Many recommendations exist for the consideration of vancomycin in the initial regimen (2,13–16,23), especially if Gram-positive cocci are seen on the Gram stain of respiratory secretions (24). To date, there are no clinical trials that have definitively established the optimal manner in which the Gram-positive component of empiric therapy for VAP should occur. There is ongoing discussion addressing whether vancomycin is the best agent when such coverage is indicated. In the absence of such data, several microbiologic and pharmacologic principles become important in formulating a rational clinical approach to cover this pathogen.

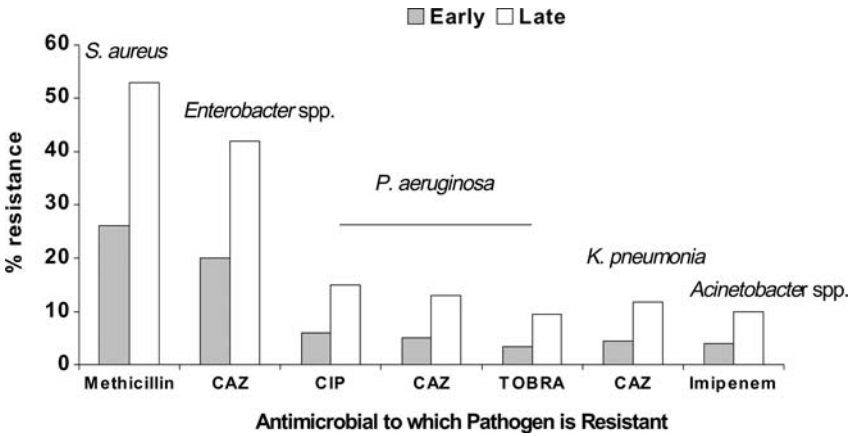

Figure 2 Proportion of isolates tested for resistance to select antimicrobial agents among pathogens associated with VAP, by early (< 7 days) vs. late (≥7 days) onset category, NNIS system, ICU component, 1989–1999. Caz, ceftazidime; Cip, ciprofloxacin or ofloxacin; Imi, imipenem; *K. pneumoniae*, *Klebsiella pneumoniae*; Meth, methicillin; *P. aeruginosa*, *Pseudomonas aeruginosa*; *S. aureus*, *Staphylococcus aureus*; Tobra, tobramycin. (Reprinted with permission: From Ref. 22.)

The mechanism of action of β-lactam antibiotics is to bind to penicillin-binding proteins (PBPs), which are enzymes located on the inner part of the bacterial cell wall and which catalyze the transpeptidation reaction that cross-links the peptidoglycan of the bacterial cell wall. Both methicillin-sensitive and methicillin-resistant strains of *S. aureus* possess four major PBPs—PBPs 1, 2, 3, and 4. True methicillin resistance is conferred by expression of the *mecA* gene, which is inserted into the bacterial chromosome via a transposon and encodes for the production of a novel PBP termed PBP 2a or PBP 2′ (25). This gene is not present in methicillin susceptible strains. In strains of MRSA, PBP 2a coexists with the high-affinity PBPs (i.e., PBPs 1, 2, and 3). Even when the high-affinity PBPs have been bound and inactivated by β-lactam antibiotics, PBP 2a (with its low affinity for binding by practically all β-lactam antibiotics) remains active. At concentrations of antibiotic that are otherwise lethal, it can still perform essential functions that would normally be performed by the high-affinity PBPs (25). The result is continued transpeptidation reactions necessary to build cell wall peptidoglycan. The presence of the chromosomal *mecA* gene does not automatically result in PBP 2a production but is considered to be the hallmark for the identification of MRSA in clinical laboratories (26).

Methicillin resistance in *S. aureus* is both misnamed and poorly understood as an in vitro phenomenon. Methicillin resistance is defined in terms of susceptibility of *S. aureus* to oxacillin, with a minimum inhibitory

concentration (MIC) of $\geq 4\,\mu g/mL$ defining resistance (27). A more important issue centers around the three patterns of methicillin resistance that have been identified: heterogeneous resistance, homogeneous resistance, and borderline resistance (25). As determined by disk diffusion or serial dilution techniques commonly employed by clinical laboratories, the terminology *methicillin resistance* does not differentiate between these three types of resistance. Even though the concept of three patterns of methicillin resistance in *S. aureus* is not well understood by most clinicians, its implications have far-reaching ramifications regarding potential approaches to empiric therapy of VAP.

The overwhelming majority of clinical MRSA isolates demonstrate heterogeneous resistance (25,28). Noteworthy in MRSA isolates is that there are mixed subpopulations of organisms, including those that remain susceptible to β-lactam antibiotics and others that are resistant. More than 99.9% of the MRSA population is susceptible to low concentrations of methicillin (i.e., 1–5 μg/mL) or other β-lactam antibiotics (25,26,28–30). In fact, heterogeneous resistance is characterized by only a minuscule fraction of organisms (e.g., 1 in 10^6) that grow at 50 μg of methicillin per milliliter (25). Heterogeneous strains can, however, appear homogeneous (i.e., 1% or more of cells grow at 50 μg/mL) under certain culture conditions. The susceptible phenotype in these heterogenous populations may lack the *mecA* gene or have this gene suppressed by the regulatory sequences responsible for *mecA* expression. In vitro, the resistant subpopulation grows much more slowly than the susceptible subpopulation and requires special laboratory techniques to promote growth (25). True homogeneously resistant MRSA isolates demonstrate an oxacillin MIC $> 800\,\mu g/mL$ (31); in contrast, the MIC of heterogeneously resistant MRSA varies and depends on the subpopulation tested. The gold standard for MIC determination remains manual serial broth dilution, and this technique uses a larger inoculum of bacteria (32). Certain microbiologic identification systems cannot differentiate between isolates with 100% subpopulation resistance and isolates with up to 99.95% subpopulation susceptibility. When such identification systems are used, *S. aureus* with either homogeneous or heterogeneous resistance will be reported as MRSA.

Also important in a discussion of methicillin resistance in *S. aureus* is the entity of borderline (or low-level) resistance. These strains are characterized by methicillin MICs at or just above the susceptibility breakpoint (e.g., oxacillin MICs of 4–8 μg/mL) and may be divided into two categories on the basis of whether *mecA* is present (25). The strains that possess *mecA* have extremely heterogeneous methicillin resistance and produce PBP 2a; the borderline strains that do not contain *mecA* have been hypothesized to have resistance that results from either modification of normal PBP genes (33) or overproduction of staphylococcal β-lactamase (26,34). These organisms will be mislabeled as MRSA if the traditional

National Committee for Clinical Laboratory Standards (NCCLS) oxacillin MIC cut-off of $\geq 4\,\mu g/mL$ is used to define resistance (27).

An understanding of heterogeneous resistance in *S. aureus* may influence empiric therapy of VAP, especially when the clinician feels that the question of how to best administer empiric therapy for VAP has not been specifically answered in an evidence-based manner. When a heterogeneous strain of MRSA is passed in the laboratory in the presence of a β-lactam antibiotic, there is an alteration in the resistant phenotype with selection of highly resistant mutant clones (35). There exists a widely recognized propensity for heterogeneously resistant MRSA to develop homogeneous oxacillin resistance when continuously exposed to the β-lactam class of antibiotics (26). Because a similar selection process occurs in patients, definitive therapy of *S. aureus* must, therefore, be directed by an organism's susceptibility profile.

β-lactam resistance in methicillin-sensitive *S. aureus* (MSSA) is largely conferred by plasmid production of penicillinase (25). Semisynthetic antistaphylococcal β-lactam antibiotics (e.g., nafcillin and oxacillin), β-lactam/β-lactamase inhibitor combinations, and cephalosporins remain stable in the presence of MSSA penicillinase. These agents would be active against sensitive phenotypes present in a heterogeneously resistant population. An important question in the decision for empiric therapy of VAP is the following: if MRSA were to grow from the patient, could therapy be changed from nafcillin to vancomycin at the 48–72 hr time line without negatively impacting clinical outcome? This takes on special significance when one considers the potential impact of treating every patient with VAP empirically with vancomycin, even though almost half of the *S. aureus* isolates in ICU infections are now methicillin sensitive (Fig. 1) (22). The association of vancomycin use with increased vancomycin-resistant enterococci (VRE) infection rates is well described (36). In *S. aureus*, both intermediate resistance to vancomycin and true resistance have been reported, with vancomycin used as a common variable in patients who have developed these patterns of resistance (37–39). Even though vancomycin may not directly lead to the mutations that cause resistance, it may select for resistant pathogens once they colonize a patient (40). The question of whether empiric therapy can be changed without consequence from nafcillin to vancomycin at 48–72 hr has not been definitively answered by clinical trials. Support for this argument was offered by Favero et al. (41) who noted the empiric success of piperacillin/tazobactam therapy for febrile neutropenic patients with MRSA infection. Despite their impaired innate immunity with lack of natural host defense by neutrophils, these patients did not suffer worse outcomes when vancomycin therapy was delayed until definitive diagnosis. This observation must be taken within the context of the data showing that inadequate initial therapy is associated with increased mortality (3–12).

Lung pharmacokinetics/pharmacodynamics suggest that empiric β-lactam therapy in the setting of severe staphylococcal pneumonia may

be superior to vancomycin therapy. In addition to its less-than-optimal activity against methicillin-sensitive *S. aureus*, the pharmacokinetic profile of vancomycin may also negatively impact this agent when used in the treatment of pulmonary infections. An important consideration is the penetration of antibiotics into pulmonary secretions and lung parenchyma. Antibiotic concentrations in collected sputum have been extensively evaluated. Translating these data into clinically useful antibiotic properties is plagued by two fundamental problems: poor concentration accuracy, and questionable relevance of sputum concentration in pneumonia (42,43). First, sputum is subject to salivary dilution, and specimens reflect pooled secretions that cannot be correlated to serum peak antibiotic concentrations. Variable sputum temperature, pH, and protein concentration create an environment which promotes antibiotic instability and spontaneous degradation. Second, sputum concentrations correlate poorly with concentrations found in other pharmacokinetic compartments that may represent the actual location of invading pathogens causing pneumonia. The validity of sputum concentration is limited to predicting the likelihood of eradicating colonization of sputum and in the treatment of infections caused by high organism burden (43). Lung levels, like bronchoscopic biopsy specimens, represent a homogeneous sample of all pharmacokinetic lung compartments.

Vancomycin is a large, polar compound that remains partially ionized at physiologic pH. Further complicating matters is that vancomycin is 45–55% protein bound, limiting the availability of free drug for penetration. A molecular weight that exceeds 1400 Da (affecting diffusion) and compound hydrophilicity (affecting polarity) drastically reduce lung penetration (44). The mechanism of entry into the pulmonary pharmacokinetic compartments has not been defined but appears to be dependent upon local inflammation (45).

Cruciani et al. (44) investigated vancomycin pharmacokinetics in 30 human lung tissue sections after a dosing strategy commonly used (1 g IV over 1 hr). A comparison of serum-to-tissue concentration over the dosing interval was used to generate a graph allowing determination of a concentration ratio. Overall, the serum-to-lung tissue concentration ratio was determined to be 21%. Not surprisingly, investigation has confirmed even poorer penetration into epithelial lining fluid (ELF), with serum-to-ELF ratios approximating 17% (45). Although caution must be used for direct number comparison with other antibiotics, vancomycin pharmacokinetic properties can be qualitatively stated to be poor.

Killing efficacy is thought to be determined by the following formula (42,46):

$$\text{organism killing efficacy} = (\text{kill rate}) \times (\text{time that tissue levels exceed MIC})$$

This basic formula can be broken down to its component elements: (1) tissue level, and (2) kill rate. In the context of lung tissue levels, a kill ratio of ≥ 2 means that an antibiotic achieves tissue concentration twice that of the organism MIC. Exceeding a kill ratio of 4 has not been proven to increase drug efficacy but may raise potential toxicity with certain antibiotics. The kill ratio is a reasonable way to compare different antibiotics in terms of their likely efficacy in treating pulmonary infections (42,47,48). As previously stated, lung tissue levels do not equal serum levels. Tissue penetration is more important than serum concentration, and accurate serum-to-lung concentration ratios are needed to predict tissue levels. Second, kill rate is less poorly defined and depends on intrinsic antibiotic properties, the specific organism targeted, and population kinetics.

Because vancomycin occupies such a prominent position in the management of patients with VAP based on the prevalence of MRSA, the following example is offered. To ensure maximal killing efficacy based on vancomycin lung tissue levels of approximately 21% of simultaneous serum levels, it would be desirable to maintain tissue levels at 2–4 times the MIC for typical staphylococci (MIC 2 μg/mL) throughout the entire dosing interval (42,49). A favorable kill ratio, therefore, would require measured antibiotic trough levels between 19 and 38 μg/mL. In many (if not most) clinical laboratories, a trough level greater than 5–10 μg/mL is reported as high. In the 1994 analysis of this topic, Moellering noted that vancomycin was originally thought to be ototoxic and nephrotoxic but that recent studies of animals had failed to confirm either when vancomycin is administered alone (50). It was further commented that definitive data proving vancomycin ototoxicity or nephrotoxicity in humans were likewise difficult to find in the literature. There was the acknowledgment, however, that one area in which considerable controversy remained was with regard to the possibility that vancomycin may produce synergistic or enhanced nephrotoxicity in patients receiving concomitant aminoglycosides. Accepting the relative lack of toxicity with vancomycin, trough levels in excess of 10 μg/mL seem more reasonable. Failure to understand the issues of vancomycin pharmacokinetics and toxicity may lead to misinterpretation of serum levels, ultimately leading clinicians to lower the drug dose, with a resultant kill ratio below the widely accepted threshold for efficacy (42).

Using the recent CDC data (Table 1) that 55% of *S. aureus* isolates are methicillin resistant (22), one would then assume that 45% of *S. aureus* isolates are methicillin sensitive. For this latter population, nafcillin and oxacillin are more efficacious in terms of microbiologic killing than is vancomycin. Given the fact that about half of the strains of *S. aureus* are methicillin sensitive and with the understanding that vancomycin is not as effective in killing sensitive strains as is nafcillin or oxacillin, one could debate the most prudent approach to empiric therapy. The dilemma becomes more perplexing when one considers vancomycin pharmacology, which was recently

reviewed in the context of Gram-positive resistance on outcome of nosocomial pneumonia (31). In that review, it was acknowledged that vancomycin is a time-dependent (or concentration-independent) antibiotic, implying that the length of time concentrations is maintained above the pathogen MIC is critical to bacterial eradication. It was noted that a key parameter for clinical success is the percentage of time that drug levels in the alveolar space exceed the MIC (time > MIC). The dosing of vancomycin every 12 hr for serious lung infection does not seem consistent with the time-dependent property of this agent.

The clinical application of this principle is that a goal in treatment of infection with a time-dependent drug like vancomycin is to maximize the time that the drug levels at the site of infection exceed the MIC of the target organism. One way proposed of achieving this has been through continuous infusion, which provides longer time above the MIC than is achieved with intermittent dosing. Although not an FDA-approved indication for vancomycin, the authors stated that their current practice was to administer 2 g/day of vancomycin in continuous infusion, after an initial bolus of 1 g, to obtain serum levels above 20 μg/mL (31). In their experience, changing to intermittent administration after defervescence of fever was associated with clinical relapse of MRSA bacteremic pneumonia, which was controlled after continuous infusion was resumed. The topic of continuous-infusion vancomycin was studied in a multicenter, prospective, randomized study designed to compare continuous-infusion vancomycin (targeted plateau drug serum concentrations of 20–25 mg/L) and intermittent infusions of vancomycin (targeted trough drug serum concentrations of 10–15 mg/L) in 119 critically ill patients with methicillin-resistant staphylococcal infections, including bacteremia and pneumonia (48). In this study, the two regimens were comparable in efficacy and tolerance, but the continuous-infusion route was 23% less expensive. Instead of continuous-infusion vancomycin, some centers have used traditional dosing intervals of vancomycin but have set 20 μg/mL as a targeted trough level for treating patients with Gram-positive pulmonary infections.

An understanding of the pharmacologic principles of vancomycin assists in interpreting the findings in the review by González et al. (51), which analyzed outcomes in 86 cases of bacteremic *S. aureus* pneumonia caused by both methicillin-sensitive and methicillin-resistant strains. The mortality associated with infection was 50% in those infected with MRSA vs. 47% in those with MSSA. The infection-associated mortality was significantly higher for MSSA patients treated with vancomycin when compared to cloxacillin (47% vs. 0%; $P < 0.01$), but the small number of patients in the cloxacillin group does not allow for a definitive conclusion to be drawn. With the poor lung penetration and time-dependent killing of vancomycin, one must consider whether it was inadequate therapy that contributed to such outcomes.

Linezolid is an oxazolidinone antibiotic with activity against MRSA. In contrast to vancomycin, linezolid has good penetration into pulmonary secretions. In a study of 25 healthy adult male subjects, the ratio of epithelial lining fluid-to-serum concentration of linezolid 4 hr after a 600 mg oral dose was 4.2 ± 1.4 (52). In a study of 10 adult patients undergoing bronchoscopy for diagnostic purposes and given oral linezolid 600 mg twice a day for a total of 6 doses, the mean epithelial lining fluid-to-serum concentration ratio was 8.35 (53). With activity against MRSA and enhanced pulmonary penetration compared to vancomycin, a basis exists for evaluating linezolid in the treatment of pneumonia caused by MRSA.

The efficacy of linezolid for MRSA pneumonia has been compared to the current standard of care, traditionally dosed vancomycin (e.g., 1 g IV every 12 hr) (54–58). The largest of these reports is a retrospective subset analysis that combined two prospective randomized, double-blind multinational trials comparing linezolid and vancomycin in patients with Gram-positive HAP and attempted to identify independent predictors of outcome (57). Each treatment regimen was given for 7–21 days. Aztreonam was included in both regimens for Gram-negative coverage, and patients were randomized to additionally receive either linezolid, 600 mg IV q12h or vancomycin, 1 g IV q12h (adjusted for renal status). A total of 1019 patients with suspected Gram-positive HAP were enrolled, including 339 patients with documented. *S. aureus* pneumonia and 160 patients with documented MRSA pneumonia. Cure rates in the MRSA subset were 59% (36 of 61 patients) with linezolid compared to 35.5% (22 of 62 patients) with vancomycin. As the study was designed, the management of vancomycin therapy was left at the institutional level, with no specific protocol requirements for dosage, dosing interval, or monitoring of serum levels. This approach allowed a comparison based on how vancomycin is given in a typical clinical setting. The conclusion of this analysis was that initial therapy with linezolid offered significantly better survival benefit and clinical cure rates than vancomycin in patients with nosocomial pneumonia caused by MRSA. These results are difficult to intepret, however, because even though results of a logistic regression analysis on this subset of patients seem to reveal a clinical cure benefit (OR, 3.3; 95% Cl, 1.3–8.3; $P = 0.011$), only a marginal survival benefit with linezolid was seen (OR, 2.2; 95% Cl, 1.0–4.8; *P*0.050) (57). The data from the same two linezolid vs. vancomycin trials were analyzed by logistic regression analysis, which showed that initial linezolid therapy was associated with significantly better clinical outcome among the 91 patients with MRSA VAP who received linezolid, there was also improved survial (OR 4.6; 95% Cl, 1.5–14.8; P=0.010). From the data presently available, one can draw conclusions of linezolid activity compared to traditional administration of vancomycin. What cannot be concluded from the data presented is whether linezolid would work as well or better than vancomycin dosed in a manner that achieves optimal killing based on the pharmacologic

properties of penetration and time-dependent killing. To be taken into consideration for empiric therapy of *S. aureus* in VAP are recent studies with linezolid reporting good in vitro activity (54) and efficacy that equals traditionally dosed vancomycin for nosocomial pneumonia (55) and MRSA infections in general (56). Kollef et al. (54) noted a 14.2% improvement in linezolid cure rates for clinically evaluable VAP.

GRAM-NEGATIVE BACTERIA

Resistance Issues

As noted in Table 1 and summarized in the recent review of VAP (2), aerobic Gram-negative bacteria are the most frequently isolated pathogens in, and implicated causes of, HAP and VAP. In decision making regarding therapy of HAP and VAP, an important consideration has been whether or not *P. aeruginosa* is likely to be an etiologic agent. The clinical approach to this pathogen has been suggested in different ways. In their guidelines for treatment of HAP, the American Thoracic Society divided HAP into three categories: (1) mild to moderate with no unusual risk factor, with onset at any time, or in patients with severe HAP of early onset; (2) mild to moderate with risk factors or with onset at any time; and (3) severe with risk factor stratification based on time of onset (13). In the first of the three groups, empiric coverage of *P. aeruginosa* was not recommended, but it was recommended in the latter two groups. The review of VAP by Chastre and Fagon (2) acknowledged the inconsistency in the definitions of early-onset vs. late-onset infection, with early-onset varying from <3 to <7 days. It was noted that high rates of *H. influenzae*, *S. pneumoniae*, methicillin-sensitive *S. aureus*, or susceptible Enterobacteriaceae were constantly found in early-onset VAP, whereas *P. aeruginosa* was significantly more frequent in late-onset VAP (as were *Acinetobacter* species, MRSA, and multiresistant Gram-negative bacilli). The consensus of a panel of international experts was that prior use of antibiotics, especially broad-spectrum antibiotics, was linked to a higher incidence of *P. aeruginosa* in patients with HAP (14). Based on the analysis perspectives offered in these three reviews, a clinically relevant approach to the Gram-negative component of VAP is to consider whether or not the infection is caused by *P. aeruginosa*.

In patients with HAP not caused by *P. aeruginosa*, six antibiotics have been suggested in the medical literature as agents that may have a role as monotherapy even with severe infection: cefeprime, piperacillin/tazobactam, imipenem, meropenem, ciprofloxacin, and high-dose levofloxacin (59–65). Noteworthy studies addressing the efficacy of these agents in infections like HAP or VAP have not compared all of the agents against each other in a single trial, and based on medical literature published thus far, it is not possible to define one agent as the gold standard for treatment of

HAP or VAP. An important factor influencing the agent used is the rate of bacterial resistance that occurs in the ICU in which the patient is being treated. According to CDC data in Figure 2, late-onset infection is associated with a higher likelihood of resistance. Failure to treat Gram-negative organisms based on their resistance patterns has been the most common reason for inadequate therapy in some series (12).

In addition to enhancing survival in bacteremic *P. aeruginosa* infections (66), combination therapy for *P. aeruginosa* has been commonly employed as an attempt to prevent the emergence of resistance. Despite its importance, there are no definitive data to prove that combination therapy will prevent the emergence of *Pseudomonas* resistance (67). However, results of clinical trials (59) and concern about this possibility based on limited data (68) have been the basis for such recommendations. Several reviews have offered the option of a fluoroquinolone with an antipseudomonal β-lactam antibiotic in empiric treatment regimens for HAP and VAP (2,13,14,23). Unfortunately, the available medical literature does not substantiate one regimen (i.e., a combination with an aminoglycoside vs. with a fluoroquinolone) as being more efficacious in terms of producing an optimal clinical outcome.

A recurring theme in the literature has been that injudicious use of antibiotics applies the necessary selective pressure that leads to resistant organisms, which in turn make episodes of VAP more difficult to treat. This must be balanced with the data that have shown that inadequate initial therapy is associated with increased mortality (3–12). In the context of these considerations, it is important that empiric treatment choices address the potential for the development of resistance. Options for empiric therapy of VAP have been summarized (2,13–16).

In hospital-acquired infections, it is important to identify those factors most associated with the selection of clinical resistance. In the study by Trouillet and colleagues (69) evaluating the risk factors for resistance in patients with VAP, the use of antibiotics within the past 15 days and mechanical ventilation of at least 7 days' duration were the most important factors (65). When these two parameters were composed, antibiotic use was a more influential factor than mechanical ventilation.

The Gram-negative pathogens most commonly encountered in patients with hospital-acquired lung infections include *P. aeruginosa, Enterobacter* species, *Escherichia coli, Klebsiella pneumoniae,* and *Acinetobacter* species (2). Although resistance in Gram-negative bacilli may occur via several mechanisms, one that fundamentally affects clinical decision making is β-lactamase production. To effectively approach the issues of how β-lactamases are impacted by clinical usage of antibiotics and how these enzymes influence management of critically ill patients, the clinician can divide them into the categories of Type I enzymes and non-Type I enzymes.

Type I β-lactamases are chromosomally mediated, with production controlled by the AmpC gene (AmpC β-lactamases). These enzymes are characteristically produced by *Serratia, P. aeruginosa,* indole-positive *Proteus, Citrobacter,* and *Enterobacter.* (These bacteria may be remembered as the "SPICE" bugs based on the first letter of their names.) According to data from the Centers for Disease Control and Prevention's NNIS System, nosocomial infections of urine, lung, skin, or blood are caused about 20% of the time by one of these pathogens (20).

Traditionally, the four classes of antibiotics that have the most predictable stability in the presence of Type I β-lactamases are aminoglycosides, carbapenems (e.g., imipenem, meropenem, and ertapenem), fluoroquinolones, and fourth-generation cephalosporins (e.g., cefepime). Because Type I β-lactamases have an affinity for cephalosporins (and have therefore been referred to by some as cephalosporinases), it is understandable that third-generation cephalosporins are not predictably stable in the presence of Type I enzymes (70). Also lacking stability are the β-lactamase inhibitors (i.e., clavulanic acid, sulbactam, and tazobactam), of which tazobactam is most likely to resist destruction by these enzymes.

Certain antibiotics may contribute to an organism's ability to produce Type I β-lactamases through two different mechanisms (1) induction and (2) the selection of spontaneous mutant strains (previously referred to as stable derepression) (71). As described by Sanders and Sanders (71), an organism with the potential to produce Type I β-lactamase (e.g., *Enterobacter*) was incubated overnight in Mueller–Hinton agar with an antibiotic added. After this incubation, an assay was done for Type I β-lactamase, and when it was detectable, the process was described as induction. Strongly inducing antibiotics are cefoxitin, imipenem, and clavulanic acid. Of note, when the inducing antibiotic was removed, the β-lactamase production ceased before the next dose of drug was due to be given. Of importance is that induction was described as a reversible in vitro phenomenon (71).

As previously noted, Type I β-lactamase is chromosomally mediated, with the control gene for the production of this enzyme being the AmpC gene and its regulatory AMPR gene. These facts are pivotal in understanding a mechanism by which induction occurs in vitro (72). Because β-lactam antibiotics do not go beyond the bacterial cell wall, they do not have the ability to directly turn on either the AmpR or AmpC genes. What has been proposed is that these antibiotics bind to PBP, forming an antibiotic/PBP complex, which then sends a signal into the cytoplasm of the cell. The result is activation of the AmpR gene, which then turns on the AmpC gene, culminating in the production of Type I β-lactamase. When the antibiotic is stopped, the antibiotic/PBP complex is eliminated, with cessation of the signal entering the cytoplasm of the cell. The AmpC gene is turned off, and the Type I β-lactamase production ceases. Hence, the induction described in Gram-negative organisms was a reversible process without genetic change

in the exposed organism. In the years since the description of induction as an in vitro phenomenon, there are no definitive data demonstrating that induction in Gram-negative organisms leads to clinically significant resistance in patients.

