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Hospital-acquired and ventilator-associated pneumonia: what's new in diagnosis and treatment?

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Nosocomial infections are an important cause of morbidity and mortality in US hospitals [1]. The cost to the country is enormous, with >$4.5 billion being spent annually on the treatment of patients with nosocomial pneumonia. According to the American Society of Microbiology, approximately 70% of nosocomial infections are caused by organisms resistant to ≥1 antimicrobial agent [2]. In addition to extended-spectrum β-lactamase–producing *Klebsiella pneumoniae* and *Escherichia coli*, and vancomycin-resistant enterococci (VRE), other problems include vancomycin-intermediate *Staphylococcus aureus* (VISA) and *Staphylococcus epidermidis*, penicillin-resistant *Streptococcus pneumoniae*, methicillin/oxacillin-resistant staphylococci, and multidrug–resistant *Pseudomonas aeruginosa*, *Acinetobacter* species, and *Enterobacter* species. Antimicrobial resistance is becoming 1 of the most important problems of the early 21st century, and it is imperative to find ways to reduce these problems.

Urinary tract infection is the most common nosocomial infection, but it has minimal associated morbidity and mortality. Pneumonia and bacteremia are the 2 most prevalent serious nosocomial infections, representing 27% and 19% of all nosocomial infections, respectively [3] (Table 1). Nosocomial pneumonia is associated with a significant increased mortality rate. The Prevalence of Nosocomial Infections in European ICUs (EPIC) study documented that nosocomial pneumonia was an independent risk factor for increased mortality, with an odds ratio (OR) of 1.91. In that study, clinical sepsis (OR, 3.63) and bacteremia (OR, 1.61) were also independent risk factors for worse mortality [4].

The pathophysiology of hospital-acquired pneumonia (HAP) and ventilator-associated pneumonia (VAP) usually requires that 2 important processes take place: (1) bacterial colonization of the aerodigestive tract, and (2) aspiration of contaminated secretions into the lower airway. These 2 processes ultimately lead to the development of bronchiolitis and subsequent development of focal or multifocal bronchopneumonia, with ultimate development of confluent bronchopneumonia.

Risk factors for hospital-acquired and ventilator-associated pneumonia

Specific risk factors for nosocomial pneumonia include the extremes of age, chronic lung disease (chronic obstructive pulmonary disease [COPD], asthma, bronchitis), previous abdominal or thoracic surgery, endotracheal intubation, and duration of mechanical ventilation [5]. Additional risk factors for nosocomial pneumonia include the use of nasogastric tubes, immunosuppression, prior antimicrobial use, poor pulmonary hygiene, aspiration, and inadequate pain control leading to splinting, hypoventilation, and subsequent atelectasis. In trauma patients (n = 7,503), Croce et al [6] documented that the incidence of postinjury pneumonia was 6%. Logistic regression analysis identified age, Glasgow Coma Scale score, Injury Severity Score, transfusion requirements during resuscitation, spinal cord injury, chest injury severity, emergent femur fixation, craniotomy, and laparotomy as independent risk factors for pneumonia.

Increased risk for VAP is related to multiple factors. Endotracheal intubation can be associated with the carriage of organisms from the oropharynx into the trachea. Once the endotracheal tube is in place, bacteria aggregate on the surface of the endotracheal tube over time and form a biofilm where bacteria reside and are protected from host defenses. Bacterial aggregates become dislodged by ventilator flow or suctioning and can be embolized into the lower respiratory tract. Furthermore, leakage around the cuff of the endotracheal tube allows pooled secretions above the cuff to enter the trachea and mainstem bronchi.

It has been well documented that mechanical ventilation increases the risk of nosocomial pneumonia by 6- to 21-fold [7]. Garrard and A'Court [8] described the incidence of VAP

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Table 1
Nosocomial infection site distribution, adult intensive care units (N = 181,993 patients, January 1992 to July 1997)

Urinary tract infection	31%
Pneumonia	27%
Bacteremia	19%
Gastrointestinal infection	5%
Cardiovascular infection	4%
Eye, ear, nose, throat infection	4%
Lower respiratory tract infection	4%
Other	6%

Data from National Nosocomial Infections Surveillance System, Centers for Disease Control, 1992 to 1997 [3].

Table 2
Ventilator-associated pneumonia (VAP) rate in specific intensive care units (ICUs)*

Type of ICU	Units (n)	Ventilator-days	Pooled mean	50th Percentile (median)
Medical				
Coronary	100	173,668	8.4	7.1
Medical	134	636,355	7.3	6.0
Respiratory	7	24,519	4.3	—
Medical–surgical				
Major teaching	121	494,941	10.5	9.4
All others	179	674,536	8.7	7.6
Pediatric	75	285,607	4.9	3.9
Surgical ICUs				
Neurosurgical	46	107,820	14.9	11.9
Surgical	152	638,321	13.2	11.6
Trauma	25	106,884	16.2	15.3
Cardiothoracic	64	251,034	10.5	9.5
Burn	18	28,935	15.9	—

* Data presented as number of VAP cases × 1,000 divided by number of ventilator-days.
Reprinted from the National Nasocomial Surveillance System/Centers for Disease Control and Prevention Web site [9].

in patients in intensive care units (ICUs) and found it increases in a linear manner for up to 30 days (Fig. 1). This observation might in part reflect the increasing prevalence of distal airway colonization and the incidence of pneumonia. VAP is such a common event that the clinician should consider not *if* pneumonia might occur, but *when* it may occur. The data from Garrard and A'Court and others indicate particular vigilance is required between the fifth and 15th days of ICU admission.

