Ventilator-associated pneumonia is a common complication in intensive care units, occurring in 9% to 24% of patients intubated for longer than 48 hours. Because of this large disease burden and the resultant attributable morbidity and mortality, there is great interest in accurately diagnosing, treating, and preventing this complication. More severely ill patients tend to develop ventilator-associated pneumonia, and identified risk factors include prolonged mechanical ventilation, reintubation after failed extubation, and a few other clinical variables. The efficacy of diagnostic and preventive strategies is somewhat controversial. Diagnosis by invasive methods requires a considerable commitment of resources but can potentially reduce cost of care; however, mortality benefit from this approach has not been demonstrated. As such, in most institutions, ventilator-associated pneumonia is best diagnosed using traditional clinical criteria. Prompt administration of appropriate antibiotics seems to be the only intervention that alters outcome once the diagnosis is established. Several strategies seem to reduce pneumonia incidence; however, mortality and cost benefits have yet to be convincingly shown.

Ventilator-associated pneumonia is defined as parenchymal lung infection occurring more than 48 hours after initiation of mechanical ventilation. This serves to differentiate this disorder from community-acquired pneumonia and highlights pathogenic features peculiar to mechanically ventilated patients. A recent multicenter European study has shown that pneumonia is now the most common infection acquired in the intensive care unit (ICU), and when acquired during mechanical ventilation it has an associated mortality of 24% to 71%. A vast literature has accumulated concerning all facets of this disease, especially regarding the efficacy of available diagnostic methods and putative preventive measures. This article reviews the current state of the art with emphasis on diagnosis, treatment, and prevention strategies.

METHODS

We searched the English-language literature using the MEDLINE database from 1966 to 1998 using search terms ventilator-associated pneumonia and nosocomial pneumonia. Additional articles were identified by reviewing the reference lists of retrieved articles. We selected articles containing information about the epidemiology, pathogenesis, diagnosis, management, and prevention of ventilator-associated pneumonia in adults. In evaluating this literature, meta-analyses, prospective cohort studies, and randomized controlled trials were given preference for inclusion; studies with less rigorous methods were excluded unless no data from preferred sources were found. Concerning interventions designed to prevent ventilator-associated pneumonia, final recommendations incorporate well-established guidelines for grading scientific evidence for medical practice, adapted as follows: grade A, recommendation based on 1 or more randomized controlled trials or meta-

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analysis in which the lower limit of the confidence interval for the treatment effect exceeds the minimally important clinical benefit; grade B, recommendation based on 1 or more randomized controlled trials or meta-analysis in which the lower limit of the confidence interval for the treatment effect overlaps the minimally important clinical benefit; and grade C, recommendation based on evidence from nonrandomized trials, case series, or expert opinion.

EPIDEMIOLOGY

Gram-negative bacillus pneumonia became recognized as a significant cause of morbidity and mortality in hospitalized patients during the 1950s,12,33 coinciding with increasing use of mechanical ventilation and antibiotic drugs. Contaminated respiratory care equipment was initially implicated as the source of these pathogens; however, despite implementation of infection control measures, pneumonia has remained the most common ICU-acquired infection,1 with an incidence of 9% to 24% in patients mechanically ventilated for longer than 48 hours.1,6,9

The risk of developing ventilator-associated pneumonia relates to host factors and to the duration and intensity of exposure to potential pathogens. Single-center multivariate analyses2,8,14,15 have implicated prolonged mechanical ventilation and reintubation as risk factors; however, not all studies have agreed, and 2 studies7,12 reached discordant conclusions regarding previous antibiotic use. A recent multicenter Canadian study19 evaluated 1014 mechanically ventilated patients and found the following independent predictors of ventilator-associated pneumonia: a primary diagnosis of burns, trauma, central nervous system disease, respiratory tract disease, or cardiac disease; witnessed aspiration; mechanical ventilation within the previous 24 hours; and use of paralytic agents. Two other important findings of this analysis are (1) a rising daily risk for pneumonia until the fifth day of mechanical ventilation, with subsequent decline, and (2) a protective effect of systemic antibiotic therapy. Factors not assessed in this study but found to be predic-

tive in other analyses include low endotracheal tube cuff pressure,13 transport outside the ICU,14 and supine body position.7 Although authors17 have identified recent surgery and altered sensorium as factors predisposing to pneumonia in mixed populations of ventilated and nonventilated ICU patients, studies6,8,16 excluding spontaneously breathing patients have consistently been unable to demonstrate this relationship, suggesting that intubation and mechanical ventilation obviate these risks.