What has been proven to occur in patients is the second mechanism—selection of spontaneous mutant strains of bacteria (71). In the organisms that have the ability to produce Type I β-lactamases, the enzymes are normally under repressor control, and the organisms initially appear susceptible to a large number of antimicrobial agents. In those Gram-negative organisms like *Enterobacter* that have the ability to produce Type I β-lactamase, there will be a certain number (often in the 10^{-6} to 10^{-7} range), which have a spontaneous mutation that allows them to express Type I β-lactamase (71). When certain broad-spectrum antibiotics are given, the sensitive nonmutated organisms are killed; however, the genetic mutant strains proliferate and become the predominant organisms. Because there is a genetic change in the spontaneous mutant bacteria that are selected, the Type I β-lactamase production continues even when the inciting antibiotic is stopped. Most notable of the antibiotics that have been described in the literature to select these stably derepressed mutants are the third-generation cephalosporins (73,74)

Enterobacter Species

Because third-generation cephalosporins are not stable in the presence of Type I β-lactamases, they may kill the nonmutant sensitive strains but leave the mutants to proliferate and demonstrate resistance. The clinical relevance of this process was demonstrated by Chow and colleagues (74) in a five center prospective trial that evaluated the therapy of *Enterobacter* bacteremia. In this study, 69% of patients with *Enterobacter* bacteremia who had received an extended-spectrum cephalosporin (e.g., ceftazidime) had a resistant organism in contrast to only 20% resistance in those who had not received an extended-spectrum cephalosporin. In this study, the development of resistance in susceptible *Enterobacter* isolates while on therapy with an extended-spectrum cephalosporin was 19%. In contrast, no significant resistance developed in those *Enterobacter* isolates treated with other β-lactam antibiotics. The clinical outcomes of the development of *Enterobacter* resistance have been addressed in a nested matched cohort study (75). In contrast to the study by Chow et al. (74), the incidence of emergence of third-generation cephalosporin resistance in *Enterobacter* was 10.3%. Forty-six patients initially had an *Enterobacter* isolate susceptible to third-generation cephalosporins but developed resistance to third-generation cephalosporins during therapy. When these patients were compared to 113 matched controls, it was noted that the emergence of antibiotic resistance resulted in a 5-fold increase in mortality, a 1.4-fold increase in hospital length of stay, and a 1.5-fold increase in hospital charges, with the latter two of these findings

having statistical significance (75). Enterobacter resistance to broad-spectrum cephalosporins has been shown to be an independent risk factor associated with 30-day mortality (76). Fourth-generation cephalosporins (e.g., cefepime) were introduced onto the market as a potential solution for the problem of resistance in organisms like *Enterobacter* to third-generation cephalosporins. Data from 1997 (published in 1998) from 102 medical centers showed activity of cefepime against 99% of *Enterobacter* strains (77). When the SENTRY Antimicrobial Surveillance Program (designed to track antimicrobial resistance trends globally over a 5- to 10-year period) published its in vitro data one year later, it was noted that the cefepime activity against *Enterobacter* was 92.8% (73). Even though cefepime remains a useful agent for treatment of infections with stably derepressed AmpC-producing organisms (e.g., *Enterobacter*), a recommendation made in the report of data from the SENTRY Program was that ongoing surveillance will be necessary to monitor increasing resistance (78).

Pseudomonas aeruginosa

Like *Enterobacter*, *P. aeruginosa* has the ability to produce Type 1 β-lactamases. The issues with *P. aeruginosa* resistance, however, are much more complex than this enzyme alone and take on special significance when one considers that *P. aeruginosa* is the most commonly isolated Gram-negative organism in patients with HAP (see Table 1). As reflected by the CDC data in Fig. 1, the susceptibility of *P. aeruginosa* varies by antibiotic class. The multiple mechanisms of antimicrobial resistance in *P. aeruginosa* have been reviewed (79). Even though enzymatic destruction of antibiotics by β-lactamases may be the best understood of these mechanisms, there is evolving importance about closure of porin channels (which prevent antibiotic entry into the bacteria) and turning on of efflux pumps (which allow for extrusion of drug that has entered the bacterial outer membrane). These mechanisms have relevance in the selection of antibiotics for empiric therapy of VAP because of the potential of some antibiotics to lead to resistance on these bases.

In addition to Type 1 β-lactamase, metallo-β-lactamases (also referred to carbapenemases) have been described in some *P. aeruginosa* strains from certain regions of the world. Even though these enzymes have the potential to inactivate carbapenems, they have a higher affinity for cephalosporins, and extended-spectrum cephalosporins have been more associated with the selection of these mutant strains than have carbapenems (80).

Efflux pumps are three-component systems that are contained within the bacterial cell wall and allow bacteria to eliminate antibiotics that have entered. Initially described in 1980 as a mechanism of resistance in tetracyclines, efflux was recognized in 1988 as a contributor to fluoroquinolone resistance (81). In recent years, the contribution of efflux to clinical resistance

has broadened further, and there are now important implications in patients with VAP. The composition of this system has been detailed well. (79,82). The pump itself (also referred to as the transporter) lies in the cytoplasmic membrane and is designated MexB, MexD, or MexF. It is attached via a linker lipoprotein (MexA, MexC, or MexE) in the periplasm, which lies between the outer and inner membranes of the bacterial cell wall. This second component is linked to the third component, the exit portal (OprM, OprJ, or OprN), which lies in the outer membrane. Normally, these three components of the efflux pump are under repressor gene control and are not, therefore, clinically active. *Pseudomonas aeruginosa* has several efflux systems, with MexAB-OprM and MexEF-OprN having particular clinical significance: the MexAB-OprM system contributing to both intrinsic and acquired resistance; and the MexEF-OprN system contributing only to acquired resistance (83). The MexAB-OprM system is expressed constitutively in cells grown in standard laboratory media, where it contributes to intrinsic resistance to a number of antimicrobials, including fluoroquinolones and β-lactams (84). The contribution of MexAB-OprM to β-lactam efflux is interesting from two perspectives: (1) reports of efflux of β-lactam antibiotics have been comparatively rare; and (2) β-lactams act on periplasmic rather than on cytoplasmic targets, in contrast to all other MexAB-OprM antibiotic substrates. Of the β-lactams, only carbapenems appear to be poor substrates for MexAB-OprM. There is variability among the carbapenems with regard to their susceptibility to efflux. Meropenem is subject to efflux, and expression of the MexAB-OprM efflux system has been correlated with resistance to meropenem (84). In contrast, imipenem is not subject to efflux (83). It has been suggested that this may be because of the need for efflux systems with MexAB-OprM to access their substrates within the cytoplasmic membrane, with meropenem being much more amphiphilic than carbapenems like imipenem.

With the recommendation that empiric therapy of VAP should include either a fluoroquinolone or an aminoglycoside (2,13,14,23), a recent report by Livermore is especially noteworthy (79). In it, the potential for fluoroquinolones to select *nfxC (mexT)* mutants of *P. aeruginosa* is described. The implication is a newly recognized mechanism for bacterial resistance in VAP, which may be unintentionally selected by antibiotic use but has potentially far-reaching ramifications. Fortunately, this mechanism is not common at the present time. The *mexT* gene present in these mutants is a positive regulator not only of the efflux pump MexEF-OprN but also of decreased expression in the OprD porin, which is coregulated with MexEF-OprN. This mutation leads to two important problems that can be associated with resistance in *P. aeruginosa*: (1) up-regulation (i.e., turning on) of the MexEF-OprN efflux pump; and (2) down-regulation (i.e., closure) of OprD, a porin that forms narrow transmembrane channels through which carbapenems enter the bacterial cell wall. Resistance to imipenem

in *nfxC* strains results not from MexEF-OprN expression but the concomitant decrease in outer membrane porin OprD in these mutants (85).

The clinical implications of these data for selection of mutant strains of *P. aeruginosa* by fluoroquinolones are important. Over the past decade, it has been the observation by some clinicians that there has been decreasing susceptibility to carbapenems even though the use of carbapenems had not increased in their institutions. This has occurred at a time when increasing use of fluoroquinolones has been associated with growing resistance of *P. aeruginosa* to ciprofloxacin (86). The clinically relevant question is whether fluoroquinolone use with selection of mutant *P. aeruginosa* isolates might be the explanation for such an observation. If so, this would have important implications in empiric antibiotic selection.

The story of increasing *P. aeruginosa* resistance became more interesting with the trial by Trouillet and colleagues (87). These investigators analyzed 135 consecutive patients who developed an episode of *P. aeruginosa* VAP using strict criteria to define pneumonia. Piperacillin-resistant *P. aeruginosa* (PRPA) VAP developed in 25% of all *P. aeruginosa* VAP episodes. According to multivariate analysis, a fatal underlying medical condition, prior use of a fluoroquinolone, and APACHE II score were independently associated with PRPA VAP. The mechanism for this resistance was not reported in the paper. However, with the recent information that fluoroquinolones can select mutant strains of *P. aeruginosa* that possess efflux pumps (79) and with the knowledge that both fluoroquinolones and piperacillin are subject to efflux (83), one might ask if efflux is a potential explanation for this observation.

A recent clinical report addressing the influence of previous antibiotic exposure on the susceptibility patterns of bacteremic *P. aeruginosa* isolates provides an important clinical insight for the critical care setting (88). Because bacteremic events that followed exposure to antipseudomonal antibiotics were more likely to be because of resistant *P. aeruginosa* strains, it was suggested that clinicians should avoid previously administered antibiotics, in particular, those that had been given monotherapy.

In a matched case study performed to identify risk factors for acquiring multidrug-resistant *P. aeruginosa* (MDRPA) in the intensive care setting, use of antibiotics with high antiseudomonal activity, particularly ciprofloxacin, was demonstrafted to have a major role in the selecting of MDRPA (89).

An evolving part of the story about antibiotic resistance centers around the potential role that certain classes of antibiotics may play in creating genetic damage, which increases the rate of mutations that lead to antibiotic resistance. A potential mechanism of resistance reviewed recently has been hypermutation (90). In this process, certain factors may lead to resistance. Antibiotics that have an effect on DNA have been shown with in vitro experiments to potentially contribute to this pattern of resistance.

Preliminary data have suggested that drugs such as fluoroquinolones, with their effect on DNA, might provide an example of a mechanism by which therapeutic agents can promote the spread of antibiotic resistance genes (91). Even though the clinical consquences of such a process have not been definitively elucidated, there is at least the theoretical concern that antibiotics causing DNA damage might lead to enhanced numbers of bacteria with hypermutations that might then be selected with antibiotic therapy.

For many years, it has been well accepted by clinicians that overuse or injudicious use of an antibiotic might lead to resistance to that agent. With evolving reports of selection of mutant strains of bacteria by one class of antibiotics (e.g., fluoroquinolones) and with the potential for resistance not only to itself but also to other classes of antibiotics (e.g., carbapenems), the clinician has a new consideration in the formula of appropriate empiric therapy of VAP. This takes on special significance when one considers the option of a fluoroquinolone plus antipseudomonal β-lactam antibiotic in the treatment of certain patients with HAP (2,13,14,23). Although such a recommendation surely has validity in the treatment armamentarium, the clinician needs to be aware of the potential problems and maintain surveillance for such patterns of resistance.

Klebsiella pneumoniae and *E. coli*

As depicted in Table 1, *K. pneumoniae* and *E. coli* are the next most frequently isolated Gram-negative organisms after *P. aeruginosa* and *Enterobacter* in patients with HAP. Although not specifically separated from the category of Enterobacteriaceae listed in the review of VAP by Chastre and Fagon, (2) it seems reasonable to assume that *K. pneumoniae* and *E. coli* are prevalent in VAP as well. Influencing clinical decision making in VAP is the fact that these bacteria have the ability to produce a unique type of non-Type I β-lactamases that were first detected in western Europe in the early 1980s in enteric Gram-negative bacilli (92). This was transferable resistance with a major propensity for extended-spectrum cephalosporins, and the enzymes responsible for this resistance were termed extended-spectrum β-lactamases (ESBLs). The ESBLs are mutant enzymes created primarily by one or more amino acid substitutions in the TEM-1 and SHV-1 β-lactamases, which are the most common plasmid-mediated β-lactamases in Gram-negative organisms (93). From in vitro data, it appears that ESBL-producing organisms are prevalent across the United States (94). The characteristic organism that has been described with resistance because of an ESBL is ceftazidime-resistant *K. pneumoniae* (95), but similar resistance is also reported in some strains of *E. coli.* Although it cannot be definitely proven with the data presented in Fig. 1, the 3.4% resistance rate of *E. coli* and the 11.2% resistance rate of *K. pneumoniae* to third-generation cephalosporins raise the question of whether or not at least some of this resistance is on

the basis of ESBL production. Genes encoding these ESBLs are typically carried on large, self-transferable plasmids that often carry other determinants of antibiotic resistance, including resistance to aminoglycosides and fluoroquinolones (96). It is the location of these genes on transposable elements which provides for the spread of resistance throughout a hospital. Molecular epidemiology of an outbreak has shown that an epidemic strain of *K. pneumoniae* may spread from the intensive care unit (ICU) throughout the hospital (97).

There are two schools of thought regarding the risk factors for organisms producing ESBLs. Several outbreaks reported in the medical literature suggest that strains possessing ESBLs arose as a result of selective pressure exerted by the use of extended-spectrum cephalosporins. (95,98,99). Some have stated that ESBLs are a product of the use of third-generation cephalosporins since these enzymes were not described before the introduction of this class of antibiotics in the early 1980s (100). A report from France has suggested that inadequate infection control, and not antibiotic use, was the major risk (101). In that report, risk factors described for infection with organisms harboring these ESBLs in an ICU were length of stay in the ICU, arterial catheterization, and urinary catheterization. Colonization was shown to be a prerequisite for infection (101). Important reservoirs for pathogens possessing these enzymes include elderly nursing home patients who have been recurrently exposed to antibiotics (102,103). A study from Chicago of a citywide nursing home-centered outbreak of infections caused by ESBL-producing Gram-negative bacilli identified the following as independent risk factors for colonization with resistant strains: poor functional level, presence of a gastrostomy tube or decubitus ulcer, and prior receipt of ciprofloxacin and/or trimethoprim-sulfamethoxazole (103).

In a molecular, microbiologic, and case–control study conducted in Chicago, the risk factors for infection with a pathogen that produced an ESBL were identified (104). Statistically significant factors include nursing home residence, elevated APACHE-II score, instrumentation (Foley catheter, gastrostomy or jejunostomy tube, central venous catheter), and prior antibiotic therapy with ceftazidime or aztreonam. A recurrent theme among these studies is that inadequate infection control is often associated with dissemination of ESBL-producing organisms. This message was well-demonstrated in an international trial which evaluated 455 episodes of *klebsiella* bacteremia and found that many of the ESBL-producing strains were clonally related, a finding suggesting dissemination of a resistant strain because of inadequate infection control (99).

A confounding issue with infection caused by ESBL-producing strains is the potential for inadequate identification of such organisms. In the guidelines of the NCCLS for susceptibility of *Enterobacteriaceae* (e.g., *K. pneumoniae* and *E. coli*), a ceftazidime MIC of $\leq 8\,\mu g/mL$ was accepted as defining susceptibility of these bacteria to ceftazidime (105). Strains with

ceftazidime MICs of 4 μg/mL and even 2 μg/mL have on occasion been shown to produce ESBLs. Based on this, the NCCLS stated that ESBL production should be suspected in *Enterobacteriaceae* with ceftazidime MICs ≥2 μg/mL (105). Unfortunately, most laboratories in the United States do not report the specific MIC but rather give a range (e.g., ≤8 μg/mL). Although such a practice generally works well, it may inadequately identify some ESBL-producing organisms. It is therefore important to be aware of the potential for a laboratory to not identify ESBL production. To prevent ESBL production by organisms with ceftazidime MICs of 4 or even 8 μg/mL, there has been discussion about lowering the breakpoint in the United States to ≤2 μg/mL, as already occuring in some European countries.

The antibiotic susceptibility profiles of bacteria possessing ESBLs have been reported (106). These enzymes classically confer high-grade resistance to ceftazidime and aztreonam. Of clinical importance is that extended-spectrum cephalosporins (e.g., cefotaxime and ceftriaxone) with MICs in the susceptible range against ESBL-producing bacteria have demonstrated an inoculum effect, in which the MIC increases significantly as the bacterial load increases (93). There is a high prevalence of resistance in these isolates to structurally unrelated antibiotics, including gentamicin, tobramycin, trimethoprim-sulfamethoxazole, and fluoroquinolones. Because the plasmid that carries the genes for ESBL production is large, it can also carry the genetic basis for resistance to agents such as aminoglycosides. In the report by Lautenbach et al. (107), 43 of 77 (55.8%) ESBL-producing *K. pneumoniae* and *E. coli* were quinolone resistant, and an independent risk factor for such resistance was fluoroquinolone use. Even though non-β-lactam antibiotics are reasonable options for treatment of susceptible strains of ESBL-producing bacteria, the ability to predict susceptibility in ESBL-producing *Klebsiella* may be limited (108). Paradoxically, ESBL-producing organisms may have in vitro susceptibility to cephalosporins in the cephamycin class (e.g., cefoxitin), but such agents have not been recommended The fourth-generation cephalosporin cefepime also does not appear to have predictable stability in the presence of ESBLs (109,110).

In a clinical review in which patients with ESBL-producing organisms were treated with cephalosporins based on in vitro susceptibility test results, none of the cephalosporins, including cefepime, was predictably active (111). Further complicating the issue is that an inoculum effect may be detectable with cefepime when tested against ESBL-producing organisms (112). The activity of the β-lactamase inhibitor combinations has been variable. Although piperacillin/tazobactam is the most active agent in this group, resistance of ESBL-producing organisms to this combination was initially stated to be about 30% (113). A concern about the stability of such susceptibility was raised by a study of isolates from 35 ICUs in Europe, in which the percentage of ESBL-producing isolates resistant to piperacillin/tazobactam rose from 31% in 1994 to 63% in 1997–98 (114). In a study assessing the

susceptibility of ESBL-producing strains, it was noted that piperacillin/tazobactam was associated with an inoculum effect in tests with strains producing SHV-derived ESBLs but not in tests with strains producing TEM-derived ESBLs (112).

Authors of an international *Klebsiella* bacteremia study reported inferior clinical outcomes even when cephalosporins or β-lactam/β-lactamase inhibitors with in vitro susceptibility were used to treat bacteremia caused by ESBL-producing organisms, and they suggested that the discordance between in vitro susceptibility and clinical outcome might be best explained on the basis of the inoculum effect (115).

Even though SHV-derived ESBLs are the most common in the United States (K. Thomson, unpublished data), the clinical relevance of the inoculum effect is controversial. When such β-lactam/β-lactamase inhibitor combinations are effective in treating infections caused by ESBL-producing bacteria, they must be given in relatively high doses (106). At the present time, carbapenems (i.e., imipenem, meropem, and ertapenem) appear to be not only the most predictably stable in the presence of these enzymes (106) but also the most predictably active against ESBL-producing organisms. Outcomes of infection by ESBL-producing organisms have been reported (115,116). It was shown that patients infected with an ESBL-producing organism had longer lengths of stay and incurred higher hospital charges than patients whose organism did not produce an ESBL.

An international trial evaluating 440 patients with 455 episodes of *Klebsiell* bacteremia showed that use of a carbapenem during the 5-day period after onset of bacteremia because of an ESBL-producing organism was independently associated with lower mortality (115).

How should the clinician select empiric therapy in response to the problem with ESBLs If every patient with risk factors for ESBL-producing organisms is given a carbapenem, which is the drug of choice for these pathogens, then what may occur has been referred to as "squeezing the balloon" (117), in which the attempt to eliminate the problem of ESBL-producing organisms may select other patterns of antibiotic resistance. In two representative reports (118,119), the resistance that occurred in *P. aeruginosa* and *Klebsiella* to imipenem was on the basis of decreased permeability and was not associated with resistance to other antibiotics. This resistance could not be attributed to a plasmid-mediated mechanism and favored a clonal or oligoclonal epidemiology (119). In contrast to the polyclonal outbreak of ESBL-producing *Klebsiella* infection that was significantly reduced by class restriction of cephalosporins (118), the clonal or oligoclonal epidemiology of imipenem resistance should be amenable to strict infection control procedures (119,120). The potential for resistance to carbapenems based on changes in permeability must be balanced with the potential for increased mortality in patients who do not receive appropriate therapy within the first few days of infection with an ESBL-producing

organism (121). This translates into the need for clinical judgment in achieving the appropriate balance for using carbapenems. It has been suggested that the development and spread of ESBLs has most likely been caused by the overuse of expanded-spectrum cephalosporins in the hospital setting (122). Even though piperacillin/tazobactam might not be predictably effective in treating infections caused by ESBL-producing bacteria, it has been shown to be associated with a decrease in both ceftazidime and piperacillin/tazobactam resistance in *K. pneumoniae* (123,124).

Because ESBL production is plasmid-mediated and may be spread to other organisms, infection control measures including hand washing and isolation of colonized or infected persons should play a significant role (125). Targeted surveillance of high-risk areas in the hospital and in long-term care facilities may play a similarly meaningful role in control of this emerging threat in critically ill patients (106).

In the considerations regarding empiric therapy of VAP, it is important to be aware of unit-specific antibiogram data. In those units where ESBLs are prevalent, the empiric regimen should include coverage for such a pattern of resistance. The clinician must also be cognizant of the major risk factors for ESBL-producing organisms: (1) inadequate infection control, and (2) prior antibiotic therapy. When the prevalence of the organism is high, the patient has risk factors, or the infection has potential for acute mortality, consideration should be given to targeting ESBL-producing organisms in the initial regimen.

Acinetobacter baumannii

In the 2002 report describing a citywide outbreak of multiresistant *Acinetobacter* in Brooklyn, New York, the authors subtitled the article "The Preantibiotic Era Has Returned" (26). This message reminds the reader that there now exist patterns of bacterial resistance for which there is almost no effective antimicrobial therapy. Even though *Acinetobacter* can be a colonizer of the airways, it is being increasingly recognized as an important cause of late-onset HAP (13) and of VAP (2). Because of this, an understanding of both the mechanisms of resistance in this organism, as well as the patterns of dissemination, is pivotal if the clinician is to develop an approach not only for therapy but also for prevention.

Mechanisms of resistance in *A. baumannii* are diverse and reflect some degree of geographic variation. In the United States, the major mechanisms have been a combination of chromosomally associated β-lactamases and porin protein mutations (127). Plasmid-mediated metallo-β-lactamases (sometimes referred to as carbapenemases) hydrolyze all β-lactam antibiotics except aztreonam, and such enzymes have been reported from Japan, Italy, Hong Kong, and Korea (127).

The recent experience with *A. baumannii* in Brooklyn, New York, demonstrated that carbapenem resistance was endemic in that city (128). In a study to evaluate the endemicity of *A. baumannii*, all unique patient isolates of this pathogen were collected from 15 Brooklyn hospitals over a 3-month period (126). Antibiotic susceptibilities, the genetic relatedness of resistant isolates using ribotype profiles, and the relationship between antibiotic use and resistance rates were determined. Among the 224 carbapenem-resistant strains of *A. baumannii*, ribotyping demonstrated that one strain accounted for two-thirds of the isolates and was present in all of the 15 participating hospitals. The strongest predisposition to this pathogen was cephalosporin use. The molecular epidemiology and mechanisms of carbapenem resistance in this outbreak have been reported (126). The preliminary findings for a small number of strains suggest that diminished production of outer-membrane porins, together with increased expression of a class C cephalosporinase, was an important factor leading to carbapenem resistance. Given the fact that *A. baumannii* resistance mechanisms include chromosomally associated β-lactamases and porin protein mutations (127), one would assume that this represents selection of mutant strains by the cephalosporins. The authors concluded that controlling antibiotic use, particularly cephalosporins, may be an important component of a strategy to limit the spread of carbapenem-resistant *A. baumannii* (129). As has been well described, the control of infections with clonal epidemiology (as is the case in carbapenem-resistant *A. baumannii*) is influenced to a significant degree by infection control techniques (119).

The β-lactamase inhibitors (i.e., clavulanic acid, sulbactam, and tazobactam) are generally considered to have no intrinsic antimicrobial activity but rather serve as suicide agents to inactivate β-lactamases. An important exception is the activity that sulbactam has when used alone against *A. baumannii*. In a retrospective analysis, the outcomes of 75 patients with 77 episodes of *Acinetobacter* VAP were compared (130). Fourteen patients were treated with ampicillin/sulbactam, and 63 were treated with imipenem/cilastatin. Treatment efficacy was similar in both groups, but adjunctive aminoglycoside therapy was used more often in the patients who received ampicillin/sulbactam. Even though this study was small, the results underscore the potential role of sulbactam in not only treating *Acinetobacter* infections but also potentially decreasing the tendency for selection of resistant strains of this pathogen. Such data take on more significance when one considers that colistin (polymixin E) and polymixin B are often the only remaining efficacious agents in patients with carbapenem-resistant strains of *A. baumanii*.

ANAEROBES

The role of anaerobes in HAP and VAP has not been completely delineated. The rates of isolation of these organisms have been variable in the medical

literature, and the CDC studies as reported in Table 1 did not predictably study these organisms. With at least equivalent results from clinical trials such as the one comparing ciprofloxacin and imipenem in patients with HAP (59), some have suggested that anaerobes may not need to be targeted with an anaerobe-specific agent even though they might be present. Unfortunately, there are no definitive answers at the present time about the role of anaerobes or the need for specific therapy in patients with HAP.

To assess the importance of anaerobes in VAP, patients with a first episode of bacteriologically documented VAP ($>10^3$ CFU/Ml) were analyzed using protected specimen brushes (PSB) (131). Of the anaerobes isolated, the most prevalent were *Prevatella melaninogenica* (36%), *Fusobacterium nucleatum* (17%), and *Veillonella parvula* (12%). The VAP with anaerobes occurred more often in patients orotracheally intubated than nasotracheally intubated ($P < 0.02$), and episodes of VAP involving anaerobic bacteria occurred more often in the first five days (early VAP) than after the fifth day (late VAP) ($P < 0.05$). Although not confirmed in multiple clinical trials, there are some data that suggest that patients with VAP who receive antibiotics active against anaerobic bacteria may have better clinical outcomes at day 10 of therapy than do patients whose regimen does not adequately cover anaerobes (132).