The incidence of VAP in surgical ICUs is significantly higher than in medical ICUs, based on data from the National Nosocomial Infection Surveillance (NNIS) group of the Centers for Disease Control and Prevention (CDC) [9]. VAP rates in surgical, trauma, and burn units range from 13 to 16 per 1,000 ventilator-days compared with VAP rates of 7 to 10 per 1,000 ventilator-days in medical and coronary care units (Table 2). Particular vigilance is therefore required in considering a diagnosis of VAP in surgical patients who require continued mechanical ventilation. Strategies for prevention of VAP are also of paramount importance in surgical patients, given their higher rates of VAP.

Diagnosis of hospital-acquired and ventilator-associated pneumonia

The diagnosis of VAP has traditionally been made clinically, including the presence of a new radiographic infiltrate, fever, leukocytosis, purulent tracheal secretions, and microorganisms isolated by nonquantitative analysis of endotracheal aspirates. No diagnostic approach to nosocomial pneumonia is without problems. Using only clinical criteria will usually overdiagnose pneumonia, and not all patients with pulmonary infiltrates actually have lower respiratory tract infections. Many noninfectious processes may lead to pulmonary infiltrates and fever, including atelectasis, pulmonary edema, postoperative changes, congestive heart failure, pulmonary hemorrhage, adult respiratory distress syndrome, pulmonary embolism, leukoagglutination reaction, chemical aspiration, sepsis with early acute respiratory distress syndrome, and drug reaction.

Polk and Mizuguchi [10] and Polk et al [11] have documented that the use of clinical criteria for the diagnosis of pneumonia is particularly problematic in surgical patients.

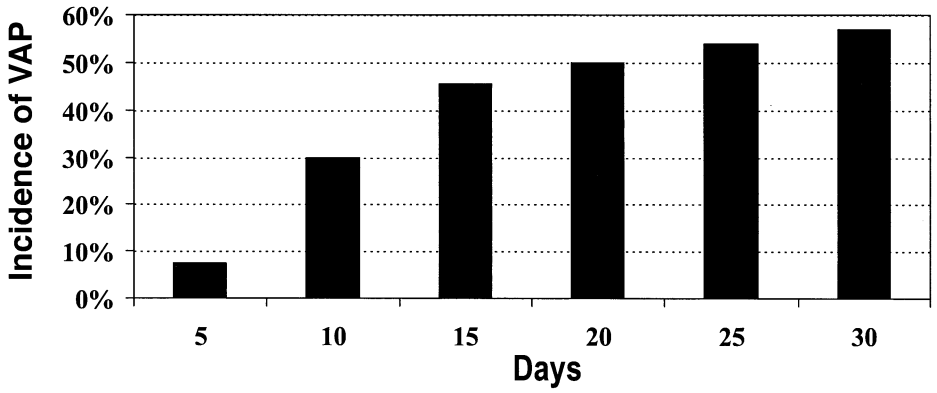

Fig. 1. Cumulative incidence of ventilator-associated pneumonia (VAP). Time course relation to duration of mechanical ventilation. VAP increases 1% to 3% with each day of mechanical ventilation, and risk of death increases 2- to 10-fold. (Adapted from *Chest* [8].)

Table 3
Most common pathogens associated with nosocomial infections: National Nosocomial Infections Surveillance System, Centers for Disease Control and Prevention, January 1989 to July 1998, medical and surgical combined data

Pathogen	Relative percentage by type of infection			
	All sites (N = 235,758)	BSI (N = 50,091)	Pneumonia (N = 64,056)	SSI (N = 22,043)
Coagulase-negative staphylococci	14.3	39.3	2.5	13.5
Staphylococcus aureus	11.4	10.7	16.8	12.6
Pseudomonas aeruginosa	9.9	3.0	16.1	9.2
Enterococcus species	8.1	10.3	1.9	14.5
Enterobacter species	7.3	4.2	10.7	8.8
Escherichia coli	7.0	2.9	4.4	7.1
Candida albicans	6.6	4.9	4.0	4.8
Klebsiella pneumoniae	4.7	2.9	6.5	3.5
Others	30.7	21.8	37.1	26.0

BSI = bloodstream infection; SSI = surgical site infection.
Adapted from *Clin Chest Med* [28].

Similarly, Croce [12] has demonstrated that the standard clinical criteria of fever, leukocytosis, purulent sputum, and infiltrate on chest radiograph are nonspecific for the diagnosis of posttraumatic pneumonia, and only approximately 50% of trauma patients with these conditions have pneumonia. The differentiation between pneumonia and other diagnoses, including adult respiratory distress syndrome, remains difficult in surgical and trauma patients, and quantitative cultures of bronchoalveolar lavage (BAL) effluent have been recommended as a more accurate diagnostic method [13]. A pivotal prospective study by Croce et al [14] in 232 mechanically ventilated trauma patients who met the clinical definition of pneumonia (fever, leukocytosis, purulent sputum, new or changing infiltrate on chest radiograph) documented that only 39% of patients had a diagnosis of pneumonia based on a positive quantitative BAL culture ($\geq 10^5$ colony-forming units/mL). This study also determined that Gram stain of the BAL effluent correlated poorly with quantitative cultures and was not reliable for dictating empiric antibiotic therapy choices.