APPROACH TO DIAGNOSIS

Respiratory failure combined with critical illness frequently culminates in pneumonia, but accurately determining whether pneumonia is present can be difficult, especially in the setting of acute respiratory distress syndrome. Standard clinical methods are insensitive in unequivocally diagnosing ventilator-associated pneumonia; positive pleural fluid culture or radiographic cavi
tation is present in only a minority of patients,18,21 and blood cultures in this setting are positive in 10% or less.8,9,18 Studies22,23 using pulmonary histological patterns as a gold standard comparison reveal that clinical acumen is incorrect in determining the presence or absence of ventilator-associated pneumonia in up to one third of patients; alternative pathological diagnoses in this situation include atelectasis, infarction, hemorrhage, and fibrosis.22 These data suggest the need for improved diagnostic methods, and, in the pursuit of more accurate diagnosis, specific features of ventilator-associated pneumonia pathogenesis become important.

Pathogenesis

Events important in the progression to pneumonia in intubated patients begin with oropharyngeal colonization by potentially pathogenic bacteria.24,25 In this setting, endotracheal tube placement creates an abnormal continuum between the upper airway and the trachea and establishes a subglottic reservoir of secretions rich in bacterial pathogens. Secretions in this subglottic pool are aspirated into the tra-
Potential sources of bacteria causing ventilator-associated pneumonia. Bacteria residing in the oropharynx and gastrointestinal tract can contaminate the subglottic secretion pool, as demonstrated. Subglottic secretions above the endotracheal tube cuff are aspirated into the trachea and disseminated into the distal airways and lung parenchyma by the force of the ventilator (inset).
form as well as invasive methods. After pneumonia is diagnosed clinically, refinements in antibiotic selection should rely on the culture of endotracheal aspirate because this method identifies potential pathogens at least as well as invasive methods. 

THERAPEUTIC CONSIDERATIONS

There are no placebo-controlled trials of the treatment of ventilator-associated pneumonia; presumption of benefit is based on the underpinning principles of antibiotic therapy, data demonstrating attributable morbidity and mortality, and the poor outcome of patients given antibiotic drugs that do not cover causative bacteria (Table 1).6,8,9,57,62,72,73

Concept of Attributable Morbidity and Mortality

Although it is clear that the presence of ventilatory-associated pneumonia adversely affects outcome, results of investigations at-
Antibiotic Selection

Appropriate antibiotic therapy for ventilator-associated pneumonia can be defined as treatment with antimicrobial drugs that cover all likely pathogens isolated from respiratory tract secretions. Caveats to this statement include that (1) samples sent for culture should reflect lower respiratory tract secretions, ie, more than 25 granulocytes and less than 10 epithelial cells per low-power field and (2) less virulent organisms such as vancomycin-resistant enterococci and coagulase-negative staphylococci might not be pathogenic; this is especially germane when more virulent bacteria are concurrently isolated (the more likely culprit) and risk factors for invasive disease are absent.

Given these caveats, one important lesson from recent studies is that antibiotic coverage should be given early after infection is suspected, and the spectrum of this agent(s) should address all reasonably suspected pathogens. Several studies have demonstrated that the need to change antibiotic drugs after culture data becomes available identifies a subgroup of patients with higher mortality. Moreover, Luna and colleagues noted that the mortality benefit of appropriate antibiotic coverage pertained only to that treatment present before invasive diagnostic testing, suggesting that an important time window exists after which antibiotic treatment, regardless of activity, is less effective. As such, the single most important management decision after a clinical diagnosis of pneumonia is whether antimicrobial activity against potentially resistant organisms such as Pseudomonas aeruginosa, Acinetobacter species, and Stenotrophomonas maltophilia is warranted. These organisms occur later in the course of mechanical ventilation, usually in the presence of previous antibiotic therapy, and are independently associated with poor outcome.

Trouillet and coworkers prospectively studied 135 patients with ventilator-associated pneumonia, comparing episodes caused by these high-risk bacteria (including methicillin-resistant Staphylococcus aureus) with those secondary to other pathogens. By multivariate analysis, duration of ventilation before pneumonia onset and previous broad spectrum antibiotic drug use were the only factors associated with high-risk organisms. Moreover, in 84 patients ventilated for 7 days or longer with previous antibiotic exposure, an empirical triple-drug regimen including vancomycin was required to obtain acceptable antimicrobial activity in 88% of episodes. With this sort of data in mind, the American Thoracic Society guidelines recommend expanded coverage for these organisms in the presence of 5 days or more of hospitalization before pneumonia onset, previous antibiotic treatment, corticosteroid use, structural lung disease, and immunosuppression.