A relevant clinical question is whether anaerobes involved in VAP might be covered by the antibiotic regimen being given for the involved aerobic organisms. With antibiotics such as piperacillin/tazobactam, imipenem, or meropenem, the anaerobic spectrum is excellent, with resistance rates in *Bacteroides fragilis* being $<1\%$ (133). The efficacy against airway anaerobes should at least be equivalent. The anaerobic activity of other antibiotics used in VAP (e.g., fluoroquinolones or extended-spectrum cephalosporins) is not as predictable against anaerobes involved in infections below the diaphragm (e.g., *Bacteroides fragilis*). As a class, the fluoroquinolones are not assumed to have predictable anaerobic activity. Several recent studies, however, provide some useful insights into the potential efficacy, at least in vitro, of cephalosporins and fluoroquinolones for anaerobes from the upper airway (131). In a trial of 1001 anaerobes isolated from human intra-abdominal infections, ceftriaxone had good in vitro activity against *Fusobacterium* spp. and most *Prevatella* isolates (134). In this trial, there were too few *Veillonella* isolates on which to comment. From a trial in patients with sinusitis on whom antral punctures were performed to obtain specimens for culture, data are available with regard to susceptibilities to levofloxacin, gatifloxacin, and moxifloxacin (135). Of the strains of *P. melaninogenica* that were tested, 92% were susceptible; for *Fusobacterium* species, 100% were susceptible; and for *Veillonella* species, 92% were susceptible to levofloxacin and moxifloxacin, and 100% to gatifloxacin. Another antral puncture trial in patients with acute sinusitis yielded similar susceptibilities (136). In a trial of patients with

sinusitis, the MIC_{90} of levofloxacin was 1.0 μg/mL for *P. melaninogenica*, 1.0 μg/mL for *Fusobacterium* spp., and 0.5 μg/mL for *V. parvula* (137).

Because of the availability of newer fluoroquinolones with enhanced pneumococcal activity, recent trials of upper airway infections have not included ciprofloxacin among the agents tested. The in vitro data for ciprofloxacin against airway anaerobes are, therefore, more limited. In a study that seems representative, ciprofloxacin activity against *Fusobacterium* spp. was about 90%, and for the pigment-producing *Prevatella* (e.g., *P. melaninogenica)*, the activity was about 81% (138). For respiratory anaerobic species, the in vitro activity of ciprofloxacin seems to be similar to that of levofloxacin.

The guidelines for HAP and VAP do not offer specific recommendations with regard to coverage for anaerobic pathogens (2,13–16). Still unresolved is whether anaerobes require specific therapy. As summarized in this section, many of the agents used to treat VAP have activity against the anaerobes that have been isolated in this infection.

HOW DE-ESCALATION CAN BE ACHIEVED

Two counterbalancing themes in VAP are: (1) that inadequate therapy is associated with increased mortality (thereby often requiring broad-spectrum therapy directed at multiresistant organisms); and (2) that a significant contribution to the worldwide epidemic of antibiotic resistance has been antibiotic therapy (hence, a mandate for as judicious therapy). The role of antibiotics in contributing to the selection of resistant organisms has shifted attention to the importance of de-escalating, or narrowing, therapy when possible. A common dilemma for the clinician in the ICU is that patients with VAP often have negative cultures, thereby making it difficult to de-escalate from an initially broad regimen. Even though de-escalation of therapy has no immediate impact on a given patient, it has both the theoretical benefit of impeding antimicrobial resistance and the tangible benefit of reducing cost (11). Unfortunately, there are no definitive, or even widely accepted, recommendations for how de-escalation should be done in the absence of a positive culture. Despite the absence of such data, it remains important to develop an approach to such a problem for two major reasons. One is that the problem occurs frequently in the intensive care setting and consistently presents a quagmire to the clinician. The second is that antibiotic usage is a major risk factor for resistance, which is a major contributor to inadequate therapy. Given these fundamentally important factors, three areas are presented to offer some important clinical insights into how this can be done, and stimulate some dialog about how such a dilemma might be better addressed in future studies.

Therapy Based on Objective Assessment of Clinical Response

Because the course of patients with infection is dynamic, it seems reasonable to objectively assess response to treatment as an aid in determining an appropriate antibiotic of therapy. In 1991, Pugin et al. (139) published a study that defined score clinical criteria to aid in the diagnosis of VAP, termed the Clinical Pulmonary Infection Score (CPIS). Variables included in the CPIS were body temperature, blood leukocyte count and number of band forms, character and quantity of tracheal secretions, oxygenation, pulmonary radiography patterns, and semiquantitative culture of tracheal aspirate. Points were ascribed for each of these variables, and the total of those points was the CPIS. Unfortunately, the original CPIS proved to be of little use in the diagnosis of VAP, largely because it relied on culture data that were not available at the time of initial evaluation. Recently, Fartoukh et al. (140) modified the CPIS by including a Gram stain of pulmonary secretions in an attempt to increase its accuracy. Their investigation found this "modified CPIS" to be marginally superior to clinical judgment alone, and led them to conclude that the physician should use the score only cautiously.

Although not its originally intended purpose, investigators have found that the CPIS can define the duration of VAP therapy. Recognizing the difficulties in the diagnosis of VAP and the overuse of antibiotics in the treatment of these patients, Singh et al. (141) used the CPIS in surgical ICU patients who had fever and pulmonary infiltrates. They evaluated the CPIS on days 1 and 3 of suspected VAP, and, if a patient had CPIS of ≤ 6, monotherapy was initiated in a randomized fashion. Investigators re-evaluated the CPIS at day 3. If the score remained ≤ 6, therapy was discontinued in the intervention group; otherwise, if CPIS became >6, clinicians continued therapy for pneumonia. Investigators compared a group of 39 patients undergoing this experimental approach to a group of 42 patients undergoing standard therapy. Investigators found no difference in mortality between patients treated with this novel approach vs. patients treated with a standard approach, but did note decreased cost, antibiotic resistance, and superinfection in the experimental group. Because of the variability in etologies of fever and pulmonary infiltrates in surgical vs. medical ICUs, some have questioned whether similar findings would be noted if the patient population had been from only a medical ICU.

Dennesen et al. (142) hypothesized that the rapid resolution of clinical parameters may indicate that shorter courses of therapy for VAP may be as effective as longer courses and may circumvent some of the detrimental effects of antibiotic use. Building upon this foundation, Luna et al. (143) in a prospective multicenter cohort evaluated the use of serial, modified CPIS evaluations in determining the time course response to treatment, and defining who may be candidates for shorter treatment courses. The

investigators recorded the modified CPIS at VAP days −3, 0, 3, 5, and 7 in both survivors ($n = 31$) and nonsurvivors ($n = 32$) of disease. They found that, as expected, the CPIS worsened at day 0 for both survivors and nonsurvivors; however, at days 3 and 5, survivors demonstrated a significantly improved CPIS while nonsurvivors did not. Interestingly, of all the clinical parameters included in their modified CPIS, PaO_2/FiO_2 emerged as the best correlate of outcome and was also found to be an accurate surrogate marker of inappropriate antibiotic therapy. Though the use of CPIS as a diagnostic tool remains in doubt, its potential use as an assessment tool has become apparent.

The Role of Negative Cultures

A discussion about the role of cultures in the management of patients with VAP must take into consideration basic pathogenetic mechanisms. For over three decades, the role of colonization of oropharyngeal secretions by potentially pathogenic micro-organisms has been recognized (144) with microaspiration of this flora as the inciting event, which predisposes to infection of the lower respiratory tract (145). One approach for evaluating cultures of the respiratory tract is to consider only those that sample the distal airways (e.g., bronchoalveolar lavage or protected specimen brush) rather than those that sample the proximal airways (e.g., endotracheal aspirate). Most of the data in the literature about cultures in the diagnosis of pneumonia have not defined a gold standard that definitely establishes the diagnosis of VAP. Given this fact along with the consideration that delay in writing antibiotic orders may be the most common reason for a decision about IDAAT (10), experts agree that some type of respiratory tract culture should be expeditiously done and then a decision about antibiotic therapy should be made in a timely manner. An additional way to utilize respiratory tract cultures is to alter therapy.

Understanding the nature of the pathology of VAP is of fundamental importance in interpreting the role of pulmonary cultures either in diagnosing the infection or defining the microbial etiology Rouby et al. (146) attempted to correlate microbiologic burden with the presence of histologic pneumonia in a post-mortem study of 83 patients who died while on mechanical ventilation. Investigators found 43 of these patients to have histologic lesions of bronchopneumonia; 17 had evidence of bronchiolitis while the remaining 23 were free of histologic evidence of infection. Histologic examination yielded a number of observations: (1) dependent lung segments in the supine patient were more often involved than others; (2) histologic lesions of bronchopneumonia often represented a minority of samples from a given segment, and usually existed within larger zones of nonspecific alveolar damage; and (3) histologic pneumonia did not imply recovery of a pathogen (35%). In cases with polymicrobial infection (28%), investigators

found a nonhomogeneous distribution of pathogens (146). Because of the patchy nature of VAP, one can understand why a negative PSB culture might not be basis enough for either definitively excluding the diagnosis or discontinuing therapy.

In recent years, the search for an accurate, reliable, noninvasive study for the diagnosis of VAP (147) has led many investigators to revisit endotracheal aspirates. In a study of tracheal aspiration for the diagnosis of VAP in long-term ventilated patients with clinical pneumonia and not on antibiotic treatment, Rumbak et al. (148) found tracheal aspirates to correlate with PSB. As compared to PSB, tracheal aspirates had a sensitivity of 97.3%, specificity of 50%, positive predictive value of 91.3%, and negative predictive value of 80%. Although one cannot necessarily extrapolate these data to acute-care patients, it does raise the possibility that endotracheal aspirates can reliably detect at least certain pathogens (e.g., MRSA and *P. aeruginosa)* that cause VAP.

Cook and Mandell (149) performed a literature search and identified nine studies that evaluated the results of tracheal aspirate cultures. The authors concluded that quantitative tests on tracheal aspirates were unpredictable and widely variable, and that qualitative cultures, when compared with quantitative invasive studies, displayed noteworthy sensitivity. Finally, they found that special studies (Gram stain, antibody coating, and elastin fibers) were unreliable. Unfortunately, likely because of variations in study design and criteria used in each, results were too widely variable to support any firm recommendations.

Sanchez-Nieto et al. (150) conducted a small, prospective, randomized trial in 51 patients on mechanical ventilation comparing invasive and noninvasive sampling techniques. The authors divided study patients into two groups: Group A had cultures collected via endotracheal aspirates, PSB, and BAL; Group B had cultures only from endotracheal aspirates. Physicians made management decisions in Group A based on invasive methods; they based those in Group B on aspirates. Patients received empiric antimicrobial therapy for pneumonia after study physicians collected samples for culture and the results of these cultures, as well as response to treatment, guided the modification of therapy. Investigators found that the incidence of VAP was similar in both the groups suggesting similar diagnostic ability. They noted more frequent antibiotic changes in Group A, with no demonstrated mortality benefit. Additionally, the investigators assessed the agreement between the invasive and noninvasive techniques by comparing results of the various methods in Group A. In 71% of cases, they found total agreement of all three methods, and in 21% endotracheal aspirates agreed with either BAL or PSB. Importantly, in no case did PSB or BAL recover a pathogen not recovered by tracheal aspiration.

A slightly larger study by Ruiz et al. (151) found comparable results. This group of investigators prospectively evaluated 76 consecutive patients

admitted to their surgical ICU with clinical suspicion of VAP. These patients were randomly divided into two groups: Group 1 underwent noninvasive evaluation while Group 2 underwent invasive evaluation. Physicians made all empiric antibiotic choices according to ATS guidelines, and although many patients received antimicrobial therapy for causes other than the episode of VAP in question, no patient received antibiotic therapy for VAP prior to collection of specimens. Investigators drew three major conclusions from this study: (1) diagnostic yields in both groups were similar; (2) morbidity and outcomes were similar between the two groups; and (3) invasive studies are significiantly more costly than noninvasive studies.

In the largest study of its kind to date, Fagon and colleagues (152) randomized 413 patients in 31 ICUs to either invasive or clinical management of VAP. Clinicians based management decisions in the invasive group on results obtained from BAL and/or PSB, and those in the clinically managed group on data collected from clinical evaluation and nonquantitative endotracheal aspirates. Investigators concluded that compared to the clinical management schema, the invasive strategy led to a lower mortality at 14 days (although this difference became insignificant by 28 days), reduced organ dysfunction, and decreased antibiotic use in cases of suspected VAP. Notably, however, of the 179 patients in the clinical management group with positive cultures, 24 (13%) initially received inappropriate antibiotic therapy, as compared to 1 of 90 in the invasive group (1%). An important consideration is whether the consequences of this disparity played an important role in the results of the study. Efforts to compare various specimen-collection techniques become difficult, as no gold standard for the diagnosis to which we can compare these methods exists (153). In attempts to elucidate the diagnostic characteristics of various sampling techniques relative to each other, a number of authors have compared noninvasive testing (endotracheal aspiration) and bronchoscopic methods (PSB and BAL) to histologic examination (142,154,155). The interpretation of data from the various sampling techniques remains controversial. The available literature on the subject suggests that the more distal specimens (i.e., those collected via BAL or PSB) may give greater specificity but have less sensitivity for detecting pneumonia in patients with positive parenchymal cultures, whereas more proximal cultures (i.e., those collected with endotracheal aspiration) may have more sensitivity.

In a prospective analysis that included patients both with and without a history of previous antibiotic therapy, Bonten et al. (156) evaluated the clinical utility of bronchoscopy in determining the treatment course of 155 patients with clinical suspicion of VAP. Cultures confirmed the suspicion of VAP in 72 of these patients. Of these patients, 40 (56%) had been started on empiric therapy prior to obtaining specimens; results allowed continuation of the initial regimen in 26 of these patients and adjustment of therapy in 14. The remaining 32 patients had not been treated empirically, and study physicians initiated therapy based on these positive cultures. In 66 of the

study patients (34 of whom had been empirically treated with intravenous antibiotics), the clinical suspicion of pneumonia could not be confirmed by bronchoalveolar lavage (BAL) or bronchoscopic PSB because of either negative or subthreshold results. In the 34 patients who received empiric treatment but had negative cultures, investigators discontinued antimicrobial therapy in 17 (50%). An observation in the study was that while positive cultures affected clinical decisions in all patients (either supporting empiric therapy, altering empiric therapy, or initiating therapy de novo), negative cultures had a less predictable effect on empiric therapy. Importantly, negative cultures influenced clinicians to choose either to continue or to discontinue therapy, but not to alter it. These findings raise questions about the understanding of, and confidence in, negative cultures. Given the premise that delaying antibiotic therapy in patients with proven VAP is an independent risk factor for increased mortality (10), responsible use of antibiotic therapy mandates that clinicians treat all patients with suspected VAP. To avoid overtreatment and the potential complications such as antibiotic resistance, clinicians must develop an understanding of how negative cultures can impact antimicrobial prescribing. For example, in the Bonten study, 32 patients (or approximately one-quarter of the study group) were not treated initially with antibiotics and subsequently had negative microbiologic cultures from bronchoscopic specimens. These patients might have been candidates for de-escalation of their antibiotic therapy, if they had actually been given therapy initially.

The observation that clinicians have little confidence in negative cultures was supported by Heyland et al. (157) who evaluated the clinical utility of PSB and BAL in a prospective cohort study of 92 patients undergoing bronchoscopy. Investigators compared the results of these patients with results from a 49-patient control group who underwent noninvasive studies. The authors attempted to determine physician confidence in the diagnosis of VAP when employing bronchoscopic techniques, as well as the impact of these studies on patient care. The study concluded that invasive testing did indeed increase the physicians' confidence in making a diagnosis; however, physicians made most antibiotic changes based on positive cultures. When BAL or PSB yielded negative results, the treating clinicians again made the decision to either continue or discontinue therapy, not to modify it. In only 9 of 34 patients (26.5%) did physicians, despite the increased level of confidence reported by the authors, choose to stop antibiotic treatment when faced with negative cultures.

One may assume from the studies by Bonten et al. (156) and Heyland et al. (157) that physicians infrequently change therapy based on negative cultures. This takes on special significance with VAP when one considers that the broadness of the empiric therapy is often influenced by the prevalence of two pathogens—*P. aeruginosa* and MRSA—which each require modifications from a monotherapy regimen. Inability to exclude these

pathogens can lead to maintenance of regimens that may be broader than necessary.

In an autopsy study comparing histologic and microbiologic techniques, Kirtland et al. (154) demonstrated the utility of negative cultures. Of the 39 patients in the study, 16 had sterile lung parenchyma by quantitative tissue culture. The authors found PSB to be the most sensitive test for diagnosing sterile lung tissue; however, they found the specificity and positive predictive value of negative PSB to be low (52% and 54%, respectively). Given these results, one would expect to have great difficulty in the interpretation of a negative culture, much as it appears the Bonten investigators did (156). For BAL and tracheal aspirates, however, Kirtland et al. (154) found much different results in relation to sterile lung tissue: though sensitivities were lower (63% and 31%, respectively), both specificity and positive predicted value of the negative test were 100% for tracheal aspirates and 96% and 91%, respectively, for BAL. It should be noted that the number of patients was too small to draw definitive conclusions from these limited data. In the case of nonsterile lung parenchyma (i.e., a microbial species was isolated from lung parenchyma), the investigators found PSB to be the most specific method in identifying the organism present at postmortem bronchoscopy and/or from histologic cultures at autopsy. Based on these findings, if there was a negative culture from either BAL or tracheal aspirate, one could ask if it is reasonable to assume that neither *P. aeruginosa* nor MRSA was involved in the infectious process. With such an assumption, then there would be the option to discontinue therapy directed specifically at these two pathogens.

While investigators confirm the clinical utility of positive cultures from both invasive and noninvasive techniques, the utility of negative cultures remains elusive. Though no clinical trials to date have definitely established the role of negative cultures, the clinician may find that what does not grow on culture is at least as important and useful as what does grow. The potential usefulness of negative endotracheal aspirates in excluding pathogens in patients with VAP has been discussed by several groups of investigators (149,158–160). Contributing to the significance of these opinions is the fact that important pathogens such as *P. aeruginosa* and MRSA usually grow readily on routine media and should therefore be isolated in culture if they are present in an infection. An important clinical application of these facts was conveyed in the American Thoracic Society guidelines for the management of patients with HAP, in which it was stated that if *P. aeruginosa*, resistant *Acinetobacter* spp, or MRSA were not isolated and the patient was improving, then it might be reasonable to change from combination therapy to monotherapy (13). Negative cultures from tracheal aspirates, and possibly BAL, may provide the clinician with much useful information and should aid in the de-escalation of antibiotic therapy.

Adding more confusion to an already complex issue is the influence of prior antibiotic therapy on such decisions. The interpretation of negative cultures seems most reasonable in patients who have not been recently exposed to antibiotics. Unfortunately, there is no consensus in the literature to define what would be considered recent, although antibiotics within the past 15 days have been considered as a risk factor for subsequent resistance (66). Ruiz et al. (151) have stated that the number of cultures with significant growth was clearly dependent on the presence of prior antimicrobial treatment and lowest in patients with a recently introduced antimicrobial treatment within the last 72 hr before microbial investigation (151). An important absence of data exists with regard to the influence of antibiotics on the interpretation of negative cultures in patients who have been on antibiotics for less than 72 hr. Although it does not definitively answer the question, the study by Souweine et al. (161) provides some important insights. In their trial, 52 patients with VAP were evaluated in terms of when antibiotics were given in relation to bronchoscopy. Patient groups included those patients who had received no antibiotic, antibiotic within 24 hr of bronchoscopy, and antibiotic >72 hr prior to bronchoscopy. Cultures were often negative for patients receiving antibiotic within 24 hr of bronchoscopy, probably because therapy was successful, not because no infection was present. In this group of patients, the best diagnostic threshold values for VAP were identified to be 10^2 CFU/mL for PSB cultures and 10^3 CFU/mL for BAL cultures. False negatives were rare if a patient received antibiotics for >72 hr hr prior to antibiotics. Although diagnostic test thresholds should be decreased for patients receiving antibiotic therapy in the prior 24 hr, sensitivity was good for patients receiving antibiotic for >72 hr prior to bronchoscopy. Unfortunately, no conclusions could be drawn for patients who received antibiotics within 24–72 hr of bronchoscopy.

Even though the exact role of negative cultures has not been elucidated, the important contribution of antibiotics to the development of resistance makes this an area deserving of more investigation and of more consideration in clinical decision making. When such data are taken within the context of a patient who is clinically improving and who has a declining clinical pulmonary infection score, then clinical judgment may support de-escalation.

Duration of Therapy

Once the clinician initiates antibiotic therapy and appropriately de-escalates therapy based on microbiologic data, a duration of antibiotic therapy must be decided upon. For cases of VAP caused by *H. influenzae* and methicillin-sensitive *S. aureus*, the ATS recommends treatment courses of 7–10 days; episodes caused by *P. aeruginosa* and *Acinetobacter* spp. carry recommended treatment courses of 14–21 days (13). These recommendations are

not based on controlled trials or prospective studies, but rather by expert opinion. Recently, these guidelines have been challenged.

In a study that initially used a bronchoscopic BAL along with clinical parameters to confirm the diagnosis of VAP but subsequently used semiquantitative tracheal aspirates for microbiologic surveillance, Dennesen et al. (142) evaluated the response to appropriate antimicrobial therapy in 27 patients with VAP. The investigators followed a number of clinical parameters (T_{max}, PaO_2/FiO_2, WBC count, semiquantitative cultures of endotracheal aspirate) after the initiation of therapy, and monitoring them for evidence of resolution. The authors found the resolution of clinical parameters to occur primarily within the first 6 days of therapy. Cultures of endotracheal aspirates showed that colonization with *P. aeruginosa* persisted throughout the duration of treatment, whereas colonization with *S. aureus*, *H. influenzae*, and *S. pneumoniae* resolved shortly after initiation of therapy. In only half of those colonized with *Enterobacteriaceae* did colonization cease. Furthermore, nearly all patients became secondarily colonized with *P. aeruginosa* during week 2 of antibiotic chemotherapy. The authors hypothesized that since most clinical parameters of infection resolved in 6 days, and secondary colonization by resistant organisms occurred during the second week of therapy, 7 days may be a more appropriate duration of therapy for VAP than the conventional duration.

Eight years prior to the study by Dennesen et al. (142), Montravers et al. (162) conducted a study using follow-up PSB to assess treatment response in patients with HAP. Specimens were collected with a second bronchoscopy 3 days after institution of antimicrobial therapy. Even though appropriate therapy resulted in a rapid bacteriological clearance of the distal airways, it was not possible to assess the effect on the proximal airways (i.e., colonization) because tracheal aspirates were not collected.

Supporting Dennesen's hypothesis that a shorter course of antibiotic therapy for the treatment of VAP may be appropriate, Ibrahim et al. (155) evaluated a clinical guideline implemented for the treatment of VAP in the ICU. This guideline included a 7-day course of antibiotic therapy, as well as explicit instructions for empiric treatment. The investigators prospectively evaluated 102 patients, 50 prior to institution of the guidelines, and 52 after institution. The authors found that initial adequate antibiotic treatment occurred more often with the implementation of the guideline. As expected, patients also underwent shorter antibiotic courses when treated with these guidelines. Importantly, investigators noted no mortality difference between the two groups, suggesting that this shortened course was both efficacious and safe. As a result of this shortened antibiotic course, those patients treated after implementation of the guideline experienced shorter ICU stays and lower antibiotic costs.

Similar to the results of Ibrahim et al. (155), Chastre et al. (163) conducted a prospective, multicenter, randomized double-blind study of 401

patients with VAP confirmed by quantitative cultures obtained by bronchoscopic PSB and/or BAL. Only patients who had received initial appropriate antibiotic therapy were included. Therapy was divided into two categories: short course, which was given for 8 days in 197 patients vs. long course, which was given for 15 days in 204 patients. The results of this study were that shorter course therapy had the same clinical efficacy as long course and led to less antibiotic use. In this study, slightly more patients with nonfermenting Gram-negative bacilli assigned to the 8-day regimen had pulmonary infection recurrences, but the authors were unable to demonstrate the inferiority of the 8-day regimen for infection by such pathogens as compared with the 15-day course. Even though such results do not definitively prove that therapy for HAP or VAP can be limited to 7 days, they offer the basis on which further studies addressing this pivotal question should be performed.

In addition to the results suggesting efficacy of short-course therapy in patients with VAP, the three trials cited above emphasize a similar point. In the Dennesen study, acquired colonization, predominately with resistant pathogens such as *P. aeruginosa* or *Enterbacteriaceae*, usually occurred in week 2 of therapy and frequently preceded a recurrent episode (142). In the Ibrahim study, a second episode of VAP was more likely to occur in the patients receiving the longer, traditional duration of therapy (155). In the Chastre study, multiresistant pathogens were more frequent causes of recurrent infection in patients who were randomized to the 15-day treatment arm (163). An important conclusion from these three trials was not only that a shorter course of therapy of VAP may be efficacious, but also that the second week of therapy tended to select the resistant pathogens that caused the next episode of pneumonia. Such consistent findings strongly support the concept that shorter durations of therapy, when possible, may be an important form of de-escalation.

The data of Dennesen et al. (152), Ibrahim et al. (155), Chastre et al. (163), and Singh et al. (141) illustrate the safety, efficacy, and potential benefit of short course antibiotic therapy for the treatment of VAP. In addition, on the foundation provided by Dennesen et al. (142), Luna et al. (143) have shown that clinical markers and the CPIS can provide important prognostic information and potentially predict recovery of patients by examining the resolution of clinical parameters. Combining the results of these investigations might allow the clinician to treat VAP in a manner vastly different from the current standard. Given the proven efficacy and safety of short course therapy for VAP, the clinician, by implementing a modified CPIS, may be able to define those patients exhibiting improvement with treatment and individualize the course of antibiotic therapy to best suit each patient.

While the suggestions for de-escalating without a positive culture have not been substantiated in clinical trials, the importance of de-escalation from a broad-spectrum regimen, when possible, cannot be overemphasized. Without early therapy broad enough to cover likely pathogens, including

those with significant resistant mechanisms, there is risk for increased mortality. Of the risk factors for selection of resistance, antibiotics are one of the main offenders. At a time when there are no significant alternatives on the horizon for treating resistant organisms, there is a need to encourage the implementation of antibiotic treatment strategies that limit the emergence of antimicrobial resistance while new drugs and technologies are being developed (164). De-escalation is one such strategy. Until more definitive recommendations can be developed on how this can be accomplished in the absence of a positive culture, it will require clinical judgment that is strongly shaped by an understanding of the relevant issues and the literature supporting them.