The role of quantitative invasive diagnostic techniques in the evaluation of patients with clinical evidence of nosocomial pneumonia remains controversial. The controversy centers around whether invasive techniques to diagnose pneumonia should be used on a routine basis or rather on a targeted basis. Fagon et al [15] performed a clinical study to evaluate the effect on clinical outcome and antibiotic use of 2 strategies to diagnose VAP. This was a prospective, multicenter, randomized uncontrolled trial in 31 ICUs in France, with 413 patients suspected of having VAP. Patients were randomized to an "invasive management strategy" (which included bronchoscopic protective specimen brush [PSB] or BAL for diagnosis of VAP, with quantitative cultures of PSB/BAL aspirates) versus a "noninvasive clinical management strategy" (diagnosis of VAP based on clinical criteria, nonquantitative cultures of endotracheal aspirates, and clinical practice guidelines for treatment of VAP). This study documented that "invasive management" was associated with reduced mortality at day 14 (16.2% vs 25.8%; $P = 0.022$), decreased mean Sequential Organ Failure Assessment Scale (SOFAS) scores at days 3 and 7, decreased antibiotic use at day 14, and more

antibiotic-free days at day 28 (11.5 ± 9.0 vs 7.5 ± 7.6; $P < 0.001$).

Multiple studies have defined that both bronchoscopic and nonbronchoscopic BAL are significantly more sensitive and specific than nonquantitative endotracheal aspirate cultures in the microbiologic diagnosis of pneumonia in mechanically ventilated patients. Nonbronchoscopic BAL is a simple, safe, inexpensive bedside procedure and should be examined in a large multicenter trial to determine whether it has equal sensitivity and specificity compared with bronchoscopic BAL [16]. This would greatly simplify the optimal procedure for diagnosis of VAP and would potentially become a standard for use in all future clinical trials in VAP. At present, VAP studies are a mix of those that use the CDC's clinical definition for VAP versus bronchoscopic BAL, making these studies difficult to compare.

The CDC performed a pneumonia pilot study to evaluate the draft NNIS Pneumonia Definitions. It was conducted from April through September 2001 in 9 hospitals that served as pilot sites. This pilot study evaluated new criteria for determining nosocomial pneumonia [17]. The CDC initiated national data collection by means of NNIS using the new definitions in January 2002. Data compilation and evaluation should be completed within the coming year.

Microbiology of hospital-acquired and ventilator-associated pneumonia

Examination of data from the NNIS group of the CDC from 1989 through 1998 documents that gram-positive organisms are the most common pathogens associated with nosocomial infections in the ICU (Table 3). In this study, which evaluated >235,000 isolates in both medical and surgical ICU patients, coagulase-negative staphylococci and *S aureus* were the 2 most common pathogens isolated from all nosocomial infections. These 2 organisms also accounted for the majority of bloodstream infections in the ICU.

Gram-positive organisms have also emerged as the predominant organisms in HAP and VAP. Among gram-positive pathogens, *S aureus* is the most common cause of nosocomial pneumonia. Recent data from the CDC have documented that *S aureus* and *P aeruginosa* are the 2 leading microbial pathogens in the etiology of HAPs [5,18].

VAP has been differentiated into early-onset and late-onset pneumonia. Early-onset pneumonia is defined as VAP occurring 48 to 72 hours after endotracheal intubation, often from aspiration complicating the intubation process. Most often antibiotic-sensitive bacteria are cultured in early-onset pneumonia, including methicillin-sensitive *S aureus* (MSSA), *Haemophilus influenzae*, *S pneumoniae*, and *Moraxella catarrhalis*. Late-onset pneumonia is defined as VAP occurring >72 hours after intubation. Antibiotic-resistant bacteria are common isolates in late-onsent VAP, including methicillin-resistant *S aureus* (MRSA), *P aeruginosa*, *Acinetobacter* species, and *Enterobacter* species [19].

Table 4
Risk factors for methicillin-resistant *Staphylococcus* species infections

Patient-related risk factors	Treatment-related risk factors
• Prior antibiotic administration	• Hospital length of stay >2 wk
• Previous hospitalization	• Invasive procedure
• Known colonization	• Intravascular catheterization
• Long-term care	• Prolonged mechanical ventilation
• Diabetes	• Prolonged stay in high-risk areas of hospital
• End-stage renal disease	
• Anergy	• Intensive care unit patients
• Immunosuppresive therapy	• Orthopedic surgery
• Liver failure	• Cardiovascular surgery
	• Surgical procedure

Methicillin-resistant *Staphylococcus aureus* pneumonia

There has been a continued progression of increasing rates of methicillin resistance in *S aureus* in the United States over the past 2 decades. Recent CDC reports document that currently 55.3% of all *S aureus* isolates in hospitalized patients are resistant to methicillin. MRSA pneumonia is associated with high reported mortality rates, from 38% to 56.3% [20–22]. Iwahara et al [20] reported the clinical features of 32 patients with pulmonary infections caused by MRSA. Most of the patients were elderly, postoperative, and had severe underlying disease. Chest radiographs typically showed bilateral and multilobar involvement.