Empirical antibiotic medication selection should take into account risk factors, as outlined above, especially time of pneumonia onset. Patients with late-onset pneumonia (≥5 days of hospitalization) or risk factors should be covered with antibiotic drugs with acceptable antipseudomonal activity (Figure 2), including select fluoroquinolones, aminoglycosides, β-lactams with or without β-lactamase inhibitors, and third-generation cephalosporins, as well as imipenem, meropenem, and aztreonam. Monotherapy with these agents (excluding aminoglycosides) is associated with clinical failure in 15% to 29% of patients, however, because of exclusion of the most severely ill patients in some of these trials, the failure rate experienced in clinical practice might be higher. High-risk organisms constitute most clinical failures, as evidenced by the ability to eradicate P aeruginosa in only 34% of pneumonia episodes in one study. Multicenter randomized trials have compared imipenem with ciprofloxacin, piperacillin-tazobactam, and ceftazidime as single-agent therapy but did not demonstrate clear-cut superiority of any one agent; however, use of piperacillin-tazobactam seemed to be more efficacious against P aeruginosa. To minimize clinical failure associated with high-risk pathogens, 2 antimicrobial agents of different action mechanisms are recommended until culture results are available. A traditional choice in this regard has been an extended spectrum β-lactam plus an aminoglycoside; however, newer agents also have excellent activity (Figure 2). Limited information suggests that piperacillin-tazobactam may be the preferred agent against high-risk organisms; one recent multicenter study comparing a combination of piperacillin-tazobactam plus amikacin with ceftazidime plus amikacin revealed a 2-fold higher rate of clinical and microbiologic failure with the ceftazidime-containing regimen (26% vs 46%; P = .023). The rea-

Figure 2. Recommended empirical antibiotic therapy for ventilator-associated pneumonia. Recommendations are adapted from the American Thoracic Society consensus statement of 1995. Risk factors consist of previous use of antibiotic drugs, use of corticosteroids, clinical shock, immunosuppression, and neutropenia. Asterisk indicates β-lactamase inhibitors, imipenem, meropenem, ceftazidime, ceferazone sodium, cefepime, and aztreonam (avoid a combination of aztreonam and an aminoglycoside if gram-positive cocci are suspected); dagger, use only fluoroquinolones with reliable anti-pseudomonal activity. See the “Antibiotic Selection” subsection for details.
Antibiotic resistance is a serious emerging problem, and data from the National Nosocomial Infections Surveillance System\textsuperscript{96} document higher levels of antibiotic resistance in patients treated in ICUs compared with non-ICU hospitalized and ambulatory patients. Because this problem is largely related to antimicrobial exposure, judicious antimicrobial use in the ICU should be a major concern in all management decisions. Extended spectrum 
\textit{b}-lactam agents are particularly likely to induce bacterial resistance to antibiotic drugs. Induction of \textit{b}-lactamases after \textit{b}-lactam use\textsuperscript{97-99} and alterations in bacterial membrane permeability after imipenem use\textsuperscript{100,101} have received considerable attention; however, no antibiotic class is immune to this phenomenon. Given these facts, antibiotic resistance should be minimized by using agents with the narrowest activity spectrum after culture and sensitivity data become available and by stopping antimicrobial therapy when infection is reasonably excluded. Other strategies to potentially prevent resistance include antibiotic class restriction\textsuperscript{100} and scheduled changes in antibiotic class used for empirical therapy in ICUs.\textsuperscript{102}

\textbf{PREVENTION}

Given the considerable attributable morbidity of ventilator-associated pneumonia and the fiscal loss to hospitals caring for these patients,\textsuperscript{103,104} prevention has become a major focus. Published guidelines\textsuperscript{105-107} emphasize the importance of infection control and surveillance, and implementation of a nosocomial pneumonia prevention policy has been shown to decrease disease incidence.\textsuperscript{108,109} Bacterial colonization of the lower respiratory tract of mechanically ventilated patients is the targeted event of most preventive strategies. Several of the more controversial topics are discussed in the following subsections (Table 3); the reader is directed to a recent comprehensive review for further information.\textsuperscript{110}

\textbf{Prevention of Bacterial Colonization}

Depending on primary disease and previous patient locale, bacterial colonization of the trachea is recognized in up to three quarters of patients on initial sampling after ICU admission.\textsuperscript{111-113} Studies are somewhat divided as to the source of these microbes; some data\textsuperscript{112} support between-patient transmission and others\textsuperscript{114-118} suggest that most pathogens are endogenous flora. Nevertheless, simple infection control measures such as hand washing are important,\textsuperscript{119} and an outbreak should prompt policy reevaluation.\textsuperscript{120-122}

Selective decontamination of the aerodigestive tract with topically applied antibiotic drugs reduces the gastric bacterial burden and prevents tracheobronchial colonization and ventilator-associated pneumonia.\textsuperscript{123-128} Factors against routine use are the
marginal mortality benefit for ventilated patients as a whole,127-129 cost of application, and risk of inducing antibiotic resistance.127,130,131 Moreover, studies reporting these findings have variously decontaminated the stomach alone, stomach and oropharynx, or both with the addition of a parenteral antibiotic drug, making the most appropriate approach unclear. Nevertheless, a subset of severely ill patients seem to derive benefit, as suggested by a reanalysis132 of previously performed studies and a recent study124 demonstrating reduced total cost of care. At present, despite reduced pneumonia incidence, more cost-benefit data are needed before selective decontamination is widely recommended.