CONCLUSION

Empirical antibiotic use is often "syndrome directed" (e.g., a patient is highly suspected of having VAP) (165). Even when recommendations are available for a disease entity, it is important for the clinician to be amenable to adapting those recommendations to meet the specific variables such as patterns of bacterial resistance that may be prevalent in the unit in which the patient is being treated. This principle takes on special significance when considering two themes in the therapy of serious infectious processes such as VAP: (1) initial therapy must be adequate to minimize mortality; and (2) selective pressure from antibiotic use leads to patterns of resistance, which make treatment of not only the present, but also future, patients more difficult. A major challenge in the empiric therapy of VAP is to have initial therapy that is broad enough to cover the likely pathogens but that is decreased in broadness, when possible, to lessen the risk of antibiotic resistance. This latter concept is important when one recognizes that certain classes of antibiotics impose unintended consequences, also termed collateral damage (166), and these lead to the resistant organisms that can then cause the next episode of clinical disease. A tendency in syndrome-directed therapy is to use the same antibiotic regimen for the majority of patients with the problem. An unfortunate consequence of such homogeneous therapy is that it may result in the selective pressure that leads to antibiotic resistance. Heterogeneous use of antibiotics (i.e., varying among patients the classes of antibiotics used) may apply less pressure and therefore be a better option for managing the resistance epidemic that is occurring globally (167). The magnitude of the problem of antibiotic resistance is so broad that in July 2004, the Infectious Diseases Society of America published a document entitled *Bad Bugs, No Drug* (168). This paper acknowledges that as antibiotic discovery stagnates, a public health crisis is brewing. In the absence of the development of new classes of antibiotics for treating resistant organisms, it is incumbent that clinicians understand how antibiotics contribute to resistance and look for patterns of antibiotic usage that may in actuality be a part of the solution of this daunting

dilemma. An understanding of the principles discussed in this chapter should contribute to careful thought processes in the decisions made about empiric antibiotic therapy in VAP. This hopefully will be part of the solution for one of the major challenges in critical care medicine.

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What Is the Role of Microbiological Surveillance in the Management of Ventilator-Associated Pneumonia?

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INTRODUCTION

ICU-acquired infection is estimated to be 5–10 times more common than infections in general wards (1–5), more expensive, and more often associated with resistant micro-organisms. The commonest nosocomial infection in ICU patients is ventilator-associated pneumonia (VAP), which increases both length of stay and mortality. The risk of developing VAP has been estimated at 1% per day of intubation and mechanical ventilation, with higher rates in patients with ARDS. Recently reported data reveal that VAP rates are lowest in pediatric and respiratory ICUs and highest in trauma and burn units (6). Table 1 is obtained from HELICS (7) and we see differences in VAP rates published in the literature, with a median rate in medical ICUs of 7.3 VAP per 1000 patient-days (8–11).

Table 1 Hospitals in Europe Link for Infection Control Through Surveillance (HELICS)

Country Network	Belgium NSIH-ICU	France (SE) REA-SE	The Netherlands PREZIES-ICU	Spain ENVIN-UCI	Germany KISS-ICU	US NNIS (CDC)
Type of surveillance	*Patient, date of admission*	*Patient, date of discharge*	*Patient, date of admission*	*Patient, date of admission*	*Unit based, 5 ICU types*	*Unit based, 11 ICU types*
Incl. patients	*>48 hr ICU (>24)*	*>48 hr ICU*	*>48 hr ICU*	*>24 hr ICU*	*All*	*All*
Period incl. data	1996–2000	1996–2000	1997–1999	1996–1997	1997–2000	1992–2000
No. of patients	63491	64658	2975	9544	250313	
Patients-days	424028	701026	27922	68915	956807	7446512
Mean LOS (days)	6.7	10.8	9.4	7.2	3.8	
P50 SAPS II	29	34		25		
P50 APACHE II			18	13		
Definition of device-day	*<24 hr use*	*<24 hr use*	*>=24 hr use*	*<24 hr use*	*<24 hr use*	*<24 hr use*
Central line days	*3 cath = 1 day*	*3 cath = 1 day*	*3 cath = 3 days*	*3 cath = 3 days*	*3 cath = 1 day*	*3 cath = 1 day*
Ventilation-days/1000 pd	377	571	608	510	430	419
Central line days/1000 pd	709	671	681	1143	721	523
Urinary cath. days/ 1000 pd		750	864	730	784	580
Definition of "ICU-acquired" infection	*Infection date > 2 days (48 hr) after admission*	*Infection date > 2 days (48 hr) after admission*	*Not present at admission*	*Not in incubation at admission*	*Not in incubation at admission*	*Not in incubation at admission*

Definition of "device-associated" infection	*>=1 day device before infection*	*>=1 day device before infection*	*Clinician decides*	*>=24 hr device in 48 hr bef. inf.*	*>=24 hr device in 48 hr bef. inf.*	*>=24 hr device in 48 hr bef. inf.*
Infection episodes in indicator	*First infection only*	*First infection only*	*All episodes*	*All episodes*	*All episodes*	*All episodes*
Definition of Pneumonia	*Large, clinical + bacteriological*	*Bacteriological BAL/PB*	*CDC + definite BAL/PB*	*CDC*	*CDC*	*CDC*
# VAP/100 admissions	5.1%	9.1%	14.0%	6.5%	1.6%	
# VAP/1000 ventilation days	20.2	14.8	24.5	17.7	9.9	10.0
# C-BSI/100 admissions	1.3%	0.8%	2.2%	1.1%	0.5%	
# C-BSI/1000 central line d	2.7	1.0	3.5	1.3	1.8	5.1
# UTI/100 admissions		8.6%	6.7%	3.1%	1.1%	
UTI rate/1000 ur. catheter d		10.5	8.2	5.9	3.7	6.6

C Suetens, National Surveillance of Hospital Infections (NSIH). Scientific Institute of Public Health, Brussels. ESQH Workshop Brussels, 30 November 2001.

A study in the United States of ICU ventilator-associated pneumonia found that the formation of a multidisciplinary team, which revised care protocols continuously and used NNIS methods, reduced the pneumonia rate from 19.7 to 7.2 per 1000 ventilator days (12). Hence, it is of great importance to achieve specific measures for VAP control in ICU patients. But surveillance, as Kollef (13) recently published, is only one nonpharmacological element of an effective infection control program. Dealing successfully with this infection requires the identification of cases and their etiology, comparison of current attack rates of infection with baseline data, characterization of epidemiologic features of the infections, development and implementation of control measures, and continuing microbiologic surveillance.

In fact, the Centers for Disease Control and Prevention published a set of 74 recommendations for preventing bacterial nosocomial pneumonia (14). Based on well-designed experimental or epidemiologic studies, those guidelines strongly recommended that all hospitals:

1. Conduct surveillance of bacterial pneumonia among ICU patients at high risk for nosocomial bacterial pneumonia (e.g., patients receiving mechanically-assisted ventilation and selected postoperative patients) to determine trends and identify potential problems (15–22); include data regarding the causative micro-organisms and their antimicrobial susceptibility patterns (23,24); express data as rates (e.g., number of infected patients or infections per 100 ICU days or per 1000 ventilator-days) to facilitate intrahospital comparisons and determination of trends (9,25–27)
2. Do not routinely perform surveillance cultures of patients, of equipment, or devices used for respiratory therapy, pulmonary-function testing, or delivery of inhalation anesthesia (21,28,29)

BASIC APPROACHES TO SURVEILLANCE

Prevalence rates of infection are usually higher than incidence rates. Conclusions about infection risk factors cannot be drawn from such data, but this method can be useful for validating total surveillance information. In general, there are advantages to a focus on targeted surveillance in patients at increased risk for VAP: (a) it permits concentration of effort on areas where infection control measures may have the greatest effect and thus a better use of limited resources; (b) it takes into account differences in infection risk for different patient populations. This type of surveillance can reduce hospital-acquired infections. In 1987, the NNIS system began reporting device-day rates to member hospitals; from then, there has been a 7–10% annual reduction in mean rates for device-associated infections among ICUs in NNIS hospitals. One disadvantage is that this approach

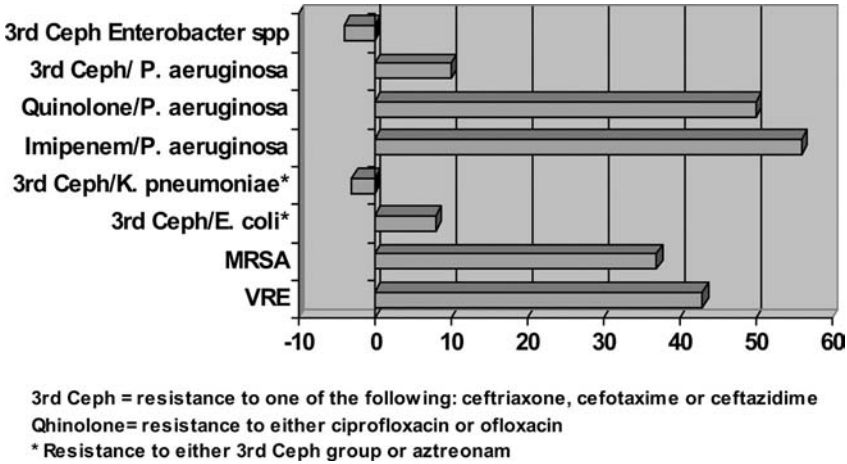

Figure 1 Percent increase in resistance 1999 vs. 1994–1998.

may miss clusters or outbreaks of infections not included in the surveillance program.

Targeted surveillance that is based on pathogen type or infection site is mainly laboratory-based. Resistance is most common in patients receiving mechanical ventilation, and in universities or teaching hospitals (Fig. 1) VAP caused by antimicrobial resistant bacteria often follows prior antimicrobial use and is an important problem. This type of surveillance approach involves infections at the same site, caused by pathogens that are epidemiologically significant: extended-spectrum β-lactamase-producing organisms (ESBL), methiullin-resistant Staphylococcus aureus (MRSA), vancomycin-resistant enterococcus (VRE), vancomycin intermediate *S. aureus* (VISA), or vancomycin resistant *S. aureus* (VRSA). It permits concentration of efforts on those areas where control measures may be most effective, but it may also miss clusters or outbreaks of infections not included in the surveillance program.

Bouletreau et al. (30) compared the accuracy and timeliness of two surveillance methods in an ICU. Data were collected either by using the selective surveillance method, derived from the NNIS ICU (device-related) surveillance component, or a reference surveillance method that involved the review of patient case records for signs and symptoms of infection for every patient in ICU. The selective surveillance method had a higher sensitivity (90.5%) and specificity (97.7%) for identifying device-related health care-associated infections, and required only one-third of the time for data collection.

MICROBIOLOGICAL CONSIDERATIONS

Bacterial Etiology

There are numerous reports that illustrate the etiologic pathogens causing VAP (13,31–42). Gram-negative aerobes are isolated in 55–85% of VAP cases with *Pseudomonas aeruginosa* the most frequently reported isolate (≈21%), followed by *Staphylococcus aureus* (≈20%). In up to 40% of patients, the origin may be polymicrobial. However, these reports should not replace hospital-specific information because micro-organisms and antimicrobial resistance in hospitals depend on numerous factors: type of ICU, length of stay, device utilization, reservoirs, outbreaks, workload, prior antimicrobial exposure in humans and animals, etc. Our group (43) conducted a study evaluating the microbiological etiology of VAP (diagnosed by bronchoscopy) in ICUs in three different cities. These data suggested that the causes of VAP varied significantly across the treatment sites, resulting in a need for variations in antimicrobial utilization that were ICU specific.

Impact of Resistance

In patients receiving mechanical ventilation, *P. aeruginosa*, *Acinetobacter* spp., MRSA, VRE, and other antibiotic-resistant bacteria assume increasing importance (44,45) (see Figs. 2 and 3). Whereas micro-organisms in the normal human flora sensitive to antimicrobials are suppressed, resistant strains persist and may become endemic in the hospital. As an antimicrobial agent becomes widely used, bacteria resistant to this drug eventually emerge and may spread in the health care setting.

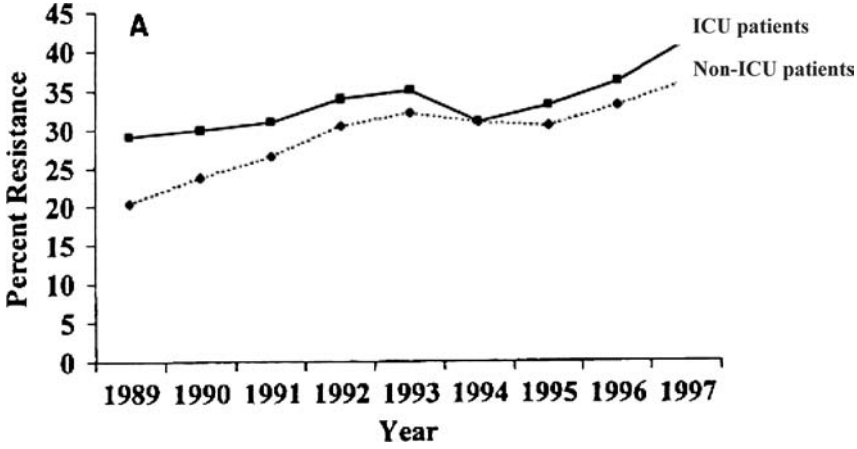

Figure 2 Increasing rates of MARSA in the United States. (From Ref. 45)

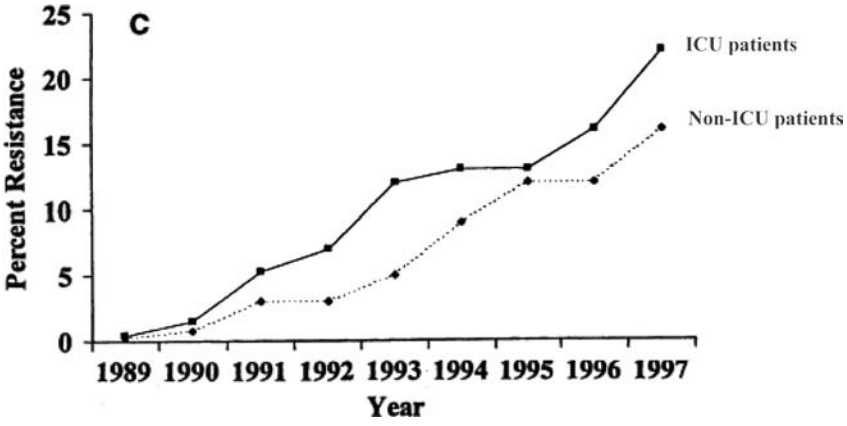

Figure 3 Increasing rates of VRE in the United States. (From Ref. 45)

VAP caused by antimicrobial resistant bacteria often follows prior antimicrobial exposure, and ICU patients often require invasive support activities that increase the risk of infection, demanding more antimicrobial treatment and exacerbating the risk of selecting resistance. Furthermore, multiresistant micro-organisms can be transmitted to the community through discharged patients, staff, and visitors, causing significant disease in the community. Empiric antibiotic selection is usually based on hospital guidelines, but several studies have demonstrated the critical importance of appropriate early antibiotic therapy for patients with VAP (46), and that rational use of antibiotics reduces the incidence of drug-resistant pathogens and the cost of treatment (37,46–48).

The NNIS System published a comparison of resistant rates among common pathogens identified from ICU patients from January to December 1999 with 1994–1998 (10). This report displayed the changes in antimicrobial resistance in United States hospitals during this time (Fig. 1): a significant increase in imipenem- and quinolone-resistant *Pseudomonas aeruginosa*, VRE, and MRSA. In the ENVIN-UCI of Spain (42), the most frequent markers of resistance were ciprofloxacin-resistant *Pseudomonas aeruginosa* (23.5%), MRSA (27.1%), imipenem-resistant *Acinetobacter baumannii* (38.1%), and ciprofloxacin-resistant *Escherichia coli* (28.9%); no glycopeptide-resistant strains of *Enterococcus* spp. or *S. aureus* were identified.

Effective surveillance is critical to understanding and controlling the spread of resistance: surveillance allows recognizing resistance trends, alerts us to new resistance mechanisms, permits the evaluation of the effects of interventions and the identification of risk factors for antimicrobial resistance. Lemmen et al. (49) reported a decrease in the occurrence of multiresistant Gram-negative pathogens with the implementation of individual

antibiotic regimens, discussed at the bedside with infectious disease experts, for the most prevalent infections.

MRSA

S. aureus is one of the most virulent and common nosocomial pathogens, and has a particular facility for nosocomial transmission. There are some published strategies on the control of MRSA (50,51) that include the use of expensive and relatively toxic antibiotics to treat a large number of *S. aureus* infections, screening of patients prior to admission and during their stay in high risk areas of a hospital, and routine treatment of patients and hospital staff in high risk areas with antistaphylococcal antiseptics. Increased costs have been associated with health care associated MRSA infections.

VRE

At present, some enterococci are resistant to vancomycin. Most VRE only cause colonization, but in other cases, such as *Enterococcus faecium* resistant to both penicillin and glycopeptide, infections cannot be effectively treated. Fridkin et al. (52) studied prospectively 126 ICUs from 60 U.S. hospitals for 3 years to determine the independent importance of any association between antimicrobial use and other risk factors for nosocomial infection on rates of VRE. They found that the higher rates of vancomycin ($P < 0.001$) or third-generation cephalosporin ($P = 0.02$) use were associated with an increased prevalence of VRE, independent of other ICU characteristics and the endemic VRE prevalence in a given site in the hospital. Decreasing the use, rates of these antimicrobial agents could reduce those of VRE in ICUs.

COST EFFECTIVENESS

The major costs for hospitals generated by nosocomial infection are because of the increased length of stay and extra treatment costs, whereas the increased mortality and loss of productivity are costs borne by society as a whole. Several years ago, the CDC initiated the Study of the Efficacy of Nosocomial Infection Control Project (SENIC) (53) to examine the effectiveness of nosocomial infection surveillance and control programs in the United States. Evaluation of program interventions demonstrated that they are relatively costly, but the cost benefit (cost per life year saved) for IC programs compared very favorably with PAP smears, cholesterol reduction, and mammography.

Some studies showed that patients who develop VAP can have as high as 7-fold increase in the number of days on mechanical ventilation, a 2- to 5-fold increase in the length of stay in the ICU, and a doubling of the overall hospital stay (54,55). Implementation of practices to decrease VAP will

improve the quality of patient care and contribute to reducing costs. The formation of a multidisciplinary teams that revised care protocols continuously and used NNIS methods not only reduced the rate from 19.7 to 7.2 per 1000 ventilator days, but also saved 6 days in ICU for each case of pneumonia prevented, saving an estimated US$130,000 per year (12).

Costs of an outbreak in eastern Australian of MRSA (56), involving 28 patients and two staff members, were estimated at US $47,000. The costs included additional overtime for medical support, additional temporary staff, consumables specifically related to the outbreak, obtaining and processing swabs for screening, antibiotics, and antiseptics. In addition, the expected annual cost of additional antibiotics, should the strain of MRSA have become endemic in the hospital, was estimated at US $248,000. The potential annual cost of prolonged patient stays was estimated at US $206,000.

Similarly, a large Australian teaching hospital experienced an outbreak of VRE in a hematology unit (56). The Infection Control Unit immediately developed a strategy to contain the spread: infection control practices were strengthened that included strict isolation precautions for colonized patients and individual nurses, and the room being comprehensively cleaned twice daily, followed by wiping of all surfaces and patient care equipment with a solution of 500 ppm sodium hypochlorite. This was followed by swabbing of environmental surfaces and culture for VRE. The room was held vacant until results of cultures were available (usually three or four days). In addition, much time and effort was spent on education of staff, patients, and their families about the risks of infection and the rationale behind the measures taken to limit the spread of the organism. In addition, there was the personal cost to the patient of increased pain and suffering, and anxiety caused by treatment complication.

SUMMARY

VAP is a serious problem in patients receiving mechanical ventilation. ICU patients often require actions that increase the risk of infection, requiring more antimicrobial treatment, and increasing the risk of selecting resistance.

The surveillance process is effective and improves patient care. To prevent and control VAP, we need to optimize microbiological surveillance, observe infection rates (rates evaluated must be epidemiologically valid), and spend much more time on education of health care workers.

The microbiology laboratory has a major role in this purpose: it provides daily reports of all identified infectious agents, generates annual reports on the changes in antibiotic susceptibility patterns of culture isolates, notifies the Infection Control Practitioner of positive cultures of highly

transmissible organisms, and reports select isolates to the Department of Health according to state requirements. However, it is very important to stress that a reduction in hospital acquired infection rates will not occur unless data are linked to feedback of rates to clinicians, and these data are linked to prevention strategies (57).

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13

Antibiotic Pharmacokinetics and Pharmacodynamics: How Can They Be Used to Optimize Therapy in Ventilator-Associated Pneumonia?

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INTRODUCTION

Ventilator-associated pneumonia (VAP) is characterized by its high prevalence, and more importantly, by its fatal consequences. Although the overall incidence of nosocomial respiratory infections including VAP is lower than urinary tract infection, accounting for 15–20% of the total, it is the most common infection in intensive care unit (ICU) settings (1,2). While mechanical ventilation increases the risk of pneumonia by 3- to 10-fold, crude mortality rates for nosocomial pneumonia range from 24% to 76% (3).

A number of factors hinder a good prognosis in VAP. Most of the patients developing VAP have severe underlying diseases, receive many medications and/or interventions, and typically have defects in the immune response to bacterial infection. Moreover, the rapid emergence and frequent transmission of antimicrobial-resistant pathogens in hospitals make the treatment of hospital-acquired pneumonia more complicated. Failure to kill the bacteria because of resistance results in clinical failure with VAP. The prevalence of organisms such as methicillin-resistant *Staphylococcus aureus*

(MRSA) and multidrug resistant Gram-negative bacteria is increasing worldwide, and these resistant bacteria are becoming major pathogens of VAP in many hospitals (4).

Because of its high incidence and mortality, serious underlying conditions of hosts and increasing antimicrobial resistance in pathogens, appropriate antibiotic therapy is tremendously important for the treatment of VAP (5–11). For simple infections in normal hosts, we can rely on the natural healing power of the immune system even when antimicrobial therapy is unable to eradicate the pathogen, but this is not expected to occur in immunocompromised hosts. In the case of a serious infection in hosts with defective systemic immune response, appropriate antimicrobial therapy would mean not only selection of antibiotics based on historical experience and in vitro susceptibility but also use of a proper dosage regimen, achieving both effective antimicrobial action and restraint of the emergence of resistance.

LIMITATIONS OF TRADITIONAL SUSCEPTIBILITY BREAKPOINTS

The advent of modern antibiotics in the 1940s changed the pattern of mortality in the developing world. Considering the great success of antimicrobial therapy, the fact that it has been used based upon crude breakpoints, such as MIC and MBC, is surprising. MIC and MBC have been the major parameters used to determine the activity of antimicrobial agents for several decades. Basically, MIC susceptibility and resistance breakpoints are established by the observed clinical response at usual doses or the presence of known genetic resistance factors (12,13). However, early in clinical trials, patients with higher MICs are often not treated or excluded from the database. Hence, there are few patients with infections by micro-organisms of marginal MIC available to determine the clinical breakpoint. The resistant subpopulation may not be observed at all, if the activity of the tested drug against the native bacteria population is very good. In addition, uniform application of MIC breakpoint, regardless of the site of infection, also causes confusion in the selection of effective antibiotics. For instance, pneumonia caused by *Streptococcus pneumoniae* with low level of penicillin resistance can be treated effectively with penicillin, whereas penicillin may fail against meningitis caused by the same organism at the same MIC (14–16).

Furthermore, MIC and MBC, as interpreted alone, provide only crude information on the time course of antimicrobial activity. The MIC approximates a continuous exposure to the drug for 24 hr at a threshold concentration. This approximate continuous infusion threshold may not reflect the relationship between the rate of killing micro-organism and peak and trough concentrations of the antibiotic. For example, although tobramycin and ciprofloxacin kill *Pseudomonas aeruginosa* more rapidly and extensively with

increasing concentrations, higher concentrations do not speed the killing rate of ticarcillin when the drug concentrations are in excess of four times the MIC (17). In addition, MIC and MBC do not offer any insight into the persistent effects of antimicrobial agents, the "postantibiotic effect (PAE)" (18). When exposed to certain antimicrobial agents, some microorganisms lag to recover and re-enter a log-growth period even after concentrations of the drugs have decreased below MIC. Introducing these concepts of time course in antimicrobial activity, killing rate, and PAE to the conventional practice of antibiotic treatment has opened a new horizon of antimicrobial therapy, and pharmacokinetic/pharmacodynamic (PK/PD) approach.

PHARMACOKINETICS/PHARMACODYNAMICS OF ANTIBIOTICS

While pharmacokinetics of the antibiotics deals with the time course of concentration of the drug itself, determined by absorption, distribution, and elimination, pharmacodynamics of antimicrobial agents expresses the relationship between serum concentration of antibiotics and their antimicrobial effect (19). Described in this manner, pharmacodynamics of antibiotics focus on the time course of their antimicrobial activity.

Pharmacodynamic Patterns of Antimicrobial Activity

The best science in antibiotic PK/PD and dosing comes from the animal model studies of the Craig and Andes (19,20). With multiple dosage regimen, including extreme intervals and doses, which cannot be performed in human studies, animal model studies have discovered major pharmacodynamic patterns of antibiotics determining their antimicrobial activity.

As many clinicians have discovered, antimicrobials with concentration-dependent killing and prolonged PAE, such as aminoglycosides and fluoroquinolones, are dependent upon peak serum level/MIC ratio and AUC (area under the concentration vs. time curve)/MIC ratio for their antimicrobial efficacy (19). We prefer to use the term AUIC (area under the inhibitory concentration–time curve) to represent the 24-hr AUC/MIC ratio (Fig. 1) (21). The antimicrobial activity of antibiotics characterized by minimal concentration-dependent killing and minimal PAE, such as β-lactams, is related with the duration of time above MIC ($T > \text{MIC}$) (19). These antibiotics can also be described in terms of AUIC values (21–24).

Clearly, the PK/PD parameters, $T > \text{MIC}$, peak/MIC, and AUIC are inter-related with each other because each is linked to doses, concentration, and MIC. Higher doses produce not only a higher peak/MIC and a higher AUIC but also a longer duration of $T > \text{MIC}$ (19,20). Especially within dosing intervals of 3–4 half-lives, the importance and ability of differentiating between these parameters diminishes (25). In this regard, AUIC (with

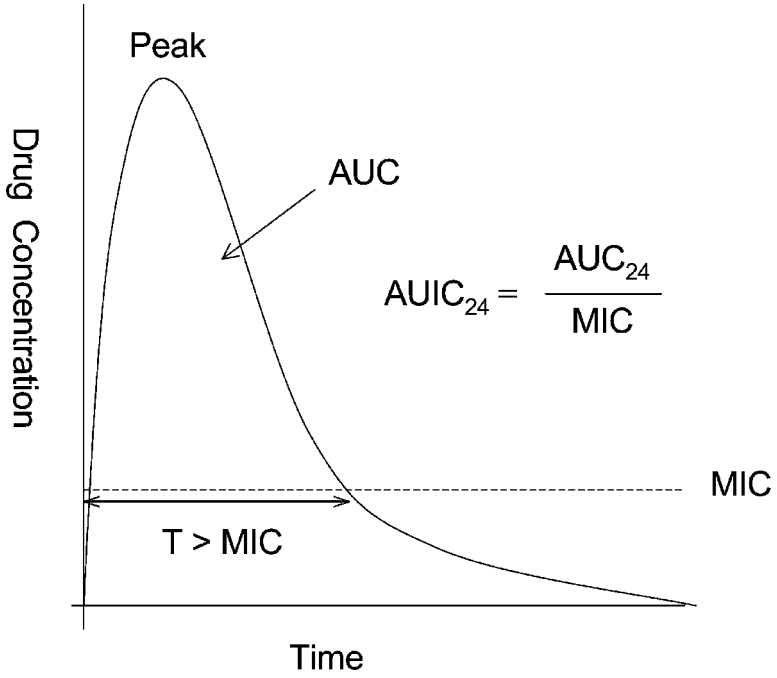

Figure 1 Relationship between the concentration vs. time curve, as area under the curve (AUC) over 24 hr (AUC_{24}), and the MIC against the organism.

advantage of reflecting both concentration and time factors) has been suggested as a good candidate for a universal parameter that applies to all classes of antibiotics, but only applies accurately when constraining the dosing intervals within 3–4 half-lives (21,25). Using the universal parameter makes it easier to compare antimicrobial activities across different classes and to evaluate the effect of antibiotics in combination (23,24).