Rello et al [21] performed a prospective analysis of all VAP caused by *S aureus* for 30 months. This study documented that MRSA-infected patients were more likely to have received steroids before developing infection (relative risk [RR], 3.45; 95% confidence interval [CI], 1.38– 8.59), to have been ventilated >6 days (RR, 2.03; 95% CI, 1.36–3.03), to have been >25 years old (RR, 1.50; 95% CI, 1.09–2.06), and to have had preceding COPD (RR, 2.76; 95% CI, 0.89–8.56) than MSSA-infected patients. MSSA-infected persons were more likely than MRSA-infected patients to have cranioencephalic trauma (RR, 1.94; 95% CI, 1.22–3.09). All patients with MRSA VAP had previously received antibiotics, compared with only 21.1% of those with MSSA infection ($P < 0.000001$). The incidence of empyema was similar in both groups; nevertheless, the presence of bacteremia and septic shock was more frequent in the MRSA group. Finally, mortality directly related to pneumonia was significantly higher among patients with MRSA infection (RR, 20.72; 95% CI, 2.78–154.35). Previous antibiotic therapy was the most important risk factor for developing MRSA infection.

Both patient-related and treatment-related risk factors for MRSS infection have been identified [23–27] (Table 4).

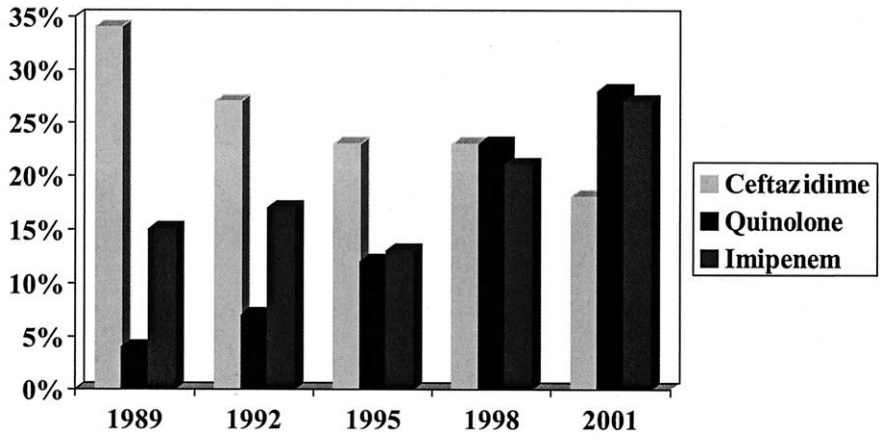

Fig. 2. Increasing resistance in *Pseudomonas aeruginosa* ventilator-associated pneumonia isolates. (Adapted from National Nasocomia Infection Surveillance/Center for Disease Control and Prevention [9] and *Clin Chest Med* [28].)

Patient-related risk factors include prior antibiotic administration, previous hospitalization, known colonization, long-term care, and comorbidities (diabetes, end-stage renal disease, anergy, immunosuppressive therapy, liver failure). Treatment-related risk factors include ICU stay, prolonged mechanical ventilation, prolonged length of stay, and surgical procedures.

A recent study [25] evaluated the risk of MRSA infection in colonized inpatients over 18 months among 209 adult patients newly identified as harboring MRSA. Of 60 patients, 29% developed subsequent MRSA infections (90 infections). These infections were often severe. Of 90 infections, 28% (n = 25) involved bacteremia and 56% (n = 50) involved pneumonia, soft-tissue infection, osteomyelitis, or septic arthritis. Of 60 patients, 80% (n = 48) with subsequent MRSA infection developed the infection at a new site, and 49% (n = 44) of new MRSA infections first became manifest after discharge from the hospital.

Increasing antimicrobial resistance in gram-negative organisms has also been identified in nosocomial infections. Fridkin and Gaynes [28], using the CDC/NNIS data, evaluated resistance patterns in isolates of *P aeruginosa* for 1989, 1992, 1995, and 1998. Whereas resistance to ceftazidime appears to have stabilized around 20%, resistance to the primary quinolone, ciprofloxacin, and to imipenem continue to increase. More recent data from 2001 confirm this continued increase in *Pseudomonas* resistance to the quinolones and imipenem (Fig. 2).

Two main risk factors have been identified as independent risk factors for antibiotic-resistant organisms in VAP—including duration of mechanical ventilation and prior antibiotic use (Fig. 3). A prospective study of 135 consecutive episodes of VAP observed in a single ICU over a 25-month period determined risk factors for VAP caused by drug-resistant bacteria [29]. Logistic regression analysis confirmed 3 significant independent variables: durations of mechanical ventilation ≥7 days (OR, 6.0), prior antibiotic use (OR, 13.5), and prior use of broad-spectrum drugs (third-generation cephalosporin, fluoroquinolone, and/or carbapenem; OR, 4.1). These findings may provide a more rational basis for selecting the initial antimicrobial therapy of patients with suspected VAP.