High gastric pH is associated with increased numbers of gastric bacteria133-135 and pH-altering drugs (antacids and histamine2 antagonists) are frequently administered to mechanically ventilated patients, potentially increasing the gastric bacterial burden. The association between treatment with pH-altering agents and nosocomial pneumonia, especially events occurring after 4 days of ventilation, has been suggested.136-138 However, meta-analyses139,140 reveal only a trend toward pneumonia reduction with non–pH-altering therapy, and a recent multicenter study141 of 1200 mechanically ventilated patients did not show a statistical difference. The poor correlation between pH-altering therapy and pneumonia is likely due to the intrinsically high gastric pH present in many critically ill patients137,142 and the fact that the stomach is the source of pathogens in only a few patients.143 Bacteria isolated from the trachea of mechanically ventilated patients arrive by different routes.111,112,142,144 Pseudomonas aeruginosa, eg, most commonly appears de novo in the trachea and therefore is unlikely to be affected by gastric pH, in contrast to the Enterobacteriaceae, which are often first found in the stomach.111,145 Consistent with these findings, the delivery site and method of enteral feeding have not convincingly altered the incidence of nosocomial pneumonia,146-148 although postpyloric feeding could theoretically reduce colonization by gastric bacteria.

### Airway Management and Respiratory Care

Airway management strategies have been studied in relation to pneumonia prevention and are the subject of a recent review.149 Two studies150,151 evaluating an endotracheal tube allowing removal of subglottic secretions demonstrated reduced incidence of pneumonia. Nasal endotracheal tubes have a higher incidence of radiographic sinusitis152 and may predispose to pneumonia. Holzapfel and colleagues153 reported a nonsignificant trend toward lower pneumonia incidence in oro-tracheally (6%) than nasotracheally (11%) intubated patients (P = .11) and in a subsequent study154 demonstrated a reduction in ventilator-associated pneumonia in nasotracheally intubated patients by using an aggressive diagnostic and treatment protocol for nosocomial sinusitis. In addition, supine position has been significantly associated with the occurrence of ventilator-associated pneumonia,1 probably because of increased aspiration into the respiratory tract, a preventable phenomenon if patients are treated upright at 45°.155,156

There is an increasing emphasis on noninvasive ventilation in the management of acute respiratory failure of diverse etiologies. Emerging data177-180 suggest that patients who tolerate noninvasive ventilation might have a lesser incidence of nosocomial pneumonia than those tracheally intubated. Moreover, because it seems that failed extubation and reintubation are also associated with an increased risk of pneumonia,181,182 management of respiratory failure without tracheal intubation holds promise regarding pneumonia prevention.

Several respiratory care practices have been the subject of study. Two recent reviews149,152 of ventilator circuit change frequency confirm that changes more often than every 7 days are unnecessary and may increase the risk of pneumonia. Despite the lack of definitive trials, heat and moisture exchangers and kinetic bed therapy also seem to reduce the incidence of pneumonia,149 but closed endotracheal tube suctioning systems do not demonstrably alter this occurrence.163,164 Larger, prospective trials are still needed to identify which of these interventions are cost-effective and which patient subgroups are most likely to benefit.

### SUMMARY

Ventilator-associated pneumonia is common in mechanically ventilated, critically ill patients, and higher severity of illness, prolonged mechanical ventilation, and intrinsic lung disease increase the risk of this complication. Invasive study of the lower respiratory tract in these patients has led to a better understanding of the pathogenic events leading to pneumonia but has not convincingly altered mortality or cost of care. Because inappropriate antibiotic drug therapy and the presence of high-risk organisms correlate with mortality secondary to ventilator-associated pneumonia, empirical antibiotic coverage should include agents with activity against *P aeruginosa* and related bacteria in the presence of prolonged mechanical ventilation and/or other risk factors. Efforts targeted at prevention have identified several respiratory care and airway management practices that seem to be efficacious. Selective decontamination of the aerodigestive tract also reduces pneumonia incidence but has not yet convincingly been shown to alter mortality or cost of care. Future investigations should include more outcomes assessments of newer diagnostic and preventive methods.

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