Extreme dosing regimens of antibiotics have been tried based on the concepts of PK/PD parameters determining antimicrobial activity. For example, once-daily dosing of aminoglycosides with very high peaks and long time below MIC has become a common dosing practice (26,27). While once-daily dosing of aminoglycosides has revealed trends for decreased toxicity relating to sustaining a lower trough level, clinical improvement achieved by this method has been trivial (28–37). The beneficial effects may be attributed to the universal use of concomitant antibiotics. Continuous infusion of β-lactams has also been used based on their PK/PD characteristics. Several small clinical studies evaluating continuous infusion of β-lactams showed that the continuous infusion regimen was associated with a shorter length of treatment, decreased length of stay, lower total drug

dose, and overall cost savings while keeping equivalent clinical cure rates (38–43). However, the cost of infusion pumps and the issue of IV access should be considered when applying this practice to patients. Clinical usefulness of extreme dosing regimens of antibiotics needs to be evaluated further, as none of the studies have demonstrated PK/PD parameters while using these regimens, and these need to be carefully evaluated as a determinant of outcome.

Target Magnitudes of PK/PD Parameters for Efficacy

Magnitudes of PK/PD parameters necessary for treatment efficacy have been presented by a number of in vitro and animal model experiments. However, the target magnitudes provided by these methods can differ depending on what end-point of efficacy they use—bacteriostasis, 1–2 log killing, maximum effect, the dose protecting 50% of animal from death (PD_{50}), maximal survival, resistance protection, etc. The target magnitudes of PK/PD parameters presented by clinical studies also tend to be different, depending on the settings of the patients and infections, and the methods of analysis.

Target Magnitudes of PK/PD Parameter for Efficacy of β-Lactams

In vivo efficacy of β-lactams was observed when $T > \text{MIC}$ was at least 30–40% of the dosing interval in animal studies (19,20). This magnitude was supported by the results that 90–100% of mice infected with pneumococci survived when $T > \text{MIC}$ was above this threshold (44–46). Human studies conducted in patients with acute otitis media also demonstrated that a similar magnitude ($T > \text{MIC}$ of 40%) could achieve an 85–100% bacteriologic cure rate (47).

On the other hand, there are data suggesting that a longer $T > \text{MIC}$ of β-lactams is necessary to treat Gram-negative organisms. To produce a bactericidal effect, *Escherichia coli* required a longer exposure to cefazolin (>60% vs. 20%) compared to *S. aureus* in an animal study (48). Maximal bactericidal activity of ticarcillin against *P. aeruginosa* was achieved when the concentrations of the drug were above the MICs for virtually 100% of the 24-hr treatment period (48). Relevant to this topic, clinical studies performed in nosocomial pneumonia with Gram-negative organisms demonstrated that 100% $T > \text{MIC}$ was needed to cure those patients with cefmenoxime, which could be achieved when AUIC was over 125 (22,25). A clinical study evaluating the efficacy of cefepime against Gram-negative infections also showed poor microbiological outcome (0%) when $T > \text{MIC}$ MIC was <100%, and showed that time over $4.3 \times \text{MIC}$ was the strongest related variable for efficacy of the drug (49).

Target Magnitudes of PK/PD Parameter for Efficacy of Fluoroquinolones

Studies in animals and humans with Gram-negative bacilli suggest that the AUIC of fluoroquinolones needs to exceed 100–125 to obtain high rates of bacteriologic and clinical cure (50,51). Values of >250 were associated with a very rapid eradication of Gram-negative bacilli from endotracheal aspirates of patients with nosocomial pneumonia (Fig. 2) (51). When the selection of bacterial resistance was examined in relation to antibiotic pharmacokinetics and organism MIC in the patients from four nosocomial lower respiratory tract infection (LRTI) clinical trials, the PK/PD parameter predictive of development of resistance was an AUIC value below 100 (Fig. 3) (52).

With regard to target level of AUIC of fluoroquinolones for Gram-positive bacteria, there still exist controversies. Animal models and some in vitro studies have suggested that the threshold AUIC of fluoroquinolones against *S. pneumoniae* is lower, in the range of 25–35 (53–56). However,

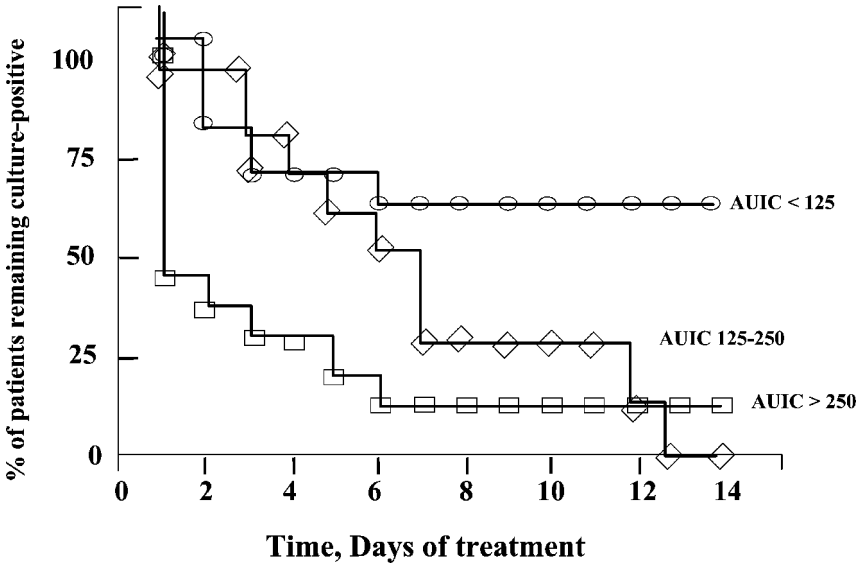

Figure 2 Relationship between the daily cultures and three groups of ciprofloxacin AUICs in 74 patients with nosocomial pneumonia. The patients with AUICs <125 (◯) had only 30% of the cultures becoming negative in 14 days. If the AUIC was 125–249 (◇), the cultures became negative in all patients, but over half required 6 days to achieve organism eradication. The patients with AUICs >250 (□) had over 60% of their cultures negative after 1 day of therapy. These data establish concentration dependence to the action of ciprofloxacin in patients. AUIC = area under the inhibitory concentration–time curve. (From Ref. 51)

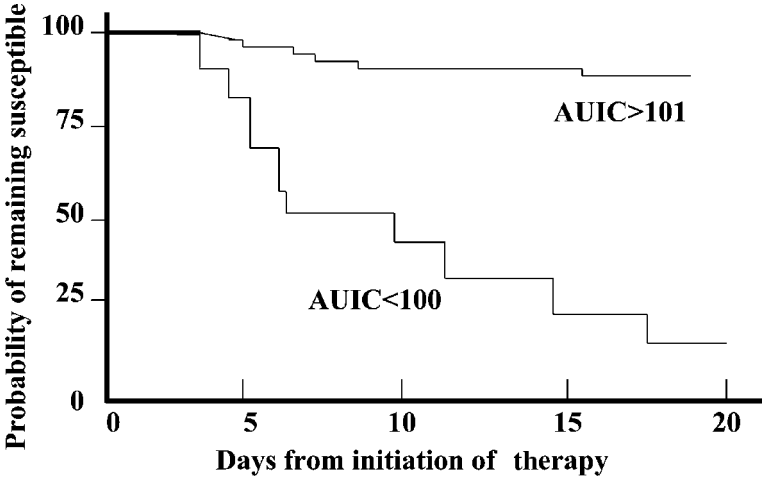

Figure 3 Relationship between the initial AUIC and the time to onset of organisms developing resistance in 127 patients. When the initial AUIC was >100, only 8% of patients developed resistant organisms to the antibiotic responsible for the AUIC >101. When the initial AUIC was <100, 93% of the patients developed resistance to the antibiotic started at that low AUIC value. This analysis employed hospitalized patients with serial cultures of the infection site, receiving a variety of antimicrobial regimens, including fluoroquinolones in many cases alone and in combination. AUIC = area under the inhibitory concentration–time curve. (From Ref. 52)

these 25–35 breakpoints in animal models targeted bacteriostatic effect (i.e., no net change in the numbers of surviving organisms) obtainable with 24-hr exposure to antibiotics (53,54). When 3-log killing of the pneumococci was the end-point in animal models, an AUIC >100–125 was also necessary (Fig. 4) (57). Although animal studies evaluating survival showed maximum animal survival at values of AUIC >25, these effects were obtained under the assistance of neutrophils (20). Hence, they represent the combined effect of bacteriostatic amounts of antibiotics and the associated impact of bacterial killing by neutrophils.

The analysis by Forrest et al. (51) to study the relationship between PK/PD of ciprofloxacin and both clinical and microbiological outcomes in patients with nosocomial pneumonia demonstrated no difference in effective levels of AUIC by target organism (51). An analysis by Preston et al. (58) to evaluate PK/PD features of levofloxacin in pneumonia concluded that a peak/MIC ratio of 12.2 : 1 was associated with an AUIC of 110 (calculated from peak) and is the break point for levofloxacin effectiveness, regardless of the species of organisms (58).

A lower target magnitude of AUIC (unbound drug AUIC >33.7) was presented by an analysis of human trials comparing the efficacy of

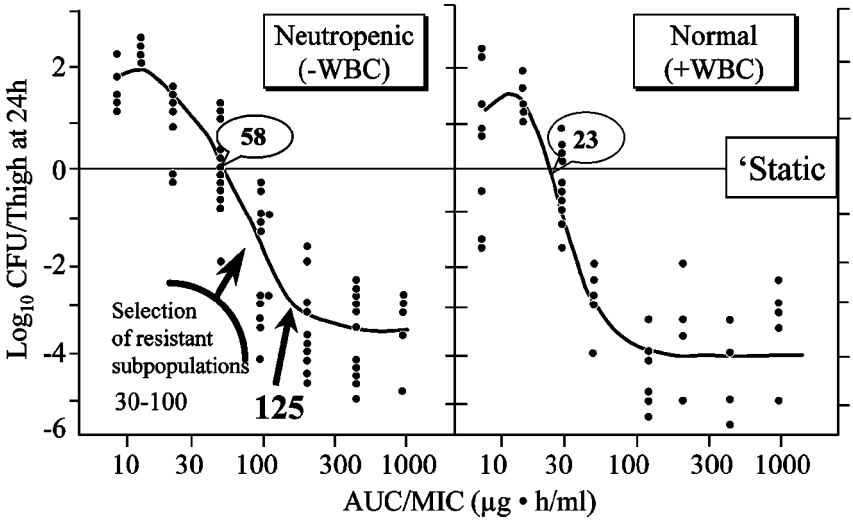

Figure 4 Relationship between levofloxacin AUIC and the surviving inoculum of *Streptococcus pneumoniae* after 24 hr of treatment in a murine thigh model of infection. Animals were given levofloxacin 4.7–300 mg/kg every 6 hr for four doses. Some of the animals were made neutropenic prior to administration of levofloxacin. The line across the data indicates the point of bacteriostatic response in this model, which is approximately equivalent to the predictive dose that produces half of the maximum effect attributable to the drug for levofloxacin. In neutropenic mice, the bacteriostatic AUIC in this model was 58, while mice with intact host defense required only an AUIC of 23 for bacteriostatic actions. A log kill in excess of 3 (i.e., bactericidal action) required AUIC values >100 regardless of the state of host defense. (We added lines and interpretive callouts.) AUIC = area under the inhibitory concentration–time curve; MIC = minimum inhibitory concentration; WBC = white blood cell. (From Ref. 57)

levofloxacin and gatifloxacin for the treatment of community-acquired LRTIs (59). However, these data have a limitation in the method for evaluating microbiologic efficacy. Patients classified as "presumed eradicated," defined as the presence of the clinical response and no available material for follow-up culture, were regarded as a microbiologic cure. There was no information on the time of negative culture or, in many cases, no proof of individual evaluation at all. Evaluation of bacterial killing rate with serial cultures was not attempted, and measurement of individual pharmacokinetics was also not performed in this study.

Data from Phase II dose-finding studies of grepafloxacin against *S. pneumoniae*, where both pharmacokinetic sampling and serial cultures of the patients were performed, demonstrated that more rapid killing of *S. pneumoniae* was associated with AUIC values >100 (60,61). AUIC <276

Table 1 Rate of Bacterial Eradication Controlled by AUIC for Fluoroquinolones

AUIC (peak:MIC)	In vitro time to eradication	Murine 24-hr eradication	Human time to eradication
30 (3:1)	8–24 hr	Static	>10 days
125 (6:1)	4–8 hr	2–4 log kill	3–5 days
>250 (15:1)	0.5–1 hr	4 + log kill	1–2 hr

AUIC = area under the inhibitory concentration–time curve; MIC = minimum inhibitory concentration.
Source: Ref. 62.

was found to be related with longer time to clinical resolution (61). The comparisons of fluoroquinolone concentration-dependent killing rates vs. AUIC across the systems of in vitro, animal, and human clinical trials are presented in Table 1 (62).

On the other hand, in the face of current increasing bacterial resistance, the need for determining magnitudes of PK/PD parameters required to prevent selection of resistance is pressing. In this regard, new in vitro parameters linked to resistance, mutant protective concentration (MPC), and mutant selection window (MSW), have been developed (63–65) and are actively being investigated, especially with fluoroquinolones (Fig. 5) (66–69). MPC is defined as an antibiotic potency above which a microbe must acquire two concurrent resistance mutations for growth, and is measured experimentally as the lowest concentration that allows no colony growth when more than 10^{10} organisms are applied to drug-containing agar plates (63,65). Achieving antimicrobial concentrations inside the MSW (concentrations between MPC and MIC) is expected to enrich the resistant mutant subpopulation selectively because, within this window, antibiotics suppress the predominant susceptible subpopulation, resulting in selection of the resistant subpopulation. The higher concentration of MPC can restrict the selection of antibiotic resistant mutants because a second mutation is needed for bacteria to overcome this level of drug concentration, which occurs very rarely. Achieving a lower concentration than MIC does not confer changes on the mutant subpopulation to be selected, as the susceptible subpopulation prevails at this level. According to this hypothesis, antibiotic concentrations above MIC, but insufficient to reach MPC, are more dangerous than a very low AUIC from the perspective of selecting resistance.

Several in vitro pharmacodynamic studies performed with fluoroquinolones supported the MSW hypothesis and revealed that the AUICs needed to protect against resistance selection were >100 and >200 for *S. pneumoniae* and *S. aureus*, respectively (66,69). At the level of AUIC around 40, emergence of resistance occurred most frequently. To find magnitudes of PK/PD for restricting bacterial resistance, further in vitro

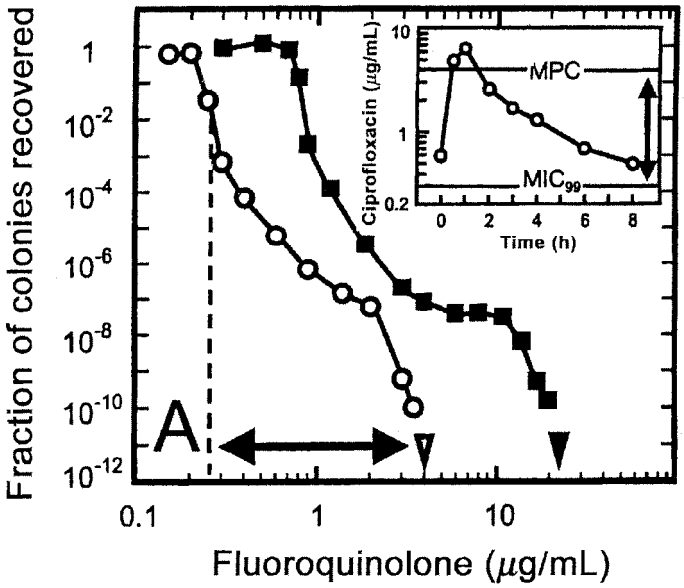

Figure 5 Mutant selection window. Treatment of *Staphylococcus aureus* cells with norfloxacin (■) or ciprofloxacin (○). The number of colonies recovered after incubation is expressed as a fraction of input cells. The dashed line indicates the MIC_{99} of ciprofloxacin. Arrow heads indicate mutant prevention concentrations (MPCs) of ciprofloxacin or norfloxacin (i.e., concentrations that inhibited colony formation when $>10^{10}$ cells were applied to agar plates). Double-headed arrows indicate the mutant selection window. *Inset*: Pharmacokinetic profile of ciprofloxacin with MIC_{99} and MPC values. (From Ref. 63)

and animal studies using mutant strains need to be conducted with a variety of organisms and antibiotics. At present, in the era of increasing antibiotic resistance, bacteriostatic endpoints from in vitro and animal models are not considered appropriate to apply to humans, at least for serious infections in immunocompromised hosts (57,62).

Issues for Further Study in the PK/PD of Antibiotics

In spite of great advances in the PK/PD of antibiotics, there are many questions to be resolved. Many investigators believe that the free form of drugs (unbound to proteins) is the fraction, which can act on bacterial targets, and advocate that adjustment for protein binding should be considered in assessment of PK/PD parameters of antimicrobials (70). However, at least one in vitro trial that tested the effects of protein binding and purulent material on the activity of fluoroquinolones against *S. pneumoniae* was unable to find any difference in killing rates in relation to the extent of protein

binding, in spite of wide range in protein binding rates of the test drugs (71). A murine pneumonia model and several human studies also showed no evidence of an impact of serum protein binding of fluoroquinolones and cephalosporins (72,73). Studies testing protein binding effects that do show impact have been published as well (74–83). Many of these involve β-lactams with staphylococcal infections (75,77,78,83). Gram-negative organisms seem less affected by protein binding (84,85), perhaps because the affinity of the drug for bacteria is greater than that for protein or because there exist serum factors enhancing antimicrobial effect against Gram-negative organisms (85).

The influence of neutrophils on the effect of antimicrobials is not well characterized also. Although a few animal studies evaluated the impact of neutrophils on pharmacodynamics of antibiotics (86–88), it has not been adequately tested in human trials. While the enhanced antibiotic activity by neutrophils is suggested to be different by organisms (88), the impact of neutrophils on antimicrobial activity among various settings of microorganisms and antibiotics needs to be investigated further. These methods must somehow be transferred to human trials to determine the importance of AUIC plus or minus host response factors.

Phamacokinetics of antimicrobials in local tissue sites also needs to be studied further. Pharmacokinetic characteristics of many antibiotics in lung, the body site of pneumonia, have been described; yet there is no clear link between success or failure and tissue levels. Antibiotics may succeed with high or low levels in blood and with high or low levels in lung tissue. Presumably, the true MIC of the organism is very important. Also, it is not known which site of drug concentration represents the lung site of infection: epithelial lining fluid (ELF) or alveolar interstitial fluid. Levels of newer macrolides (clarithromycin and azithromycin) in ELF and alveolar macrophage cells are much higher than in serum (89,90), and these new macrolides are delivered to the site of infection by phagocytic cells responding to chemotactic mechanisms (91,92). Because of these characteristics, newer macrolides are considered to be appropriate for treatment of intracellular pathogens with relatively high MICs, and azithromycin can be used successfully for the treatment of respiratory tract infections, despite its lower serum concentrations (93). The influence of different pharmacodynamics of newer macrolides in lung tissue needs to be supported by animal and clinical studies. Also, investigations on pharmacodynamics of other antibiotics in lung tissue and other body sites are warranted.

APPLICATION OF ANTIBIOTIC PK/PD IN THE TREATMENT OF NOSOCOMIAL PNEUMONIA

The predominant pathogens responsible for nosocomial pneumonia are *S. aureus*, *P. aeruginosa*, and other Gram-negative enteric bacteria (3). As

stated previously, the rates of resistance in these pathogens are increasing, which makes nosocomial pneumonia difficult to treat. Increasing rates of methicillin resistance and the potential of rising vancomycin resistance in *S. aureus* are of special concern to those who must manage nosocomial LRTI. Growing prevalence of multidrug resistant nonfermenters such as *P. aeruginosa* and *Acinetobacter* is also a difficult problem. In this discussion, we focus on the strategies of antimicrobial therapy based on PK/PD for nosocomial pneumonia caused by resistant *S. aureus* and *P. aeruginosa*.

Antimicrobial Therapy for Nosocomial Pneumonia Caused by Resistant *S. aureus*

Increasing Resistance in *S. aureus*

Currently, MRSA is replacing its methicillin-susceptible counterpart as a dominant nosocomial pathogen. *S. aureus* was reported to be the most common cause of nosocomial pneumonia developing in ICUs in the United States (1). The last National Nosocomial Infection Surveillance (NNIS) System report in August 2002 stated that the rates of methicillin resistance in hospital acquired *S. aureus* isolates were 51.3% in ICUs and 41.4% in non-ICU, respectively (4). Furthermore, the rates of methicillin resistance in *S. aureus* are still increasing.

For treatment of infections with MRSA, glycopeptides such as vancomycin and teicoplanin have been used for over 40 years. However, intermediate level vancomycin resistance was reported first in a clinical isolate of *S. aureus* (MIC = 8 mg/L) from Japan in 1996 (94), while additional vancomycin intermediate *S. aureus* (VISA) isolates have been reported worldwide, including in the United States (95). Recently, *S. aureus* strains harboring high level resistance to vancomycin (MIC $\geq$ 32 mg/L) were isolated from two American patients suffering chronic wound infections (96,97).

In fact, vancomycin resistance is not a problem restricted to *S. aureus*. In enterococci, vancomycin resistance began to appear in the mid-1980s, and the prevalence is increasing steadily (98). In the United States, the rates of vancomycin resistance in enterococci are reported as 12.8% in ICUs and 12.0% in non-ICUs, respectively (4). High-level vancomycin resistance in *S. aureus* is considered to originate from vancomycin resistant enterococci (VRE) by transfer of its resistance gene (*van*A) (99,100). The emergence of vancomycin resistant *S. aureus* is considered to be a greater threat to mankind than VRE, for *S. aureus* is a more virulent and commoner pathogen than enterococcus.

Application of PK/PD to Vancomycin Therapy Against Resistant *S. aureus*

Although vancomycin demonstrates concentration-independent killing of Gram-positive bacteria, AUIC is closely associated with clinical outcome

(19). A retrospective analysis of 84 patients receiving vancomycin therapy for Gram-positive infections suggested that those with an AUIC <125 had a higher likelihood of failure and selection of a resistant subpopulation (101).

When the vancomycin is given at a dose regimen of 750 mg every 12 hr, it results in a 24-hr AUC of approximately 393. Most susceptible Gram-positive organisms have vancomycin MICs of ≤1.0 mg/L producing an AUIC of ≥393, which is higher than the level required for clinical success, 125 (102). However, in the case of pathogens with intrinsically high baseline vancomycin MIC, such as *E. faecium* (MIC = 4.0 mg/L), the AUIC obtainable from the above dosage regimen is just 98, which is insufficient to suppress the emergence of resistance. Actually, the problem of vancomycin resistance in enterococci started with *E. faecium*. An AUIC of 190 can be obtained when vancomycin is given 1000 mg every 8 hr, which may be enough to cover micro-organisms with an MIC of 4.0. However, if the vancomycin MIC is 8 or 16, then the use of new antibiotics or of vancomycin in combination would be mandatory to achieve adequate AUICs.

Recently conducted studies at our institution have identified a correlation between measured vancomycin AUIC and clinical and microbiological outcomes with MRSA (103). In these studies, vancomycin treatment of *S. aureus* LRTIs with an AUIC <125 was clearly suboptimal, and considerably higher values were needed for positive outcomes. At predicted AUIC values of ≤345, only 23% of the patient cases experienced a successful clinical outcome. However, at predicted AUIC values of >345, clinical success occurred in 78% of patient cases. At predicted AUIC values of ≤866, microbiological eradication occurred in only 39% of the patient cases, while AUIC values of ≥866 yielded significantly improved microbiological outcomes. It was not immediately clear why those high AUIC values were needed to eradicate *S. aureus* in LRTI. Possible reasons may include the onset of vancomycin tolerance, protein binding, high inoculum, low tissue penetration, or heterogenous vancomycin resistant status in these organisms. Further investigations to clarify the meaning of microbiological failures are warranted.

Our study data suggest that nonresponsiveness to vancomycin may occur in *S. aureus* even when the vancomycin MIC is less than 8.0 mg/L. In fact, we are observing cases of clinical failure of vancomycin against infections caused by "fully susceptible" *S. aureus* strains. For example, heterogenous vancomycin resistant staphylococci (h-VRSA), which has an MIC level of 1–4 mg/L for vancomycin, sometimes fails to respond to treatment with conventional dosage regimen of vancomycin (104–106). Resistant subpopulations of h-VRSA are readily selected in vitro by the pressure of vancomycin. Many institutions including our own are facing an increasing number of failures of vancomycin to treat MRSA with susceptible MIC level (≤4 mg/L), especially in respiratory tract infections and bacteremias.

To combat the problem of declining responsiveness of MRSA strains to vancomycin and the threat of selecting vancomycin resistance in them, more refined dosing regimens based on PK/PD of vancomycin should be applied. The dosage regimen of vancomycin should be designed to cover the required AUIC for effective clinical response and restraint of resistance (the high AUIC level necessary for treatment of MRSA pneumonia should be evaluated with the target of 400 in mind (103)). The dosage regimen also needs to be individualized to both AUC and MIC (even MPC) to accomplish this. With MIC data on the infecting pathogen from the individual patient, and patient-specific pharmacokinetics, the effective dosage regimen can be customized to the individual patients (22,107). Although this individualization requires collection of multiple blood samples for assay of drug concentration, it is worth the effort for serious infections in compromised patients. When the required amount of vancomycin cannot be reached because of the risk of complications or difficulty in administration, alternative or combination therapy rather than high-dose vancomycin monotherapy must be considered.

New Antibiotics Against Resistant *S. aureus*

Several alternative antimicrobials against resistant Gram-positive organisms are available now. Quinupristin-dalfopristin (Synercid) and linezolid are being used clinically, while daptomycin has just been approved (but not for LRTI), and oritavancin and LY-333328 are under development.