Significant advances have been made in the rapid detection of resistant organisms such as MRSA. A rapid procedure, providing results in <6 hours, was recently reported using multiplex quantitative polymerase chain reaction for the identification of MRSA directly from sterile sites or mixed flora samples, such as nasal swabs [30]. A 96-well format assay allowed analysis of 30 swab samples per run and detection of MRSA with exquisite sensitivity compared with optimal culture-based techniques that require 2 to 3 days. Such new rapid diagnostic technology will allow us to minimize overuse of antibiotics and use targeted antibiotic therapy in attempts to prevent widespread antimicrobial resistance.

Treatment for hospital-acquired and ventilator-associated pneumonia

The mainstay of treatment of HAP and VAP is systemic antibiotic therapy. Other adjunct treatment measures are also important, including maintenance of adequate perfusion and hydration, prevention of atelectasis, provision of aggressive pulmonary toilet, and weaning from mechanical ventilation as quickly as possible. Antibiotic selection in VAP is particularly important [18]. Broad-spectrum coverage is required for both gram-negative and gram-positive organisms. Empiric coverage should include antibiotics with activity against *Pseudomonas* and *S aureus*, the 2 most common organisms isolated in HAP and VAP. We should choose antibiotics with documented efficacy, and those that achieve a high level of activity in the lung with minimal side effects are preferred. Antibiotics that can be considered in VAP treatment include the semisynthetic

	Odds ratio	*P* value
Prior mechanical ventilation >7 days	6	0.009
Prior antibiotics	13	<0.001
Prior broad-spectrum antibiotics	4	0.025

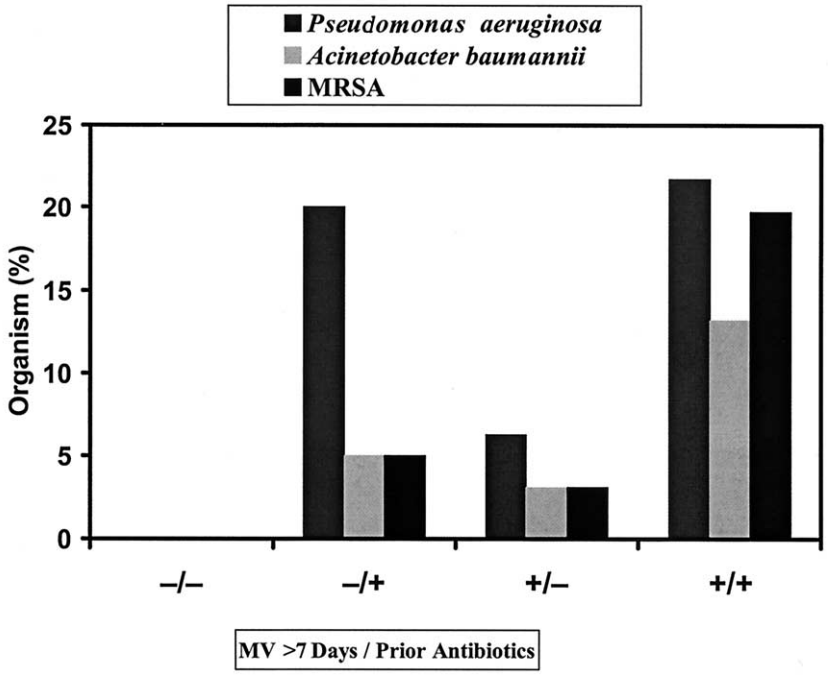

Fig. 3. Specific risk factors for antibiotic-resistant ventilator-associated pneumonia (VAP). Mechanical ventilation (MV) for >7 days and prior antibiotic use are independent risk factors for VAP resulting from antibiotic-resistant organisms, including *Pseudomonas aeruginosa*, *Acinetobacter baumannii*, and methicillin-resistant *Staphylococcus aureus* (MRSA). (Adapted from *Am J Respir Crit Care Med* [29].)

penicillins, fluoroquinolones, fourth-generation cephalosporin, and carbapenems. Empiric treatment for MRSA with vancomycin or linezolid should be mandatory in all patients with any risk factors for MRSA (Table 4) and in hospital settings where MRSA is endemic. Knowledge about local patterns of antimicrobial resistance, particularly in the ICU setting, is of particular importance in determining appropriate empiric antibiotic therapy for pneumonia. Antimicrobial therapy should be tapered down once sputum or BAL cultures return, with antibiotics adjusted based on culture results.

Inadequate antimicrobial therapy

Several investigators have examined the appropriateness of the initial antimicrobial regimen in reducing overall mortality in nosocomial pneumonia and VAP. In these studies, "appropriate antimicrobial therapy," defined as an empiric regimen following the recommendations from the literature, was changed according to the antibiotic susceptibility reports, and the timing, route, dosage, and duration of the therapy were correct. Inadequate antimicrobial therapy is common in VAP, ranging from 20% to 70%. Multiple studies [31–35] have confirmed increased mortality associated with inadequate antimicrobial therapy in the treatment of nosocomial infections, including VAP and bacteremia (Fig. 4). Inadequate antimicrobial therapy of VAP is also associated with increased resource utilization, including increased ventilator days and increased length of stay (Fig. 5) [36].