Quinupristin–dalfopristin (Q–D) is a combination antibiotic composed of two streptogramins (streptogramin A—dalfopristin, streptogramin B—quinupristin) (108,109). The Q–D combination shows antimicrobial activity against most Gram-positive bacteria, including vancomycin resistant strains by inhibiting early- and late-stage protein synthesis via their consecutive binding to 50S ribosomes. Its antimicrobial activity against Gram-negative micro-organisms is minimal. Although resistance can occur by target modification (e.g., *erm* genes) and by efflux, the occurrence is uncommon in staphylococci. The PK/PD parameter most associated with efficacy in animal models is the AUC (110), and the usual dosage regimen is 7.5 mg/kg iv every 8 hr. In vitro and animal studies revealed indifference to synergistic effects of combining Q–D with other antibiotics against VRE and/or MRSA (108,111–117). Synergistic effects were found against *S. aureus* when combined with cefepime, ciprofloxacin, rifampin, or vancomycin.

Linezolid is an antimicrobial in the class of oxazolidinones (109,118). The oxazolidinones were originally developed as monoamine oxidase inhibitors for treatment of depression. As they were discovered to have antimicrobial activity, linezolid was developed through chemical modifications to increase antimicrobial activity while decreasing toxicity. Linezolid has in vitro activity against all the major Gram-positive pathogens. However, in almost all cases, the effect of linezolid is bacteriostatic against target

organisms. Linezolid has little to no activity against Gram-negative bacteria. Linezolid exhibits its antimicrobial activity through inhibiting bacterial ribosomal protein synthesis with a unique mechanism. It interferes with the first step of assembling the 70S initiation complex from 50S and 30S ribosomal subunits. No other known antimicrobial inhibits this process, and this peculiar mechanism of action provides no cross-resistance. However, resistance to linezolid has been found in clinical isolates of VRE, MRSA, and other organisms (119–123). The major PK/PD parameter related to efficacy in animal models is also the AUIC (124) or $T > \text{MIC}$ (125). While $T > \text{MIC}$ of 40% produces bacteriostatic effect in animal models, the target magnitude of $T > \text{MIC}$ is considered to be 100%. The usual dosage regimen in adults is 600 mg iv or oral, twice daily. Linezolid is 100% bioavailable and can be used as oral follow-on therapy in an outpatient setting.

A few old drugs retain activities against resistant *S. aureus*, even to VRSA. These include trimethoprim-sulfamethoxazole, tetracycline, minocycline, chloramphenicol, rifampin, and aminoglycosides (49,95,96,126). However, clinical experiences with these antibiotics in the treatment of resistant *S. aureus* are limited, and resistance tends to occur easily in *S. aureus* against these drugs. Fosfomycin and fusidic acid also have activity against resistant *S. aureus*, but their effectiveness has not been established clinically. Resistance also develops quickly to these agents, both in vitro and in vivo.

Combination Antibiotic Therapy Against Resistant *S. aureus*

Combination therapy would be a promising strategy for treatment of resistant *S. aureus* infections that are nonresponsive to maximally tolerated vancomycin regimens. Combinations may also prevent emergence of resistance in the pathogen. The first case of VISA was treated with arbekacin and sulbactam/ampicillin combination therapy (94). Several studies suggest that β-lactams and vancomycin work synergistically against VISA or hetero-VRSA (127–130). In addition, combination of newer antibiotics with other antimicrobials is being investigated (131–133).

Among them, a couple of clinical reports have demonstrated synergy with vancomycin and synercid (Q–D) in antimicrobial effect against MRSA (134–136). We have been exploring synercid plus vancomycin as synergistic in this regard. When this combination (7.5 mg/kg Q–D q 8 hr plus vancomycin targeting troughs of 10 mg/L) was compared with high dose vancomycin (achieving troughs of 20 mg/L) to treat 114 episodes of MRSA infection failing conventionally dosed vancomycin, synercid and vancomycin combination showed better clinical success than vancomycin even at higher doses (81.8% vs. 64.3%) and led to a quicker bacterial eradication (4.0 days vs. 9.5 days) (137). The effects of this combination regimen will be investigated further with a randomized and double blind clinical trial.

Other Strategies to Combat Resistant *S. aureus*

Cycling of antimicrobials is considered to be a good strategy to restrict increasing resistance (138,139). Traditional means of controlling resistance include the restriction of antimicrobial diversity by applying formularies. Formularies used to consist of one or two antimicrobials with narrow spectrum and cheaper price. However, this monopolistic antibiotic use may foster resistance, which will lead to larger cost in turn. The formulary needs to open up to a variety of agents to lessen the selective advantages afforded to certain bacteria. For MRSA or VRE, cycling between vancomycin and new antimicrobials effective against Gram-positive pathogens (Q–D, linezolid) in cycles of 6 months may be considered (102).

Antimicrobial Therapy for Nosocomial Pneumonia Caused by *P. aeruginosa*

The multidrug resistance of *P.aeruginosa* is based in part on a permeability barrier provided by the bacterial outer membrane and in part on multiple drug efflux pumps (140). Specific bacterial enzymes, such as β-lactamases, supplement the intrinsic antimicrobial resistance of *P. aeruginosa*. A number of newer antimicrobials with antipseudomonal activity have become available, which include fourth-generation cephalosporins, carbapenems, and broad-spectrum fluoroquinolones.

Fourth-Generation Cephalosporins

Fourth-generation cephalosporins, such as cefepime and cefpirome, have positively charged quaternary ammonium at C-3, which enhances its penetration of the Gram-negative bacterial outer membrane. They have been used as single-agent therapy for *P. aeruginosa* urinary tract infections and LRTIs. Simulation studies using population pharmacokinetics and pooled MIC levels (Monte Carlo analysis) were conducted to evaluate the effect of cefepime against *P. aeruginosa* (141,142). Although one study determined that current dosing recommendation of 2 g doses every 12 hr readily achieved target magnitudes of PK/PD parameter ($T > \text{MIC}$) (141), another suggested a potential failure of cefepime monotherapy. The discrepancy derives from application of different endpoints of the PK/PD parameter, several MICs of target organisms in these studies, and varying viewpoints of analysis.

While the simulation study of Ambrose et al. targeted the endpoint of $T > \text{MIC}$ as 60–70%, the study of Tam et al. (49) suggested to apply $T > \text{MIC}$ of 100% or $T > 4 \times \text{MIC}$ for 100% of the time to optimize dosing of cefepime against *P. aeruginosa*, based on data from their own clinical data. Tam et al. also analyzed their data by subgroups according to MIC levels and creatininine clearance (CLcr). Even when a lower $T > \text{MIC}$ of 67% was targeted, an 80% likelihood of achieving the target

could not be achieved for organisms with MICs ≥ 4 mg/L, particularly when creatinine clearance exceeded 120 mL/min. These findings support the notion that individualization of dosage regimen of antibiotics is necessary, especially when the likelihood of achieving target magnitudes of PK/PD is marginal. In addition, the endpoint of $T > \text{MIC}$ of fourth-generation cephalosporin needs to be at least 100% in case of serious infections by *P. aeruginosa* in immunocompromised hosts, which could be achieved when AUIC was over 125.

Carbapenems

A simulation evaluated the probability that $T > \text{MIC}$ of meropenem can reach 40% of an 8-hr dosing interval using Monte Carlo analysis (143). At all dosage regimens except 0.5 or 1 g infusion for 0.5 hr every 8 hr, probability over 80% was obtained. However, the author recommended the dosage regimen of infusing 2 g meropenem over 3 hr every 8 hr to lower the probability of resistance.

It is known that *P. aeruginosa* increases the MICs four-fold when downregulating oprD2. This is the major source of influx of carbapenems. Thus, if we treat a susceptible *P.aeruginosa* that has a subpopulation with MIC of 4 mg/L to meropenem, the MIC can increase to 16 mg/L by oprD2 downregulation. The target attainment for killing of *P. aeruginosa* with an MIC of 16 mg/L obtained from above simulation analysis was >80% in the regimen of 2 g infusion over 3 hr. In other dosing settings, acceptable rates of maximal killing were not anticipated. Sometimes, *P. aeruginosa* increases its MIC to meropenem by 8 to 32-fold through a combination of oprD2 downregulation and stable derepression of the ampC enzyme. In this case, combination of other antibiotics will be needed. This hypothesis is based on in vitro data and requires further investigation in clinical trials. However, dosage lowering strategies can foster resistance and should be approached with caution, especially when employing carbapenem monotherapy.

Fluoroquinolones

Ciprofloxacin, a second-generation fluoroquinolone, remains the most potent antipseudomonal quinolone in terms of in vitro microbiological activity. Newer generation fluoroquinolones armed with more potent antimicrobial effect against Gram-positive pathogens are considerably less active than ciprofloxacin against *P. aeruginosa*. When we select fluoroquinolones to treat nosocomial pneumonia, balance between strength against *P. aeruginosa* and Gram-positive pathogens should be considered, as a single fluoroquinolone will clearly not cover both ends of the microbiologic spectrum. Some, like levofloxacin, are weak against both *P. aeruginosa* and Gram-positive organisms like *S. aureus* and *S. pneumoniae*. They have the potential

to select resistant strains of *P. aeruginosa* (144), *S. aureus* (145), and *S. pneumoniae* (146–148).

As stated earlier, many in vivo studies agree that the magnitude AUIC for fluoroquinolones should be 100–125, to get effective clinical outcomes against *P. aeruginosa*, and an AUIC ratio greater than 100 is also associated with a significant reduction of emergence of resistance in Gram-negative bacteria, including *P. aeruginosa*. A recent study analyzed the target magnitude of AUIC to suppress amplification of fluoroquinolone resistance in *P. aeruginosa*, using data derived from mice and a mathematical model (149). The AUIC value that would suppress the mutant subpopulation obtained by this method was 157, while the value of 52 amplified the resistant subpopulation readily. When a 10,000-subject Monte Carlo simulation was performed, the target value for suppression of resistance in *P. aeruginosa* was achieved in 61.2% treated with 750 mg iv daily regimen of levofloxacin, and in 61.8% treated with 400 mg iv every 8 hr of ciprofloxacin. Unfortunately, none of the currently available fluoroquinolones achieve the target AUIC value ($\geq$125 or 157) against *P. aeruginosa* at a rate of $\geq$90% with routine dosage regimens. Therefore, combination therapy should be considered for the treatment of VAP caused by *P. aeruginosa* when a quinolone is employed. Preferred agents for combination are antipseudomonal β-lactams such as imipenem, meropenem, cefepime, ceftazidime, or piperacillin. These compounds, when combined with quinolones, are additive rather than synergistic.

Other Strategies to Combat Resistant *P. aeruginosa*

Combination therapy and cycling effective antibiotics (139,150–152) and individually tailored dosage regimens based on individual PK/PD characteristics are also worthy of use in the treatment of resistant *P. aeruginosa*.

CONCLUSION

Pneumonia is still a frequent and sometimes fatal complication in patients receiving mechanical ventilation, while antibiotic resistance in major pathogens is increasing. Besides the development of new antimicrobial agents without cross-resistance, the use of proper dosing is a necessary strategy to overcome VAP caused by resistant organisms. Recent advances in our knowledge of PK/PD targets for antibiotics provide many useful opportunities for realizing the goals of this strategy.

To combat VAP successfully, a more refined approach of antimicrobial therapy is needed. Empirical antibiotics should be chosen based on predicted attainment of target PK/PD magnitude (e.g., AUIC >125 or even 250 for rapid killing value). For treatment of serious infections in immunocompromised hosts such as VAP, breakpoints of PK/PD should be targeted at the levels that are bactericidal and high enough to prevent emergence of

resistance. Dosing regimen needs to be tailored individually according to specific pharmacokinetics of individual patient and specific susceptibility levels of the pathogen obtained from each patient. Clinical application of MPC and MSW, rather than MIC, for determining target magnitudes of PK/PD parameters needs to be investigated further. Combination antibiotic therapy may be needed to overcome the limitations of single antibiotics to achieve their target PK/PD magnitudes. However, even in combination regimens, the total AUIC of 125–250 will need to be achieved with the chosen combination. Cycling effective antibiotics can also reduce the increasing resistance.

To apply PK/PD of antibiotics more efficiently in clinical practice, several unsolved issues, such as the influence of serum factors, the impact of neutrophils, and PK/PD in local tissues need to be addressed. More investigations, especially clinical studies, to clarify target magnitudes of PK/PD parameters are warranted and the results should be applied to patient care as rapidly as possible.

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14

Prevention of Ventilator-Associated Pneumonia

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INTRODUCTION

Ventilator-associated pneumonia (VAP) is the most frequently occurring nosocomial infection among mechanically ventilated patients and has been associated with increased morbidity, attributable mortality, and higher health care related costs. As a result, preventive strategies for VAP have been a subject of extensive study over the last 30-plus years. These strategies can be viewed in five categories: (a) those reducing bacterial colonization by using antimicrobial agents (such as selective decontamination of the digestive tract [SDD], oropharyngeal decontamination or systemic antimicrobial prophylaxis) or other measures (such as sucralfate and acidified enteral feeding to maintain low gastric pH); (b) those aiming to reduce the risk of aspiration (such as subglottic aspiration and semirecumbent patient positioning); (c) those improving host defense (see Chapter 15); (4) those improving general infection control measures to limit cross-infection risks and (5) those reducing risk of contamination of the patients' inanimate environment. In this

chapter, we focus on the potential benefits and risks of preventive strategies aimed at modulating colonization and reducing aspiration.

GUIDELINES AND SYSTEMATIC REVIEWS

Guidelines for the prevention of VAP have been formulated by the American Thoracic Society (1) and the Centers for Disease Control and Prevention with the consensus recommendations of the Healthcare Infection Control Practices Advisory Committee (2). These documents have been revised in 2004. Recently, 433 studies of strategies for preventing VAP, performed between 1966 and 2001, were analyzed and systematically reviewed (3). The reviewers concluded that semirecumbent positioning, use of sucralfate instead of H_2-antagonists for stress-ulcer prophylaxis, and SDD were the preventive measures with the strongest supportive evidence; that aspiration of subglottic secretions and use of oscillating beds may be useful in selected patient groups; and that the available evidence did not support the use of any specific methods of enteral feeding or the use of increased frequency of ventilator circuit changes. After evaluating potential risks related to the effective preventive measures, the authors concluded that sucralfate should be used only in patients at low to moderate risk for gastrointestinal bleeding and that SDD should not be used because of its potential to increase antimicrobial resistance.

PREVENTION OF COLONIZATION

Selective Decontamination of the Digestive Tract

In 1971, the concept of "colonization resistance" was proposed by van der Waaij, who suggested a beneficial effect of the anaerobic flora in resisting colonization by aerobic Gram-negative bacilli in the digestive tract (4). Selective decontamination of the digestive tract (SDD) was developed to selectively eliminate aerobic Gram-negative bacilli and yeasts from the digestive tract, leaving the presumably protective anaerobic flora unaffected. In the early 1980s, Stoutenbeek et al. (5) adapted SDD for ICU patients. Their strategy included continuous use of intestinal and oropharyngeal decontamination with nonabsorbable antimicrobial agents (colistin, an aminoglycoside and amphotericin B) that do not affect the anaerobic intestinal flora, supplemented by systemic prophylaxis (cefotaxime 50–100 mg/kg/day i.v.) from arrival to ICU until no more potential pathogens were isolated from surveillance cultures of the oropharynx or respiratory tract.

Since the introduction of this strategy, scores of studies of SDD in a variety of ICU populations have been performed; the majority of these trials were undertaken in European ICUs (for a recent review see Ref. 6). Eight meta-analyses of SDD studies have been published (7–14); in each, use of SDD was associated with significant reductions in rates of VAP (Table 1).

Table 1 Preventive Strategies for VAP—Modulation of Colonization and Reduction of Aspiration

Intervention	Rationale	Efficacy		Comments	Recommendation
		Reduction of VAP incidence	Reduction of ICU mortality		
Modulation of colonization					
Selective digestive decontamination (SDD) Refs. 5,7–9 Refs. 10–13 Refs. 14–17 Refs. 18,19	Eradication of potential pathogenic micro-organisms from oropharynx, stomach, and intestines in combination with a short course of systemic prophylaxis	Yes	In meta-analyses and unpublished data	High potential for selection of pre-existing multiresistant bacteria (especially MRSA)	May be useful in wards with very low levels of antibiotic resistance
Oropharyngeal decontamination Refs. 32–35	Eradication of potential pathogenic micro-organisms from oropharynx	Yes	Not demonstrated	High potential for selection of pre-existing multiresistant bacteria (especially MRSA)	May be useful in wards with very low levels of antibiotic resistance
Systemic prophylaxis Refs. 23–25,27	Short-term peri-intubation systemic prophylaxis of VAP	Possible	Not demonstrated		Not recommended, more studies needed

(*Continued*)

Table 1 Preventive Strategies for VAP—Modulation of Colonization and Reduction of Aspiration (*Continued*)

Intervention	Rationale	Efficacy		Comments	Recommendation
		Reduction of VAP incidence	Reduction of ICU mortality		
Sucralfate for stress-ulcerprophylaxis Refs. 31,36–39	Maintenance of low intragastric pH (to suppress overgrowth of aerobe Gram-negative bacilli)	No, or only slightly	Not demonstrated	Less efficient for stress-ulcerprophylaxis than H_2-antagonists	Not recommended
Intermittent enteral nutrition Refs. 42–44	Maintenance of low intragastric pH (to suppress overgrowth of aerobe Gram-negative bacilli)	No	Not demonstrated		Not recommended
Acidified enteral nutrition Ref. 45	Maintenance of low intragastric pH (to suppress overgrowth of aerobe Gram-negative bacilli)	No	Not demonstrated	Associated with tendency to higher ICU-mortality in one study	Not recommended

Immunonutrition Refs. 46–48	Improvement of local and systemic immunity	Possible	Not demonstrated		Not recommended, more studies needed
Reduction of aspiration					
Subglottic secretion drainage Refs. 49–52	Reducing aspiration of pooled tracheal secretions	Probable	Not demonstrated	Possibility of tracheal injury and necrosis	Not recommended, more studies needed
Semirecumbent patient position Ref. 54	Reduction of aspiration of oropharyngeal and gastric secretions	Probable	Not demonstrated	Feasibility and minimal degree of treatment position unknown	Recommended, but more studies are needed to address the comments
Postpyloric nutrition Ref. 57	Reduction of gastric aspiration	No	Not demonstrated		Not recommended

In one meta-analysis, the risks of VAP and of ICU mortality were related to the methodological quality of the individual studies, i.e., studies judged to be of lower quality showed greater benefit of SDD for preventing VAP (13). For evaluating the preventive effects for VAP, a double-blind design and appropriate allocation of intervention (preferably computer generated or with random number tables) had the largest effect on study outcome; i.e., benefits of SDD were lowest in studies with these quality characteristics.

Analysis of studies of SDD is complicated by the heterogeneity in study design, the variety of patient populations evaluated, and the range of individual SDD regimens that have included >10 combinations of oropharyngeal, intestinal, and systemic antimicrobial agents. In two meta-analyses, ICU mortality was significantly reduced in studies that used a combination of topical and systemic therapy (7,8). Because these two meta-analyses found no significant benefit for studies that compared only topical prophylaxis to placebo, or that gave both study groups systemic prophylaxis (7,8), reviewers have suggested that systemic prophylaxis was the component of SDD that was responsible for the beneficial patient outcome.

Most recently, two large prospective trials have supported the contention that SDD improves patient survival (15,16). In a double-blind study, Krueger et al. (15) stratified (via APACHE II scores) and then randomized 265 ventilated patients to a regimen containing intravenous ciprofloxain for 4 days and topical colistin and gentamicin applied to nostrils, mouth, and stomach for the duration of ventilation, or to intravenous and topical placebo. The overall relative risk for ICU mortality was 0.76 (0.53–1.09), but in the subgroup of patients with intermediate APACHE II scores of 20–29, the relative risk was 0.51 (0.3–0.88), a significant reduction. In the second study, an impressive reduction in both ICU (36% decrease) and hospital mortality (23% decrease) was demonstrated among patients receiving SDD (16). This is the highest mortality reduction reported in any trial of SDD and even exceeds the most positive predictions in any of the eight meta-analyses. In addition to that study, patients receiving SDD had a shorter length of ICU stay and fewer patients acquired colonization with antibiotic-resistant Gram-negative bacteria.

The major disadvantage of SDD is the potential for selection of antibiotic-resistant micro-organisms. In fact, the only studies in which SDD did not result in significant reductions in risk of VAP were undertaken in ICUs with high pre-existing levels of antibiotic-resistant micro-organisms. Methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant enterococci (VRE) have been the pathogens that are most susceptible to the increased selection pressure created by SDD (17–19). The two recent, very positive trials of SDD occurred in settings where MRSA was either completely absent (16) or found only sporadically and aggressively contained (15). Therefore, we suggest that the usefulness of SDD will depend on the endemic level of antibiotic resistance and the infection control

measures that can be implemented to overcome selection and transmission of resistant micro-organisms. The recent findings of fully vancomycin-resistant MRSA in two US cities (20) confront us with a potentially grim scenario of progressively more resistant micro-organisms, that are increasingly at risk for selective pressure induced by antibiotics, limiting the usefulness of SDD in many settings.

Considering all available evidence, SDD, in some settings, has been an effective method to prevent VAP and may improve patient outcome. Multicenter studies to assess the recently reported reductions in mortality are needed.

Systemic or Oropharyngeal Prophylaxis

Several studies have evaluated individual components of SDD—either systemic prophylaxis or oral decontamination—as more targeted approaches for preventing VAP. Those who favor "traditional" SDD feel that the entire regimen—oral, gastrointestinal, and systemic prophylaxis—is required for maximum benefit and also as the best way to reduce selection of resistant pathogens (21). Others view the more targeted approach as having a potential for benefit with less exposure to antimicrobials and therefore less "selective pressure" for antibiotic resistance (22).

Systemic prophylaxis: Prevention of pneumonia with systemic antibiotics was attempted soon after the discovery of antimicrobials, but these studies were either unsuccessful or aborted because of increased incidences of infections caused by resistant bacteria (23–25). In 1989, Mandelli et al. (26) randomized 570 ICU patients, half of whom were intubated, to receive either 24 hr of cefoxitin, penicillin G, or no prophylaxis. The incidence of early-onset VAP (diagnosed within 4 days of ICU admission) pneumonia, which was the primary outcome measure, was 6.1% in patients receiving antibiotics and 7.2% for controls. More recently, systemic antibiotic prophylaxis with cefuroxime (two 1500 mg doses) in mechanically ventilated patients with coma resulted in a lower incidence of VAP than in a control group (12/50 (24%) vs. 25/50 (50%); $p = 0.007$). This difference was caused by a reduction in the episodes of early-onset VAP in the cefuroxime group (8/50 (16%) vs. 18/50 (36%); $p = 0.022$; RRR 0.56), while the incidences of late-onset VAP were more comparable (8% vs. 14%) (27). These findings suggest that a short course of peri-intubation systemic prophylaxis may reduce the occurrence of VAP and could be used analogous to peri-operative prophylaxis to reduce the risk of surgical site infections.

Oropharyngeal Decontamination

Landmark studies from Johanson in the 1970s clearly identified the pivotal role of the oropharynx in the development of hospital-acquired pneumonia (28,29). In the 1980s, the role of gastric colonization and the

"gastro–pulmonary route" was considered to be essential in the pathogenesis of VAP (30). The role of gastric aspiration, however, has been reassessed in recent years (31). Most of the studies of SDD cannot distinguish between the relative importance of oropharyngeal and gastric colonization, as both sites are decontaminated with antibiotics. The effects of oropharyngeal decontamination as a single strategy have been assessed in a few studies. In a double-blind trial, a solution of antibiotics applied to the oropharynx reduced colonization with aerobic Gram-negative bacteria in both the oropharynx and stomach, with an associated relative risk reduction of VAP of 0.79 (32). In a smaller study, an oropharyngeal paste completely prevented pneumonia in 13 patients, whereas 11 (73%) of 15 patients receiving a placebo paste developed pneumonia (33). In a prospective randomized placebo-controlled double-blind study, 87 patients received topical antimicrobial prophylaxis in the oropharynx and 139 patients received placebo. Oropharyngeal colonization was effectively modulated, without influencing gastric and intestinal colonization, which resulted in a relative risk reduction for VAP of 0.62 (95% CI 0.26–0.98) (34). Another way to achieve oropharyngeal decontamination, and to avoid antibiotic use, is topical application of an antiseptic/disinfectant, such as chlorhexidine. In a trial among 353 cardio-surgical patients, an oral rinse of 0.12% chlorhexidine reduced the incidence of respiratory tract infections from 9% in control patients to 3% in those who received chlorhexidine (35).

Oropharyngeal decontamination seems to be a very effective method to reduce late-onset VAP. However, it is yet to be shown that this method of infection prevention is associated with less selection of resistance than the traditional SDD regimen, and current studies have been underpowered to demonstrate benefits in patient survival or reductions in duration of ventilation and length of stay. The use of antiseptics that are not used as antibiotics might offer significant advantages, but more studies are needed to determine their efficacy.

Stress-Ulcer Prophylaxis

Because critically ill patients on mechanical ventilation have been considered to be at high risk for development of gastritis and/or gastric ulcers, stress-ulcer prophylaxis has been routinely provided for years. In this respect, gastric acidity may be reduced by neutralizing gastric acid (antacids) or by inhibiting acid production (H_2-antagonists, H^+K^+ATPase inhibitors). However, each of these approaches decreases the natural protection against bacterial overgrowth afforded by a low gastric pH. In addition, the volume challenge created by large amounts of antacids may increase risks of aspiration. In contrast to these agents, sucralfate has been claimed to prevent stress ulcers without influencing gastric acidity and with less volume.

Theoretically, patients who receive sucralfate should maintain lower intragastric pH values compared with patients receiving antacids or H_2-antagonists, which in turn should prevent gastric bacterial overgrowth and based on the gastro–pulmonary theory of pathogenesis of VAP reduce the incidence of VAP. Although sucralfate was associated with lower incidences of VAP in two trials (36,37), the only two randomized, double-blind studies (and other controlled but not double-blind trials, see Ref. 31) failed to confirm these preventive benefits (38,39). In a meta-analysis, however, sucralfate, when compared to H_2-antagonists, was associated with a 4% absolute risk reduction in the incidence of VAP (40). But because ranitidine provided better prevention for stress-ulcer bleeding than did sucralfate in the largest study performed to date, the routine use of sucralfate cannot be advised. Thus, there is only limited evidence that the use of sucralfate will be of value for preventing VAP.