Inadequate antimicrobial treatment is also an important factor in the emergence of infections resulting from antibiotic-resistant bacteria, and subsequent increased mortality in patients infected with antibiotic-resistant bacteria. Kollef et al [37,38] and Ibrahim et al [31] have published several studies evaluating the clinical impact of inadequate antibiotic therapy. In a cohort study of 2,000 consecutive patients requiring admission to a medical or surgical ICU, it was determined that 169 of 655 patients (25.8%) assessed to have either community-acquired or nosocomial infections

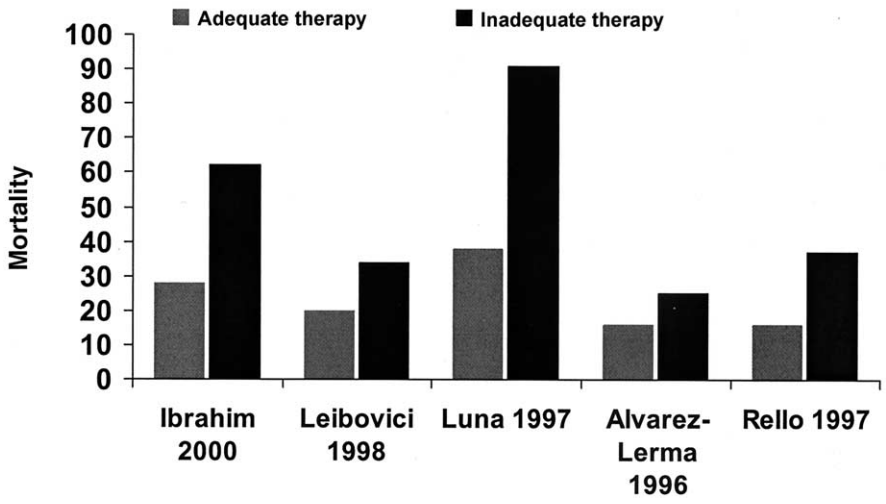

Fig. 4. High incidence of inadequate antibiotic therapy in nosocomial infections (ventilator-associated pneumonia and bacteremia) and its association with increased mortality. (Adapted from *Chest* [31,33], *J Intern Med* [32], *Intensive Care Med* [34], and *Am J Respir Crit Care Med* [35].)

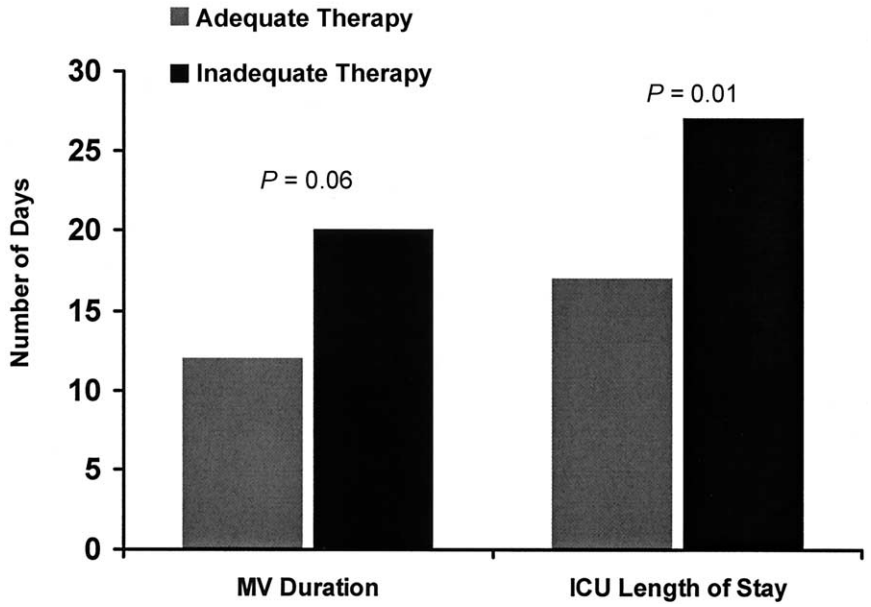

Fig. 5. Inadequate antibiotic therapy in ventilator-associated pneumonia is associated with increased resource utilization. ICU = intensive care unit; MV = mechanical ventilation. (Adapted from *Intensive Care Med* [36].)

received inadequate antimicrobial treatment for their infections [37]. The infection-related hospital mortality rate for critically ill patients with infection who received inadequate antimicrobial treatment (42.0%) was significantly greater than the mortality rate of infected patients receiving adequate antimicrobial treatment (17.7%, $P < 0.001$). Similar results were confirmed in subsequent studies [31,38]. These authors stressed the importance of appropriate antibiotic therapy in pneumonia treatment because it is 1 of the few prognostic factors amenable to intervention.

The implementation of a protocol-based therapy for VAP has been documented to significantly decrease the rate of inadequate antibiotic therapy and was associated with improved outcome and mortality. These protocols mandate the early administration of combination antimicrobial therapy based on unit-specific antibiogram to patients with suspected VAP. Sputum cultures are obtained before the initiation of antimicrobial therapy in VAP patients. Antimicrobial therapy is then modified once microbiologic data are available from sputum cultures. Ibrahim et al [39] documented that 1 such protocol, using a carbapenem, quinolone, and vancomycin as empiric VAP therapy, was associated with a significant improvement in adequate initial antibiotic treatment from 42% in the prestudy period to 95% in the VAP protocol period. Antibiotic duration of VAP was also significantly reduced, and the development of secondary VAP episodes was also signifi-

cantly reduced. Additional studies report similar results, and the current evidence supports development of HAP/VAP treatment protocols in all ICUs.

Antimicrobial treatment for methicillin-resistant *Staphylococcus aureus* hospital-acquired and ventilator-associated pneumonia

Vancomycin has long been the standard treatment for MRSA pneumonia and until recently was the only antimicrobial available. The emergence of new antibiotics with activity against MRSA is now challenging the efficacy of vancomycin therapy for MRSA pneumonia. Linezolid, the first of the new class of oxazolidinone antibiotics, is available in both intravenous and oral formulation and has excellent activity against gram-positive organisms, including MRSA. Quinupristin-dalfopristin is from the streptogramin antibiotic class and is available only in an intravenous formulation. Clinical studies comparing these 2 new antimicrobials to vancomycin in the treatment of presumed gram-positive pneumonia have been completed.

A prospective randomized study compared quinupristin-dalfopristin with vancomycin in the treatment of presumed gram-positive HAP [40]. Aztreonam was allowed for treatment of gram-negative organisms. Clinical cure rates were similar (56% for quinupristin-dalfopristin vs 58% for vancomycin) in the bacteriologically evaluable group. Examination of the small group of patients with MRSA pneumonia (n = 38) confirmed much lower clinical cure rates (30.9% for quinupristin-dalfopristin vs 44.4% for vancomycin).

Rubinstein et al [41] reported the results of a prospective study randomizing patients with presumed gram-positive nosocomial pneumonia to linezolid versus vancomycin. Clinical cure rates were similar (70% for linezolid vs 68% for vancomycin) in the microbiologically evaluable group. Further examination of patients with VAP, and specifically MRSA VAP, documented higher clinical cure rates with linezolid compared with vancomycin, despite significantly higher severity of illness by Acute Physiology and Chronic Health Evaluation (APACHE) scores in the linezolid group.

A number of studies have documented that vancomycin penetration into lung tissue is poor. Cruciani et al [42] examined lung tissue concentrations of vancomycin after a 1-g dose in 30 patients. Vancomycin lung tissue concentrations were below minimum inhibitory concentration (4 μg/mL) in all patients at 6 and 12 hours after antibiotic administration, and no detectable vancomycin levels were present in lung tissue in 3 of 7 patients at 12 hours after vancomycin dosing. Vancomycin serum concentrations are 6-fold higher than lung tissue concentrations.

In contrast, linezolid penetration into lung tissue is excellent, achieving approximately 4-fold higher concentration in lung tissue than in serum [43]. Lung epithelial lining fluid concentrations of linezolid range from >60 μg/mL at 4 hours after a 600-mg dose, to >20 μg/mL at 12 hours after the dose, all well above the minimum inhibitory concentration of 1 to 4 μg/mL for *S aureus*.

A recent prospective study in 340 patients with presumed gram-positive VAP documented that *S aureus* was the most frequent pathogen isolated, and 68% of isolates cultured were MRSA [44]. Patients were randomized to linezolid versus vancomycin, with aztreonam for gram-negative coverage. Logistic regression analysis confirmed that linezolid was superior to vancomycin in clinical cure rates. Age, APACHE score, and renal, vascular, and respiratory comorbidities were also identified as significant independent predictors of outcome in VAP. Logistic regression analysis of the entire cohort of patients with HAP and VAP (n = 1,019) documented that linezolid treatment was an independent predictor of improved survival [45].

Reduced duration of antibiotic therapy for ventilator-associated pneumonia treatment

While research to date supports the imperative to prescribe initial appropriate antibiotic treatment in VAP, the duration of therapy for VAP remains controversial. Clinicians have commonly used arbitrary durations of antimicrobial treatment ranging from 10 to 21 days. Recent data suggest that other end points for defining duration of VAP treatment can be considered, such as clinical pulmonary infection score. Serial measurements of clinical pulmonary infection score in VAP patients may help define strategies to shorten duration of therapy for VAP [46].

Future studies in hospital-acquired and ventilator-associated pneumonia

A number of studies are ongoing to evaluate optimal treatment strategies for HAP and VAP, including increased vancomycin-dosing trials, with drug dosing by area under the inhibitory curve or increased serum trough concentrations (15 to 20 μg/mL). New injectable antimicrobials, including new injectable cephalosporins (CP6679 and CAB 175) with potent activity against MRSA and gram-negative bacteria are also being actively investigated.

Prevention of ventilator-associated pneumonia

Strategies aimed at prevention of VAP are focused on decreasing aspiration incidence and reducing bacterial colonization in the airways. Two strategies have been clearly documented to reduce VAP and should be used in all ICUs: ventilator-weaning protocols and the semirecumbent position.