Modulation of Enteral Feeding

Enteral nutrition has been considered a risk factor for the development of VAP, mainly because of an increased risk of aspiration (41). Hence, modulation of enteral feeding has been used as a possible approach to interrupt the gastro–pulmonary route of colonization and to reduce the incidence of VAP. In this regard, intermittent enteral feeding would be expected to be superior to continuous enteral feeding, as gastric acidity increases during the periods when feeding is discontinued. Three studies have been performed with conflicting results. Lee et al. (42) reported lower intragastric pH values and lower rates of VAP in patients receiving intermittent enteral feeding compared with a historical control group that received continuous enteral feeding. Skiest et al. (43) randomized 16 patients to either intermittent enteral feeding or continuous enteral feeding. Intermittent enteral feeding resulted in lower postfasting gastric pH and lower rates of gastric colonization with pathogenic organisms, but no patients developed nosocomial pneumonia during the 5-day study period. In the largest prospective randomized trial of 60 patients, intermittent enteral feeding had no beneficial effects on intragastric acidity, gastric colonization, or incidence of VAP (44). The preventive effects of acidified enteral nutrition have been evaluated in a randomized multicenter trial (45). Acidified nutrition was associated with reduced gastric colonization but did not prevent the development of VAP.

Another nutrition-related approach to preventing VAP has been enteral immunonutrition. Several small studies (<296 patients/study) determined the effects of enteral feeding enriched with specific immunonutrients (such as arginine, purine nucleotides, and ω-3 polyunsaturated fats) on outcome in critically ill patients (46). In a few studies, there was a trend toward better clinical outcome for patients who received immunonutrition (46). In a

randomized double-blind trial, immunonutrition failed to decrease hospital mortality in critically ill patients. However, in the subgroup of patients who received enteral nutrition within 72 hr after admission, reductions in requirement for mechanical ventilation and length of hospital stay were found. Unfortunately, incidences of nosocomial pneumonia were not reported (47). In another randomized and controlled study among trauma patients, enteral nutrition was enriched with glutamine, which is an important protein for lymphocytes and enterocytes. The incidence of nosocomial pneumonia decreased from 43% to 17% ($p < 0.02$) and of bacteremia from 42% to 9% ($p < 0.005$). However, pneumonia was diagnosed with nonspecific criteria, colonization of the respiratory tract was not studied, and glutamine levels were significantly elevated in study patients only from day 3 to 5 of treatment. Since almost all infections, in both study groups, occurred within the first week of study, the mode of action leading to prevention of VAP is unclear (48). At present, there is insufficient evidence to support modulation of enteral feeding practices as an effective preventive measure for VAP, and more studies are needed to confirm the initial observations on the reported preventive benefits of immunonutrition.

PREVENTION OF ASPIRATION

Subglottic Secretion Drainage

During mechanical ventilation, subglottic secretions and oropharyngeal fluids containing large concentrations of micro-organisms may accumulate above the inflated endotracheal tube cuff. Microaspiration along the cuff may lead to infection of the lower respiratory tract. The role of drainage of subglottic secretions with specifically designed endotracheal tubes, as a preventive strategy for VAP, has been evaluated in four studies. Each showed statistically significant or strong tendencies toward significant reductions in the incidence of VAP in relatively small numbers of patients (<344 patients/study) (49–52). Anecdotal reports, however, have raised concerns that longer-term use of subglottic suction has led to tracheal injury and necrosis. Although this is a promising preventive measure, more studies carefully addressing these concerns and the diagnostic criteria for VAP are needed.

Body Position

Any couch potato will agree that microaspiration of oropharyngeal secretions or gastric contents are more likely in individuals in a supine, rather than an upright, position. In fact, in experimental trials, patients receiving radio-labeled nasogastric tube feedings while in supine positions had higher cumulative counts of radioactivity in endobronchial secretions than did patients who were fed in a semirecumbent position (53). A subsequent randomized trial demonstrated a 3-fold reduction in the incidence of VAP

in ICU patients treated in a semirecumbent position compared to patients maintained completely supine (54); the occurrence of VAP was strongly associated with the administration of enteral nutrition. Therefore, as our couch potato would advise, a semirecumbent position when receiving enteral feeding appears to be a preventive measure for VAP. Unfortunately, the feasibility of this intervention is unknown (e.g., patients may prefer to sleep supine, partially negating the benefits of semirecumbent feeding), and the very positive results of this single, small, randomized trial need to be confirmed in other settings.

Postpyloric Feeding

In another attempt to reduce aspiration, gastric nutrition has been compared to postpyloric feeding. In two studies where feeding had been labeled with radioisotopes, findings of increased risks of aspiration with gastric feeding were not conclusive (55,56). Seven studies evaluated the risks for VAP in patients randomized to either gastric or postpyloric feeding (57). Although significant differences were not demonstrated in any individual study, postpyloric feeding was associated with a significant reduction in VAP in a meta-analysis (relative risk 0.76 (0.59–0.99)) (57).

CONCLUSIONS

Several preventive measures for VAP have been tested in carefully conducted, controlled trials. There is clear evidence that antibiotic-containing preventive strategies, such as SDD and oropharyngeal decontamination, are very effective in some patient populations. However, selection of antibiotic resistance remains the major disadvantage of these approaches, limiting their applicability in settings with high existing levels of resistance. Systemic antibiotic prophylaxis, especially peri-intubation, cannot be recommended at present, but warrants multicenter study. Of the nonantibiotic containing preventive strategies, subglottic aspiration was effective in several studies; other strategies, such as immunonutrition with glutamine or the maintenance of a semi-recumbent patient position, were effective in single studies. For these interventions, more data are needed on the generalizability, feasibility, and cost efficacy. Few data support the use of sucralfate for stress-ulcer prophylaxis or the modulation of enteral nutrition practices as preventive measures for VAP.

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15

Pulmonary Host Defense: Basic Mechanisms and Strategies for Immunomodulation

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The primary function of the lungs is to perform gas exchange with the atmosphere. For this purpose, a great degree of complexity is required to facilitate the diffusion of oxygen and carbon dioxide while maintaining homeostasis. Branching airways terminate in as many as 300 million alveoli, resulting in the largest epithelial surface area of the body (1). This surface area consists of an alveolar-capillary interface, which is estimated to provide 50–100 m^2 for gas diffusion (2). Therefore, the constituents of inspired air have extensive contact with the epithelial surface of the lung. This contact predisposes the body to many harmful agents such as dust, pollen, bacteria, and other micro-organisms, making the lung a uniquely susceptible portal for infection. Accordingly, the respiratory tract is equipped with numerous defense mechanisms that enable it to neutralize potential pathogens. These mechanisms begin in the nose with anatomic barriers such as nasal vibrissae

and extend to the alveoli where resident phagocytic cells constitute the first line of defense at the site of gas exchange.

ANATOMIC BARRIERS AND INNATE DEFENSES

During inspiration, many barriers exist that effectively filter particles and prevent them from reaching the terminal airways. Assuming nasal breathing, hairs in the nasal cavity almost completely remove particles larger than 10–15 μm in diameter from inspired air. Depending on the size, airborne particles become deposited along airway surfaces (3). Larger particles often collide with airway surfaces because of inertia. The tonsils and adenoids, which represent areas of secondary lymphoid tissue, are common sites of impaction, and are particularly suited for the removal of foreign materials because of their large resident leukocyte populations. Smaller particles ($<$10 μm in diameter) enter the branching airways where the parallel distribution decreases airflow velocity, reducing the probability of impaction. However, such particles often sediment along the airway mucosa while extremely small particles ($<$0.5 μm in diameter) are simply exhaled. Particles in the vicinity of 4 μm in diameter are most likely to be deposited in the alveoli, as they are large enough to avoid exhalation yet small enough to avoid early mucosal impaction (4). The removal of deposited material is further augmented by the cough and sneeze reflexes.

Mucus lining the airways is an important component of innate airway defense. Mucus is composed mostly of water and also lipids, minerals, and proteins (5). Among these, proteins are glycoproteins called mucins that capable of binding and arresting micro-organisms (6). Besides the direct mucin-mediated effects on particle removal, mucus also facilitates clearance via the "mucociliary escalator." This term refers to the layer of mucus-covered cilia, that lines the majority of the respiratory tract. As particles bind to mucus, cilia propel sheets of mucus from the lower airways toward the pharynx where they are eliminated by either swallowing or expectoration.

Bacteria range from 1 to 5 μm in diameter (7), the optimum size for alveolar deposition. Therefore, factors other than the initial anatomic barriers must also be present to maintain lung sterility. Among these are a multitude of well-described antimicrobial substances, some of which include the defensins, lysozyme, lactoferrin, complement, fibronectin, immunoglobulins, and collectins (8–11). These molecules possess a wide variety of bacteriocidal characteristics that can directly and/or indirectly facilitate microbial clearance. For instance, lysozyme catalyzes the hydrolysis of glycoside bonds in the bacterial cell walls, resulting in bacterial cell death (10). Lactoferrin, a similar molecule, is an iron-chelator capable of disrupting iron-dependent bacterial growth. Another family of antimicrobial molecules, the defensins, is a family of small, single-chained cationic peptides

that are capable of directly permeabilizing bacteria. Defensins are classified as either α- or β-defensins, based on their sequence homology, and their expression during bacterial pneumonia is both constitutive (β-defensin 1) and inducible (β-defensin 2). Both classes of defensins are capable of chemokine stimulation, complement activation, and $CD4^+$ T-cell proliferation. High salt concentrations, as seen in disease states such as cystic fibrosis, inhibit defensins, minimizing their contribution to host defense in such patients. Other substances, such as complement, immunoglobulins, and fibronectin, indirectly augment bacterial clearance through opsonization, making them more recognizable by phagocytes of the innate immune system. These phagocytes express opsonin-specific receptors (such as the Fc receptor for immunoglobulins and the C3b receptor for complement fragment C3b). Upon successful binding, the phagocyte internalizes the target microbe, leading to the formation of a phagolysosome. The phagolysosome then acts in concert with reactive oxygen and nitrogen species (respiratory burst) and other factors to destroy the engulfed organism (12).

The collectins represent yet another family of antimicrobial molecules within the lung. Collectins are calcium-dependent lectins (C-type lectins) that selectively bind to carbohydrate residues uniquely expressed on microbial surfaces (13). Surfactant proteins A and D (SP-A and SP-D), the two major lung collectins, influence many aspects of pulmonary host defense, including chemotaxis (14), phagocytosis (15), bacterial permeabilization (16), and cytokine production (17). Though similar in structure, differences have been observed in their ability to enhance specific pathogen clearance. For example, SP-A is more efficient than SP-D for opsonization of *Pseudomonas aeruginosa* (*P. aeruginosa*) and *Mycobacterium tuberculosis* (*M. tuberculosis*), while SP-D is more effective of the two in promoting the formation of large aggregates of both bacteria and viruses. These large aggregates are then more easily cleared by phagocytosis and the mucociliary escalator (18). The importance of collectins in pulmonary host defense has been shown in experimental models utilizing SP-A and SP-D deficient mice (19,20).

PATHOGEN RECOGNITION: THE GATEKEEPER OF HOST DEFENSE

The anatomic barriers and antimicrobial peptides of the airways comprise the constitutive elements of pulmonary host defense in the normal host, which are in place to respond to invading pathogens. However, the presence of these factors is not always sufficient to prevent bacterial infection, making additional defense mechanisms necessary to prevent pneumonia. The onset of such immune responses requires pathogen recognition through a clear distinction between "self" and "non-self."

Immune cell identification of pathogens occurs, to a large extent, via pattern-recognition receptors (PRRs). As microbes and other foreign materials bypass the constitutive barriers and defenses of the lung, they reach the alveoli where they come in contact with alveolar macrophages (AMs). AMs, which constitute the primary intra-alveolar constitutive leukocyte population of healthy individuals, are considered the first cellular line of immunosurveillance in the lung (21). These cells bear a multitude of PRRs, allowing them to efficiently recognize and respond to invading micro-organisms. The function of PRRs is to unambiguously recognize unique components of invading microbes designated as pathogen-associated molecular patterns (PAMPs) (22,23). PAMPs include microbial components such as lipopolysaccharide (LPS), lipotechoic acid (LTA), flagella, bacterial DNA, and double-stranded RNA that are required for microbial metabolism and/or survival. PAMPs are relatively invariable among different classes of microbes; hence, their constitutive expression increases the likelihood of host recognition. PAMP recognition by PRRs on AMs initiates important immune processes such as phagocytosis and cytokine production. Fortunately, there is a wide variety of these PRRs, including the mannose receptor, scavenger receptors, and the Toll-like receptors (TLRs) (24–27). The TLRs embody a large group of PRRs and have emerged as an extremely important aspect of innate immune recognition. Toll-like receptor 4 (TLR4), which is expressed on various immune and nonimmune cells, is currently the most well-studied PRR (22). TLR4, the first discovered mammalian TLR, was recently identified as the major receptor for LPS, and is perhaps the most prevalent PAMP of Gram-negative bacteria (28). Currently, at least nine other TLRs have been identified, along with their corresponding PAMPs (23). Besides TLR4, TLRs 2 and 9 also serve as important PRRs during the host response to bacterial pneumonia. TLR2 binds to peptidoglycan, a major structural component of Gram-positive bacterial cell walls, while TLR9 recognizes the unmethylated CpG DNA that is unique to bacteria. Given its strong immune activating ability, the use of CpG DNA as a vaccine adjuvant has been shown in animal models to provide added protection from bacterial pneumonia compared to standard immunization (29). An appealing strategy involves pulmonary delivery of this bacterial product to protect against the subsequent development of bacterial pneumonia.

The recognition of bacteria by AMs is a complex process that is critical for the initiation, expansion, maintenance, and resolution of a host-defense response within the lung. Upon activation, cytosolic signaling cascades within AMs initiate antimicrobial processes and host-defense functions, including phagocytosis, respiratory burst, and the production of proinflammatory cytokines (21). The signaling pathways required for cytokine production by AMs primarily involve the inflammatory transcription factor nuclear factor-kappa beta (NFκB) (30), although NFκB independent pathways have also been identified (31). Upon activation, NFκB translocates to

the cell nucleus, binds to its DNA promoter, and initiates the transcription of multiple proinflammatory cytokines. Taken together, these functions allow AMs to act as both an architect and a conductor of the inflammatory events directed at eliminating pathogens from the lower respiratory tract.

PULMONARY NEUTROPHIL RECRUITMENT AND THE INFLAMMATORY CASCADE

When AMs alone are incapable of successfully eradicating a bacterial challenge, the recruitment of polymorphonuclear leukocytes (PMNs; neutrophils) becomes the next wave of defense. Neutrophils represent the most abundant population of circulating phagocytes, and their ability to rapidly migrate into infected tissue sites is an integral aspect of immune defense (32). PMN recruitment is driven by the expression and/or activation of various proinflammatory molecules. Among these are tumor necrosis factor-α (TNF-α) and interleukin-1β (IL-1β), which act to initiate, maintain, and localize the pulmonary host-defense response (11,33). TNF-α and IL-1β are pleotropic cytokines that are released early in response to infection, and influence multiple aspects of inflammation and host defense (34,35). TNF-α is particularly important in this response, as evidenced by previous studies in which inhibition of TNF-α using a neutralizing antibody significantly attenuated pulmonary bacterial clearance of *Streptococcus pneumoniae* (36). Other animal studies have shown adverse outcomes of TNF-α neutralization in the pulmonary immune response to *Pneumocystis carinii*, *Klebsiella pneumoniae*, and other causative agents in bacterial pneumonia (37,38). Likewise, adenoviral-mediated overexpression of TNF-α soluble receptors, which block normal TNF-α signaling, impair the pulmonary host-defense response to both LPS and *P. aeruginosa* (39). Opposite effects are seen when TNF-α activity is upregulated in the lung. Standiford et al. (40) locally administered an adenovirus encoding TNF-α to mice challenged intratracheally with *K. pneumoniae*. Overexpression of TNF-α decreased lung bacterial burden and the incidence of bacteremia in a dose-dependent fashion (40). However, Wunderink et al. (41) have shown that an excessive expression of TNF-α, because of a polymorphism in the TNF-α promoter gene, causing excessive TNF-α production that correlates with an adverse outcome in patients with community-acquired pneumonia, CAP. Together, these data show that effective but carefully regulated TNF expression is essential for optimal pathogen clearance.

Neutralization of IL-1β results in a similar phenotype as animals deficient in TNF-α (42,43). However, while IL-1β clearly facilitates the immune response in certain models, a recent investigation by Schultz et al. (42) suggests that IL-1 knockout mice actually have an improved outcome following intranasal *P. aeruginosa*. Although it is surprising that an impaired inflammatory response is beneficial for the clearance of *P. aeruginosa* from the

lung, other investigators have reported similar findings (44,45). It is possible that the inflammation induced by *P. aeruginosa* is worse compared to that caused by other Gram-negative agents, suggesting *P. aeruginosa* as a model of lung injury as well as lung infection. If this is the case, a "low" dose inoculum of *P. aeruginosa* may represent a controllable scenario during which proinflammatory strategies augment pulmonary immunity, while higher doses are perhaps a model of lung injury during which anti-inflammatory interventions prevent the worsening of tissue damage. In support of this speculation, Karzai et al. showed that enhancing pulmonary neutrophil recruitment worsens bacterial clearance in rats receiving a high intrapulmonary dose of *P. aeruginosa*, while the opposite results are true using a low dose bacterial challenge.

Immunohistochemical analyses and AM depletion studies have shown that AMs are the major sources of both TNF-α and IL-1β during an intrapulmonary infection (46–50). Once released by AMs, the autocrine and paracrine effects of these two proinflammatory mediators activate leukocytes, increase vascular permeability and adhesion molecule expression, and stimulate cytokine and chemokine production (34,35). Thus, TNF-α and IL-1β, along with other AM-derived mediators, create the inflammatory environment necessary to eliminate the offending pathogen, which is characterized by a neutrophilic alveolitis.

As neutrophils travel through the lung, the small diameter of pulmonary capillaries causes PMNs to temporarily sequester within the lung. Consequently, the concentration of PMNs in the pulmonary capillary bed can be as much as 100-fold higher than in the extra-pulmonary circulation (51). Because of their slower transit time through the lungs, this marginated pool of neutrophils can readily respond to infectious stimuli within the intra-alveolar space. The transmigration of neutrophils from the blood into the intraalveolar compartment involves the coordinated expression of adhesion molecules, chemoattractants, and subsequent PMN cytoskeletal rearrangement (52).

The margination and rolling of neutrophils on vascular endothelium is initiated by the expression of selectins, a family of glycoprotein adhesion molecules. L-selectin, which is constitutively expressed on the surface of neutrophils, binds to sulfated sialomucins on endothelial cells. Under normal conditions, L-selectin induces PMN margination within the lung vasculature (53), although more recent studies also highlight the importance of PMN deformability for pulmonary margination (54). Neutrophils eventually pass through the pulmonary circulation, albeit slowly, and continue their passage through the systemic vasculature. In response to intrapulmonary infection, however, proinflammatory mediators generated within the intra-alveolar space upregulate the surface expression of multiple adhesion molecules on endothelial cells, including E-selectin, P-selectin, and intracellular adhesion molecule-1, ICAM-1 (55–57). These adhesion molecules then

bind to their respective ligands on the surface of marginated neutrophils, increasing their adherence to the vascular endothelium. In addition to E-and P-selectins, lung-derived chemokines, such as IL-8, are also presented on the endothelial surface in association with glycosaminoglycans (58,59). These molecules are critical in mediating PMN firm adhesion to the endothelium and subsequent migration into inflamed tissues.

The interaction of selectins and chemokines with their respective binding sites propagates transmembrane signaling pathways within neutrophils, leading to the expression of the β_2-integrin molecules CD11b/CD18 (macrophage antigen-1; Mac-1) and CD11a/CD18 (lymphocyte-associated function antigen-1; LFA-1), and the shedding of L-selectin (60,61). Mac-1 is the more critical of these two PMN-associated integrins (62). Firm adherence of neutrophils to the endothelial surface is established via the ligation of integrins with ICAM-1 and -2. Recent studies by Doerschuk et al. (63,64) suggest that the importance of integrin-mediated firm adhesion in neutrophil transmigration may be dependent on the particular stimulus. Using CD18 deficient mice and Mac-1 neutralizing antibodies, their experiments show that intra-alveolar neutrophil migration is not inhibited in response to certain stimuli, including *S. pneumoniae, Staphylococcus aureus* (*S. aureus*), hydrochloric acid, and complement protein C5a, but is markedly decreased toward Gram-negative stimuli such as *Escherichia coli* (*E. coli*), *P. aeruginosa*, and *E. coli*-derived endotoxin.

Once sequestered within the pulmonary microvasculature, firmly adherent PMNs home toward and through intercellular junctions in a process known as chemotaxis (65,66). While the above-mentioned processes mediate the positioning and movement of PMNs through the pulmonary vasculature, their directed migration toward infected alveoli depends on the expression of PMN chemoattractants. Neutrophil chemoattractants released during inflammation include leukotriene B_4 (LTB_4) (67), C5a (68), platelet activating factor (PAF) (69), and the chemokines (70). In addition to these host-derived molecules, bacterial-derived products such as formyl-methionyl-leucyl-phenyalanine (fMLP) represent yet another potent class of PMN chemoattractants (71). All these factors are present within infected airways, where they form a gradient for neutrophil chemotaxis. As neutrophils migrate toward and bind to chemoattractants, intracellular signaling events induce cytoskeletal rearrangements, allowing neutrophils to migrate through vessel walls. Migrating neutrophils then pass through spaces in fibroblast-type II epithelial junctions and enter the alveolar space in a process that remains poorly understood (72) (Fig. 1).

Of all the factors produced within an inflammatory locus, it is perhaps the chemokines that play the most important role in leukocyte trafficking toward the site of infection. Chemokines represent a family of cytokines that are chemotactic for all leukocytes, including neutrophils, eosinophils, basophils, monocytes, mast cells, dendritic cells, natural killer cells, and

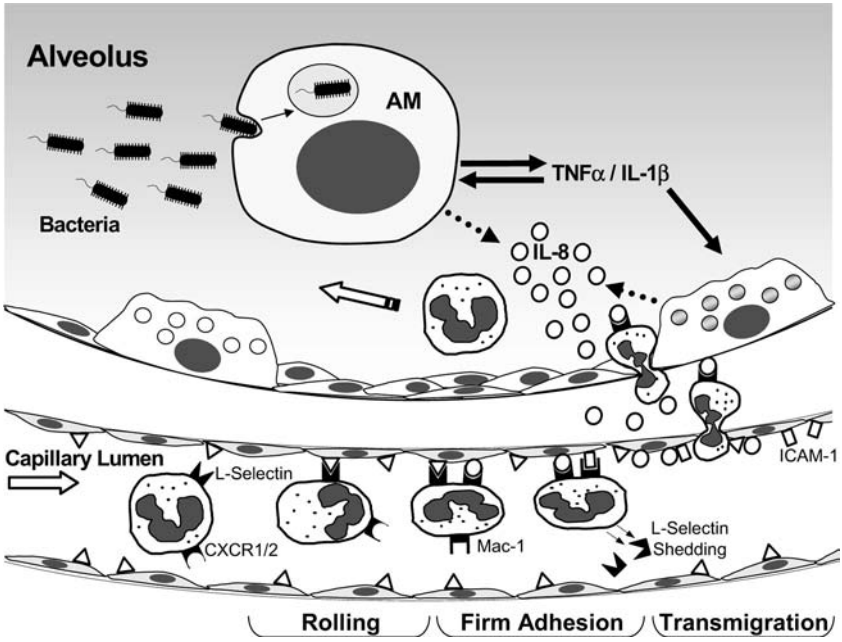

Figure 1 Recognition of bacteria by an alveolar macrophage (AM) initiates the production of TNFα, IL-1β, and other proinflammatory cytokines (not shown). The chemokine IL-8 is produced in response to both the challenge itself and the aforementioned cytokines. Changes that take place on or near the perfusing capillary include the increased expression of adhesion molecules (ICAM-1 shown) and the presentation of IL-8 and other local chemoattractants (not shown). As circulating neutrophils flow through the pulmonary capillary, they randomly adhere to the vessel lumen via ligation of L-selectin with constitutively expressed sulfated sialomucins (triangles). Once the rolling neutrophils are in the inflamed area, they bind IL-8 via the chemokine receptors CXCR-1 and -2. CXCR1/2 and L-selectin binding promotes surface expression of the β-integrins (Mac-1; CD11b/CD18 shown). As β_2-integrins attach to ICAM-1 molecules, neutrophils firmly adhere to the endothelium at which point they follow the chemoattractant gradient established by IL-8 and other neutrophil chemoattractants. Neutrophils then transmigrate past the endothelium, through the pulmonary interstitium, and across the epithelium to reach the infected alveolar space.

lymphocytes (73). These peptides are produced by many cell types in response to inflammatory stimuli such as bacterial products and host-derived cytokines (70,74), and their functional capacity is dependent on the expression of specific receptors on the surface of leukocytes (75).

Chemokines are basic proteins that usually display high affinity for glycosaminoglycans such as heparin. These proteins are generally small, ranging

between 70 and 125 amino acids, and have similar tertiary structures (76,77). With one exception, lymphotactin, all chemokines have four NH_2-terminal cysteine residues by which they are classified. Based on the number of amino acids between the first two cysteine residues, chemokines are divided into the CC, CX_3C, C, and CXC families.

The CXC chemokines are characterized by the presence of a single amino acid between the first two cysteine residues. However, the classification of CXC chemokines can be further subdivided based on the presence or absence of an N-terminal glutamate–leucine–arginine (ELR) motif upstream of the initial cysteine molecule. CXC chemokines bearing this motif are designated as ELR^+ and are potent activators of neutrophil chemotaxis and angiogenesis. In contrast, the ELR^- chemokines are chemotactic for mononuclear cells and are inhibitors of angiogenesis (78).

Neutrophil recruitment into the lower respiratory tract is critically dependent upon ELR^+ CXC chemokine expression. Consequently, the neutralization of ELR^+ CXC chemokines significantly attenuates pulmonary neutrophil recruitment and bacterial clearance (79–81). ELR^+ chemokines are typified by interleukin-8 (IL-8), which is the primary neutrophil chemoattractant in humans (82). The ELR motif on IL-8 and other ELR^+ chemokines allows the peptide to recognize the CXCR1 and -2 receptors expressed on neutrophil surfaces (83). In fact, ELR^- chemokines, which do not normally bind to neutrophils, can be made to do so if they are genetically mutated to express the ELR sequence. Once bound to their heterotrimeric G protein-coupled CXC receptors, chemokines induce multiple signaling pathways that typically converge at mitogen-activated protein kinase (MAPK) activation (84). This interaction results in cytoskeletal shape changes and the extension of lamellipodia, which allow neutrophils to migrate toward a chemotactic stimulus (77). As discussed earlier, CXC ligand–receptor interaction also induces the expression of β-integrins and the shedding of L-selectins from the surface of neutrophils, both of which are important processes in neutrophil transmigration (60,61,85).

Functional characterization of IL-8 and its rodent counterparts has increased our knowledge of the events regulating neutrophil migration toward the infected lung. Rodent homologs of IL-8 in mice include the keratinocyte-derived chemokine (KC) and macrophage inflammatory protein-2 (MIP-2) (86). In rats, two major ELR^+ CXC chemokines include cytokine-induced neutrophil chemoattractant (CINC) and MIP-2, which share marked homology with murine KC (92%) and MIP-2 (89%), respectively (85). In response to infection, CINC and MIP-2 synthesis is stimulated by proinflammatory cytokines such as TNF-α, as well as other inflammatory stimuli such as LPS (87–89). As with IL-8 in humans, local production of CINC and MIP-2 establishes a gradient through which neutrophils migrate toward an area of higher chemokine concentration (90,91). Thus,

manipulation of this chemotactic gradient can alter the ability of neutrophils to migrate toward an infected locus (47,79–81).

In the context of pulmonary inflammation, AMs serve as a major source of both CINC and MIP-2 (47,79). Multiple studies have now shown the importance of CINC and MIP-2 in pulmonary host defense. Ulich et al. (81) reported that CINC antiserum reduces neutrophil recruitment by 60–70% in response to intratracheal LPS or IL-1. Similar work has been performed in a model of IgG immune complex-induced lung injury (80). Likewise, MIP-2 neutralization decreased pulmonary neutrophil recruitment by 60% in a murine model of *K. pneumoniae* pneumonia, and was associated with a decrease in bacterial clearance (79). The importance of chemokine–receptor interaction has been shown in mice using a specific antibody against CXCR2, the shared receptor for CINC and MIP-2 (92). When the binding of KC and MIP-2 to CXCR2 was disrupted, neutrophil recruitment was suppressed, resulting in a 100-fold increase in lung bacterial burden and increased mortality in response to intratracheal *Nocardia asteroides.* Experiments performed in our laboratory have correlated alcohol-induced defects in neutrophil migration with the suppression of CINC and MIP-2 expression, further highlighting the importance of these two chemokines in pulmonary neutrophil recruitment (93,94). Conversely, local overexpression of CXC chemokines augments pulmonary neutrophil migration. Frevert et al. (60,85) showed that intratracheal CINC or MIP-2 directly induces a marked neutrophilic alveolitis. The influence of pulmonary KC on neutrophil recruitment has also been shown in transgenic mice locally overexpressing this chemokine (95). Following an intratracheal challenge with *K. pneumoniae*, these mice exhibit increases in pulmonary neutrophil recruitment, bacterial killing, and survival. The same group also showed beneficial outcomes of transgenic pulmonary KC expression in a model of intratracheal *Aspergillus fumigatus* (86). In their study, antibody-induced neutralization of CXCR2 (shared receptor for KC and MIP-2) resulted in a disease state similar to that seen in neutrophil-depleted animals. Not surprisingly, transgenic mice constitutively expressing pulmonary KC were resistant to this pathogen, as indicated by reductions in both fungal burden and mortality.

Once within the alveolar space, neutrophils become the primary phagocytic cell population (21). Neutrophil-mediated killing of bacteria involves phagocytosis, the respiratory burst, and the continued production of proinflammatory peptides, all of which are facilitated by opsonins, cytokines, and other factors within the inflammatory milieu. Not surprisingly, defects in neutrophil recruitment are predictably associated with impaired bacterial clearance and increased mortality (79,93). Thus, the host's ability to direct a robust PMN response to the invading pathogen is essential.

PULMONARY G-CSF AND THE MAINTENANCE OF NEUTROPHIL HOMEOSTASIS

As neutrophils are recruited from the intravascular to the intrapulmonary space, the pool of circulating neutrophils can be diminished (96). Therefore, the ongoing release of new neutrophils from the bone marrow is crucial for the maintenance of blood neutrophil counts and an intact host-defense response. Prior to their release, neutrophils are synthesized via the proliferation and differentiation of bone marrow-derived precursors. The importance of neutrophil repopulation is emphasized by their short circulating half-life (4–8 hr), which requires a continuous release of new neutrophils into the circulation in order to maintain a normal neutrophil count (97). It is known that the transit time of maturing neutrophils in the mitotic and postmitotic pools within the bone marrow is decreased during pneumococcal pneumonia (98). Yet, the mechanisms by which the bone marrow responds to a local infection such as pneumonia remain unknown.

Granulocyte colony-stimulating factor (G-CSF), a hematopoietic growth factor and activator of neutrophil function, is expressed in response to intrapulmonary infection (99) and represents one possible link between local infection and peripheral granulopoiesis. This cytokine is an approximately 20-kDa glycoprotein belonging to a functionally related family of cytokines termed colony-stimulating factors (CSFs) (100). G-CSF is produced by multiple cell types including monocytes, macrophages, lymphocytes, epithelial cells, fibroblasts, endothelial cells, astrocytes, and bone marrow stromal cells (101). G-CSF synthesis is initiated by various proinflammatory stimuli, and LPS is a potent inducer of its expression (102). Tazi et al. (103) showed that AMs recovered by bronchoalveolar lavage from healthy volunteers produce very little G-CSF prior to LPS treatment, but large amounts thereafter. In the same study, macrophages recovered from pneumonia patients spontaneously released G-CSF. In addition to bacterial products such as LPS, certain proinflammatory cytokines are also capable of inducing G-CSF synthesis. Both TNF-α and IL-1β stimulate G-CSF production by multiple cell types. In support of this, our laboratory has shown that a neutralizing antibody for TNF-α significantly attenuates the G-CSF response in rats challenged with intravenous *E. coli* (104). IL-17, another cytokine involved in neutrophilic inflammation, has also been shown to stimulate the production of G-CSF and CXC chemokines (105). Following an intrapulmonary challenge with *K. pneumoniae*, mice lacking a functional IL-17 receptor have an impaired G-CSF and MIP-2 response, delayed pulmonary neutrophil recruitment, and increased mortality (105).

The effects of G-CSF signaling in neutrophils include chemotaxis (106), adhesion molecule expression (107), phagocytosis (108), and respiratory burst (109). In addition, the stimulatory effect of this cytokine on granulopoiesis is perhaps its most important role during infection. G-CSF

stimulates both the proliferation of granulocytes within and mobilization from the bone marrow. The proliferation of myeloid stem cells to become mature neutrophils is enhanced by G-CSF at almost all stages of neutrophil development (110). This property, in addition to the G-CSF-induced mobilization of granulocytes from the bone marrow, is fundamental for the maintenance of blood neutrophil counts. Indeed, the pharmacokinetic properties of G-CSF allow it to increase blood neutrophil counts when administered exogenously (111). As a result, G-CSF is widely used clinically to re-establish blood neutrophil levels in neutropenic patients such as those undergoing chemotherapy (111,112). The mechanisms governing G-CSF-induced PMN mobilization are poorly understood, but appear to involve coordinated alterations in adhesion molecules that normally anchor cells within the bone marrow environment. Among these, interactions are those mediated by integrins (113), selectins (114), and cytokines such as stromal cell-derived factor-1 (SDF-1) and stem cell factor (SCF) (115). Evidence suggests that G-CSF upregulates the expression of proteases (elastase, cathepsin G, and matrix metalloproteinases), which cleave interactions between the aforementioned retention molecules and their corresponding ligands located on the surfaces of PMN progenitors (115).

With the advent of molecular biology, the role of G-CSF in maintaining steady-state levels of blood neutrophils has been firmly established in animal models of G-CSF and G-CSF receptor deficiency. Genetically engineered knockout (KO) mice, incapable of expressing G-CSF, have chronic neutropenia and an impaired ability to control infection, suggesting that G-CSF is integral for the maintenance of both steady-state and "emergency" granulopoiesis (116). In the same study, KO mice treated with exogenous G-CSF recovered from neutropenia, verifying the defect in G-CSF/G-CSFR signaling as the initial cause of neutropenia. The importance of G-CSF in steady-state neutrophil homeostasis is also dependent on intact signaling through its receptor. Mice lacking a functional gene for the G-CSF receptor not only have chronic neutropenia, but also have defects in neutrophil viability (117–119). Similarly, dogs treated with recombinant human G-CSF develop antibodies that cross-react with canine G-CSF, resulting in chronic neutropenia (120).

Despite the clear importance of G-CSF in regulating bone marrow granulopoiesis, the role of lung-derived G-CSF in this process remains uncertain. We have recently shown that lung-derived G-CSF, in contrast to certain other cytokines such as TNF-α, IL-1β, and IL-8, is not compartmentalized within the lung during pulmonary infection (99,121). In this study, intratracheal *E. coli* increased levels of G-CSF detected in both bronchoalveolar lavage fluid (BALF) and plasma, as opposed to TNF-α, which was only measurable in BALF. However, G-CSF mRNA expression was confined to lung tissue, identifying the lung as the source of plasma G-CSF in response to the intrapulmonary *E. coli* challenge. In further experiments, the appearance of

G-CSF in the plasma corresponded with increased numbers of myeloid progenitors in bone marrow, blood, and spleen 48 hr postintratracheal *E. coli* (Nelson et al., unpublished data). Similar results occurred following an intratracheal injection of recombinant G-CSF. Taken together, these results support a functional role for the selective decompartmentalization of G-CSF observed in response to an intrapulmonary infectious challenge.

The immunomodulatory effects of G-CSF make it a potential therapeutic agent for bacterial pneumonia in non-neutropenic hosts. Our laboratory investigated the effects of G-CSF pretreatment in rats challenged intratracheally with *K. pneumoniae* in the presence and absence of acute ethanol intoxication (122). Two days of G-CSF pretreatment augmented the recruitment of neutrophils into the lungs of control animals and significantly attenuated the adverse effects of ethanol on neutrophil delivery into the challenged lungs 4 hr after intratracheal infection. Other beneficial outcomes of G-CSF therapy in this study included reduced bacterial burden and decreased mortality. Similarly, we have performed experiments using G-CSF as an adjunct therapy in the intrapulmonary response to endotoxin. Two days of G-CSF treatment significantly enhanced pulmonary neutrophil recruitment, neutrophil phagocytosis, adhesion molecule expression, and respiratory burst (123). In addition to alcohol abuse, splenectomy is another known risk factor for increased morbidity and mortality in patients with pneumococcal pneumonia (124). In a murine model, G-CSF administration, either before or after the infection, improved survival among splenectomized animals exposed to aerosolized challenges with *S. pneumoniae* (125).

Four trials have been completed studying the effects of G-CSF in non-neutropenic patients with pneumonia. The first trial was a phase I study in which 30 non-neutropenic patients with CAP received intravenous antibiotics in addition to G-CSF (75–300 μg) subcutaneously daily for a maximum of 10 days (126). By day 4 of G-CSF administration, absolute neutrophil counts reached peak levels that were approximately 200% higher than the median baseline value. There were no adverse systemic or pulmonary side effects attributable to G-CSF, aside from mild bone pain. In a phase III, double-blinded, placebo-controlled trial of recombinant human G-CSF for the treatment of hospitalized patients with CAP, 756 patients enrolled in 71 centers in the United States, Canada, and Australia were randomized to receive 300 μg/day G-CSF (376 patients) or placebo (380 patients) in addition to conventional antibiotic therapy (127). The primary objectives of this study were to determine safety and the effect of G-CSF on TRM (time to resolution of morbidity). TRM, a useful index for determining whether a patient with pneumonia is benefiting from therapy (128), was reached in this study to check whether a patient had either an improved or stable chest radiograph, resolved tachypnea, loss of fever, and improved or normalized oxygenation. While neither mortality (6%), length of stay (7 days), nor TRM (4 days) were different in either treatment group. G-CSF did increase

blood neutrophils 3-fold, significantly accelerated radiological resolution of pneumonia and reduced serious complications (i.e., ARDS and disseminated intravascular coagulation, DIC) that were particularly evident in patients with multilobar (>2 lobes) pneumonia. G-CSF has also been studied in 18 patients with pneumonia and severe sepsis (129). Three of 12 G-CSF-treated patients died while 4 of 6 placebo-treated patients died. In addition, septic shock resolved in 9 of 10 G-CSF-treated patients and none of the 4 placebo-treated patients. ARDS resolved in 2 of 5 G-CSF-treated patients and 1 of 4 placebo-treated patients. G-CSF was well-tolerated in these septic patients. These favorable trends led to additional trials in patients with multilobar pneumonia and in patients with severe pneumonia with sepsis. In one such trial, 480 patients with multilobar CAP were randomized to receive G-CSF (237 patients) or placebo (243 patients) (130). G-CSF treatment was well-tolerated, increased WBC counts, and showed a trend toward decreased mortality in patients receiving G-CSF, although this was not statistically significant. In another more recent multicenter clinical trial, 701 patients with bacterial pneumonia were randomized to receive 300 μg/day G-CSF (348 patients) or placebo (353 patients) (131). G-CSF was administered for 5 days or until white blood cell counts reached 75.0×10^9 cells/L or higher. G-CSF treatment was well-tolerated and significantly increased white blood cell counts, but had no significant effect on mortality. However, there was a noticeable trend where patients receiving G-CSF in combination with a quinolone antibiotic had a decreased mortality compared to placebo-treated patients receiving this antibiotic class (29% vs. 40%, respectively). Although no significant effect was observed on the outcome of patients with pneumonia and severe sepsis in this trial of G-CSF therapy, additional controlled studies may more clearly identify which patients might benefit from this therapeutic intervention.

It remains unclear at this time whether the potential benefits of G-CSF therapy are solely attributable to increases in neutrophil number or to the enhancement neutrophil function. As previously discussed, G-CSF augments the ability of neutrophils to respond to infection by influencing functions such as chemotaxis, phagocytosis, and oxidative burst. Furthermore, G-CSF has been shown to alter the uptake of certain antibiotics by neutrophils (132). As G-CSF therapy also increases neutrophil delivery to infected tissue sites in animal models, it is reasonable to speculate that certain antibiotics could be targeted to infected tissues by administering them in combination with G-CSF therapy. However, the use of G-CSF as adjuvant treatment for bacterial pneumonia should be approached with caution to prevent disruption of the fine balance by which the host-defense system operates. Loss of this regulation could result in excessive inflammation and organ injury.

INNATE IMMUNITY AND THE ACQUIRED IMMUNE RESPONSE

As discussed, the innate immune system is primarily responsible for the acute inflammatory response to an offending bacterial pathogen. While not widely appreciated, the acquired immune response is also initiated within hours of infection through complex interactions with the innate immune system. A key proximal event requisite for the genesis of an acquired immune response is recognition of the specific antigen. AMs, as mentioned earlier, are the phagocytes primarily responsible for host defense once bacteria reach the alveolar space. They can also potentially function as antigen presenting cells (APCs) by internalizing, processing, and presenting foreign peptides on surface MHCII molecules. These complexes are recognized by the specific cognate T-cell receptor on lymphocytes that are then stimulated to proliferate and further amplify the immune response. However, AMs are not particularly robust APCs because of their relatively low expression of MHCII and several important T-cell costimulatory molecules CD40, CD80, and CD86. Another resident immune cell of the lung, the dendritic cell (DC), has been identified as the professional APC in the setting of lung infection. DCs, like the AM, are also of bone marrow origin and migrate into the lung interstitium to assist in immunosurveillance. Prior to an antigenic challenge, DCs are considered "immature" and possess a wide range of pattern-recognition receptors to a wide range of pathogens. After encountering a specific pathogen, DCs undergo a dramatic phenotypic change as they migrate to areas of lymphoid tissue. A loss of phagocytic and antigen recognition abilities is exchanged for a markedly increased propensity for antigen presentation through upregulation of the aforementioned surface molecules (Fig. 2). After stimulation by antigen-loaded DCs, T cells bearing the specific T-cell receptor for this foreign protein begin to proliferate in the local lymph nodes. This expansion occurs in one of two generalized subtypes of CD_4^+ T-cell responses: the T-helper 1 (Th1) and Th2 phenotypes. The Th_1 response is characterized by cell-mediated immunity and is strongly induced by IL-12, a product of AMs and DCs. The Th1 response pattern is characterized by the production of IL-2, IL-12, IL-18, GM-CSF, and IFsN-γ. The Th2 response is characterized by cytokines such as IL-3, 4, 5, 10, and 13 and favors humoral immunity by stimulating B-cell antibody production.

It is predominantly through the Th_1 response that T cells coordinate the specific immune response to bacterial pneumonia. Human IL-12 deficiency leads to recurrent pneumococcal pneumonia (133), indicating the importance of intact Th1 immunity in pulmonary host defense. Furthermore, local administration of IL-12 through adenoviral-mediated gene transfer was shown to be protective in a murine model of *K. pneumoniae* (134). As the signature cytokine of the Th1 response, IFN-γ has also been shown to have significant effects on AM function in bacterial pneumonia by increasing TNF-α production, enhancing phagocytosis, and augmenting

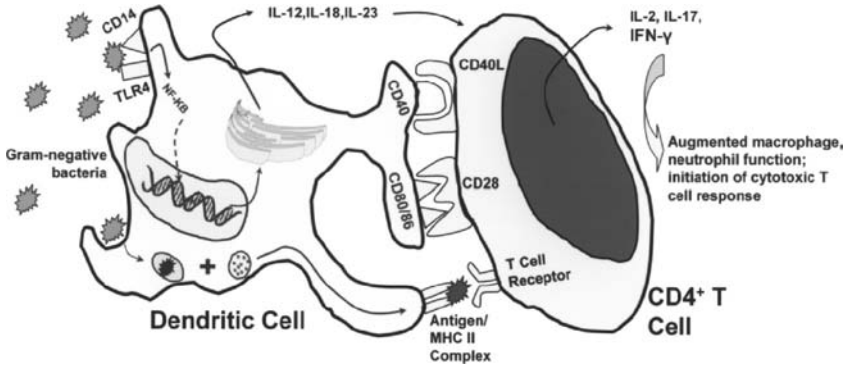

Figure 2 Dendritic cell (DC) recognition of pathogen via TLR4 leads to activation and nuclear translocation of the inflammatory transcription factor NFκB. Dendritic cells then secrete multiple cytokines that directly stimulate T-cell activation. Concurrently, phagocytosis of bacteria and lysosome fusion allow for presentation of bacterial antigen to a specific T-cell receptor, which, in coordination with co-stimulatory signals, leads to activation and clonal expansion of pertinent T-cell subsets. These T cells also secrete cytokines that enhance both innate and adaptive immune functions.

their bacteriocidal capacity (135). Conversely, absence of IFN-γ is associated with poor outcomes in animal models of Gram-negative pneumonia (136), while overexpression of IFN-γ is protective in models of bacterial pneumonia caused by *Legionella* and *Pseudomonas* sp. (137,138). As human administration of recombinant IFN-γ has been shown to be relatively safe and appears to be limited to the pulmonary compartment when delivered locally, interest continues in the development of this drug as a therapeutic immunomodulator. Because HIV and many forms of immunosuppression are associated with decreased $CD4^+$ T-cell function and/or number, interest exists in T-cell independent immunostimulation to combat pulmonary infection in such patients. Modifying DCs to directly express CD40 ligand (a cell surface marker normally found on T cells) and exposing these cells to *Pseudomonas* before adoptive transfer into normal or $CD4^+$-depleted mice can protect animals from lethal pulmonary *Pseudomonas* infection (139).

Through direct cell-mediated toxicity and enhancement of innate immune responses, the acquired immune system plays an important role in host defense against bacteria. In the naïve host, however, specific immunity requires a week or more to become fully operational. The development and persistence of clonal memory T cells allows a more expedient and robust immune response for the previously exposed host. One of the more recently discovered means by which memory CD_4^+ T cells can rapidly assist the

innate immune system is through the expression of IL-17. Cloned more than a decade ago, IL-17 has been identified as a proinflammatory cytokine expressed by T cells in animals exposed to *Borrelia burdorferi*, *Helicobacter pylori*, mycobacterial products, and LPS (140). Recent work has demonstrated rapid (within 6 hr) induction of significant levels of IL-17 in a mouse model of pulmonary infection with *K. pneumoniae* (141). Recognition of a pathogen through the pattern-recognition receptor TLR4 is the key proximal event for an IL-17 response to this Gram-negative bacteria. The primary effect of IL-17 secretion by T cells is increased PMN recruitment through the induction of neutrophil chemokines KC and MIP-2, functional homologs of human IL-8. Also, IL-17 has been found to directly increase human IL-8, adhesion molecule (ICAM-1), and G-CSF expression (142). Animals deficient in the receptor for IL-17 display a marked deficiency in G-CSF production in bacterial pneumonia, further implicating IL-17 in the pulmonary recruitment of PMNs. IL-23, produced exclusively by antigen presenting cells, is capable of inducing IL-17 (143). We have shown that IL-23 is the major stimulus for T-cell expression of IL-17 in response to *K. pneumoniae* infection, via intact TLR4 signaling (141). As HIV infected patients are at increased risk for bacterial pneumonia, immunomodulatory therapy with recombinant IL-17 or IL-23 may be of benefit to these patients.

REGULATION OF THE PULMONARY HOST RESPONSE

The generation and maintenance of an inflammatory response is essential for the bacterial clearance in the lower respiratory tract. Yet, the inflammatory cascade can be viewed as a ''double-edged sword,'' causing tissue damage, shock, or even death in some patients. During local infections such as pneumonia, the degree of inflammation must be adequate to clear the infection, yet focused to avoid organ injury. Disruptions in this balance can result in systemic inflammation and disrupt physiologic homeostasis. Fortunately, mechanisms exist that serve to regulate the production and distribution of proinflammatory cytokines and ensure the prevention of a ''rogue'' inflammatory response.

The expression of anti-inflammatory cytokines is one mechanism that enables the host to harness the inflammatory response. Interleukins 4 and 10 represent two such cytokines (144). IL-4 induces the activation of STAT6, which subsequently recognizes the same binding site as another transcription factor, STAT1. Binding of STAT6 to the STAT1 DNA-binding domain prevents the initiation of downstream IFN-γ induced pro-inflammatory gene expression. IL-4 can have either positive or negative influences on survival, depending on the context of infection. In a lethal model of Gram-negative sepsis, IL-4 pretreatment improved survival while the opposite results were seen after a sublethal challenge (145). These findings suggest that IL-4 can ''fine tune'' the inflammatory response.

IL-10 is another anti-inflammatory cytokine that decreases both the expression and stability of LPS-induced proinflammatory cytokine mRNA. As with IL-4, the anti-inflammatory effects of IL-10 have shown to be either beneficial or detrimental, depending on the circumstances of infection (146–149). For example, IL-10 treatment decreases inflammation and improves survival in mice infected endobronchially with *P. aeruginosa*, despite no change in bacterial burden (146). In contrast, van der Poll et al. (149) reported that intranasal IL-10 reduces lung levels of TNF-α and INF-γ and decreases bacterial clearance and survival in mice challenged with intrapulmonary *S. pneumoniae*. In the same study, the investigators showed that neutralization of IL-10 increased bacterial clearance and survival. Furthermore, investigators recently determined that human overexpression of IL-10 via a gene polymorphism is associated with an increase in severity of the systemic inflammatory response syndrome (SIRS) in patients with CAP, presumably because of an inappropriate curtailment of inflammation prior to eradication of the pathogen (150).

Another mechanism by which the body controls inflammation is by preventing its spread to distant uninfected loci. Our laboratory and others have shown that many proinflammatory cytokines are confined to an infected tissue compartment. We reported that following intratracheal endotoxin administration, levels of TNF-α significantly increase in bronchoalveolar lavage fluid (BALF), with no detectable increase in the systemic circulation (151). In the same study, i.v. endotoxin induced a plasma TNF-α response that was not associated with an increase in lung levels of this cytokine. These results demonstrated that TNF-α remained compartmentalized within the intra- or extrapulmonary space, depending on the origin of the infectious stimulus. This work was further supported by Boujoukos et al. (152), who measured intrapulmonary protein and mRNA expression of TNF-α, IL-1, IL-6, and IL-8 in patients. Following intravenous LPS, neither BALF protein nor lung mRNA expression was increased for any of these four cytokines compared to baseline values. The intrapulmonary compartmentalization of proinflammatory cytokines has also been studied in hospitalized patients with unilateral pneumonia (121,153). Here, the investigators showed that IL-8, TNF-α, IL-1, and IL-6 are largely compartmentalized to the infected lung of patients with unilateral pneumonia.

Excessive lung injury can result in the "leak" of cytokines into the systemic circulation. This was shown in a previous study from our laboratory in which lung injury abrogated the intra-alveolar compartmentalization of TNF-α (154). To induce lung leak, α-naphthylthiourea (ANTU) was intraperitoneally administered to rats. Following lung injury, isolated perfused lungs were intratracheally instilled with LPS or recombinant TNF-α to increase intra-alveolar TNF-α content. In the absence of ANTU treatment, both LPS-induced and recombinant TNF-α remained confined to the intrapulmonary space. In contrast, ANTU-induced lung injury significantly

increased perfusate levels of this cytokine after i.t. LPS or TNF-α. Using a different model of lung injury, Haitsma et al. (155) showed that injurious mechanical ventilation can disrupt both the intrapulmonary and intravascular compartmentalization of TNF-α.

It is now evident that even in the absence of tissue "leakage," certain cytokines do not exhibit the "normal" compartmentalized presence within the lung. The physiologic functions of certain cytokines dictate that they must exit from the inflammatory locus. As previously discussed, G-CSF is one such cytokine that enters the systemic circulating following its synthesis within the lung (99), and its selective release may be a prominent mechanism in facilitating bone marrow granulopoiesis. Similarly, the ELR^+ CXC chemokine CINC is also decompartmentalized from the lung, unlike the much-related chemokine MIP-2 (156). This surprising phenomenon is perhaps explained by the finding that systemic CINC administration enhances pulmonary neutrophil recruitment. The specialized distributions of G-CSF, CINC, and possibly other as-of-yet unidentified cytokines likely represent an important aspect of the pulmonary host-defense response, which may be targeted for future therapeutic interventions.

CONCLUSION

In summary, the respiratory tract possesses an extensive array of defense mechanisms, and successful integration of innate and adaptive immune components is essential in maintaining the sterility of the lung. In the face of increasing antibiotic resistance, as well as in the number of immunosuppressed patients, it is imperative that we reach a greater understanding of the precise mechanisms through which host and pathogen interact in the setting of bacterial pneumonia. Such advances may lead to the development of novel therapeutic modalities for the prevention and treatment of pneumonia.

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about the book . . .

Analyzing preventive strategies, as well as emerging trends in the bacteriology, pathogenesis, diagnosis, and management of disease, this reference explores factors that lead to the development of severe pneumonia, the most effective treatment methods for the condition, and recent efforts to improve disease outcomes—describing patients at risk for severe pneumonia, mortality predictors in ventilator-associated pneumonia, and mechanisms of antibiotic resistance in the intensive care unit.

Covering community-acquired, ventilator-associated, and nosocomial pneumonia, this guide examines the pathogenesis, bacteriology, and key clinical features associated with severe pneumonia…details the role of mechanical ventilation in the pathogenesis of illness…reviews appropriate dosing and dosing regimens for antibiotic therapy…discusses controversies surrounding the use of mono vs. combination therapy for the management of ventilator-associated pneumonia…examines the role of microbiological surveillance in the management of ventilator-associated pneumonia…analyzes controversies in the diagnosis of pneumonia…considers the optimization of pharmacokinetic and pharmacodynamic approaches for the treatment of patients with severe pneumonia…and presents new approaches in the treatment and prevention of ventilator-associated pneumonia.

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