Ventilator-weaning protocols

It is clear that duration of mechanical ventilation is associated with increased risk for VAP. The use of non–physician-directed protocols and guidelines for the management of sedation and weaning has been shown to reduce the duration of mechanical ventilation for patients with acute respiratory failure when compared with conventional physician-directed practices. It is therefore of paramount importance that all ICUs use these protocols and guidelines as a strategy to ensure timely weaning from mechanical ventilation, which may ultimately have an impact on reducing the incidence of VAP in the ICU [47,48].

Semirecumbent position

The semirecumbent body position has been documented to reduce the frequency and risk of nosocomial pneumonia, especially in patients receiving enteral nutrition, by reduction of gastroesophageal reflux and subsequent aspiration [49]. However, semirecumbency is inconsistently used in practice in the ICU [50]. Multidisciplinary efforts are mandatory to implement this simple measure that has been definitively associated with reduced risk for HAP.

Continuous aspiration of subglottic secretions

Continuous aspiration of subglottic secretions (CASS) is an approach that has been evaluated for prevention of VAP. CASS has been determined to be a convenient and safe method for suctioning accumulated secretions in the subglottic space and uses a large elliptical evacuation port located on the dorsal side proximal to the cuff to provide effective evacuation. The integral suction lumen allows continuous suctioning without risking trauma to the vocal cords, as with manual catheter suctioning.

Initial small trials yielded positive results with the use of CASS, with significant reduction in VAP rates [51,52]. More recent studies have provided conflicting results with the use of CASS. Kollef et al [53] studied 343 cardiac surgery patients requiring mechanical ventilation, who were randomized to CASS or control groups. No significant difference in VAP incidence was identified, with 8 of 160 patients (5.0%) in the CASS group compared with 15 patients (8.2%) in the control group (RR, 0.61; 95% CI, 0.27–1.4; $P = 0.238$). Importantly, this study did identify that VAP occurred later in CASS patients, with mean time to VAP documented as 5.6 ± 2.3 days in the CASS group versus 2.9 ± 1.2 days in the control group ($P = 0.006$).

In a smaller recent prospective randomized study of 150 patients requiring mechanical ventilation for >72 hours, CASS was associated with a significant reduction in the incidence of VAP [54]. VAP was identified in 3 patients (4%) in the CASS group compared with 12 patients (16%) in the control group (RR, 0.22; 95% CI, 0.06–0.81; $P = 0.014$). No difference in ICU or hospital length of stay, or mortality was identified in this study. CASS has demonstrated potential benefit in small studies, but a large multicenter randomized study has not yet been accomplished.

Chlorhexidine oral rinse and protegrins

Other strategies to reduce bacterial colonization in the posterior pharynx have been investigated, including the use of chlorhexidine gluconate oral rinse and protegrins. DeRiso et al [55] studied 353 consecutive patients undergoing cardiac surgery, randomized to control or chlorhexidine 0.12% oral rinse for oropharyngeal decontamination. The overall nosocomial infection rate was decreased in the chlorhexidine-treated patients by 65%, with a 69% reduction in respiration infections. Mortality reduction in the chlorhexidine group was also noted (1.16% vs 5.56%). No change in bacterial antibiotic resistance was noted in the experimental group.

In a subsequent prospective study in noncardiac surgical ICU patients [56], improved oral hygiene by means of topical chlorhexidine application in conjunction with the use of a ventilator-weaning protocol was effective in reducing the incidence of VAP, duration of mechanical ventilation, and mortality.

Protegrins are extremely broad-spectrum antimicrobial peptides, active against many bacterial and fungal species, including those resistant to conventional antimicrobial drugs, by attaching to and destroying the integrity of the lipid cell membrane [57]. The first protegrin to undergo clinical trial is iseganan hydrochloride oral solution and is in phase 2/3 clinical trials for the prevention of VAP. Inhaled protegrins are also being investigated for the active treatment of respiratory tract infections in patients with cystic fibrosis.

Silver-coated endotracheal tubes

The efficacy of silver-coated endotracheal tubes is being investigated, using silver and hydrogel technology that is commonplace in the use of urinary catheters, and has been associated with reduced incidence of urinary tract infections [58]. This has been hypothesized to occur by the antibacterial properties of silver and its ability to prevent biofilm formation. It is well known that biofilms harbor large concentrations of bacteria that display an inherent resistance to therapy with systemically administered antibiotics.

Noninvasive positive-pressure ventilation

Noninvasive positive-pressure ventilation (NPPV) has been documented to reduce VAP in patients with acute respiratory failure caused by exacerbations of chronic pulmonary disease [59]. Cost reduction associated with NPPV in this group is attributed to the prevention of VAP by avoidance of endotracheal intubation. The benefit of NPPV for patients with acute nonhypercarbic hypoxemic respira-

tory failure is less clear, and more clinical studies are necessary in this area.

Educational programs on VAP

It has been clearly documented that a focused educational intervention can dramatically decrease the incidence of VAP. Educational programs should be more widely used for infection control in the ICU setting and can lead to substantial decreases in cost and patient morbidity attributed to hospital-acquired infections [60]. The CDC and the Healthcare Infection Control Practices Advisory Committee have developed a comprehensive Guideline for the Prevention of Healthcare-Associated Pneumonia 2002, which reviews all potential therapies for prevention of VAP and the available evidence supporting their use [61].

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