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Ventilator-Associated Pneumonia: Diagnosis, Treatment, and Prevention

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INTRODUCTION

Patients in the intensive care unit (ICU) are at risk for dying not only from their critical illness but also from secondary processes such as nosocomial infection. Pneumonia is the second most common nosocomial infection in critically ill patients, affecting 27% of all critically ill patients (170). Eighty-six percent of nosocomial pneumonias are associated with mechanical ventilation and are termed ventilator-associated pneumonia (VAP). Between 250,000 and 300,000 cases per year occur in the United States alone, which is an incidence rate of 5 to 10 cases per 1,000 hospital admissions (134, 170). The mortality attributable to VAP has been reported to range between 0 and 50% (10, 41, 43, 96, 161). Studies have provided different results when determining attributable mortality, in part because of very different populations (less-acute trauma patients, acute respiratory distress syndrome [ARDS] patients, and medical and surgical ICU patients) and in part as a result of variances in appropriate empirical medical therapy during the initial 2 days. Furthermore, the organisms recovered have an impact on outcome, with higher mortality rates seen in VAP caused by *Pseudomonas aeruginosa*, *Acinetobacter* spp., and *Stenotrophomonas maltophilia* (109). Beyond mortality, the economics of VAP include increased ICU lengths of stays (LOS) (from 4 to 13 days), and incremental costs associated with VAP have been estimated at between $5,000 and $20,000 per diagnosis (20, 206, 211).

Ventilator-associated pneumonia is defined as pneumonia occurring more than 48 h after patients have been intubated and received mechanical ventilation. Diagnosing VAP requires a high clinical suspicion combined with bedside examination, radiographic examination, and microbiologic analysis of respiratory secretions. Aggressive surveillance is vital in understanding local factors leading to VAP and the microbiologic milieu of a given unit. Judicious antibiotic usage is essential, as resistant organisms continue to plague intensive care units and critically ill patients. Simple nursing and respiratory therapy interventions for prevention should be adopted. Over the past several decades our understanding of VAP has grown significantly with regard to pathogenesis, risk factors, diagnostic testing, therapies, and prevention by modifying risk factors. This paper is designed for the practicing clinician in addressing diagnosis, treatment, and prevention of VAP.

DIAGNOSIS

Clinical Diagnosis

Ventilator-associated pneumonia is usually suspected when the individual develops a new or progressive infiltrate on chest radiograph, leukocytosis, and purulent tracheobronchial secretions. Unfortunately, and unlike for community-acquired pneumonia, accepted clinical criteria for pneumonia are of limited diagnostic value in definitively establishing the presence of VAP. In a postmortem study by Fabregas et al., when findings on histologic analysis and cultures of lung samples obtained

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immediately after death were used as references, a new and persistent (>48-h) infiltrate on chest radiograph plus two or more of the three criteria (i) fever of >38.3°C, (ii) leukocytosis of $>12 \times 10^9$/ml, and/or (iii) purulent tracheobronchial secretions had a sensitivity of 69% and a specificity of 75% for establishing the diagnosis of VAP (60). When all three clinical variables were required for the diagnosis, the sensitivity declined further (23%); the use of a single variable resulted in a decrease in specificity (33%). The poor accuracy of clinical criteria for diagnosing VAP should not be surprising considering that purulent tracheobronchial secretions are invariably present in patients receiving prolonged mechanical ventilation and are seldom caused by pneumonia. In addition, the systemic signs of pneumonia such as fever, tachycardia, and leukocytosis are nonspecific; they can be caused by any state that releases the cytokines interleukin-1, interleukin-6, tumor necrosis factor alpha, and gamma interferon (33, 34, 63, 135). Examples of such conditions include trauma, surgery, the fibroproliferative phase of ARDS, deep vein thrombosis, pulmonary embolism, and pulmonary infarction. Reasonable clinical criteria for the suspicion of VAP include a new and persistent (>48-h) or progressive radiographic infiltrate plus two of the following: temperature of >38°C or <36°C, blood leukocyte count of >10,000 cells/ml or <5,000 cells/ml, purulent tracheal secretions, and gas exchange degradation (5, 103).

The sensitivity of the clinical criteria for VAP outlined above is even lower in patients with ARDS, where it may be difficult to detect new radiographic infiltrates. In the setting of ARDS, Bell et al. reported a false-negative rate of 46% for the clinical diagnosis of VAP (11). Consequently, suspicion for VAP in the setting of ARDS should be high. The presence of even one of the clinical criteria for VAP, unexplained hemodynamic instability, or an unexplained deterioration in arterial blood gases should prompt consideration of further diagnostic testing (129).

When purulent sputum, a positive sputum culture, fever, and leukocytosis are present without a new lung infiltrate, the diagnosis of nosocomial tracheobronchitis should be entertained. In mechanically ventilated patients, nosocomial tracheobronchitis has been associated with a longer ICU stay and time on the ventilator, without increased mortality (158). In one randomized trial of intubated patients with community-acquired tracheobronchitis, antibiotic therapy resulted in a decreased incidence of subsequent pneumonia and mortality (156). However, prospective, randomized, controlled trials are required before antibiotic therapy can be recommended for the routine treatment of nosocomial tracheobronchitis. Furthermore, differentiation of tracheobronchitis from pneumonia is dependent upon the radiograph, which in the ICU is portable and often of poor quality. Hence, the clinician should utilize a clinical pulmonary infection score (CPIS) (see below) to direct therapy.

Radiologic Diagnosis

While the portable chest radiograph still remains a mandatory component in the diagnosis of ventilated patients with suspected pneumonia, as with clinical criteria for diagnosing VAP, it too has problems with both sensitivity and specificity. Poor-quality films further compromise the accuracy of chest X rays. Although a normal chest radiograph makes VAP unlikely, in one study of surgical patients, 26% of opacities were detected by computed tomography (CT) scan but not by portable chest X ray (25). In addition, asymmetric pulmonary infiltrates consistent with VAP can be caused by numerous noninfectious disorders, including atelectasis, chemical pneumonitis, asymmetric cardiac pulmonary edema, pulmonary embolism, cryptogenic organizing pneumonia, pulmonary contusion, pulmonary hemorrhage, drug reaction, and asymmetric ARDS. The overall radiographic specificity of a pulmonary opacity consistent with pneumonia is only 27% to 35% (116, 216).

Nonetheless, because of their high specificity, certain chest radiograph findings can be useful in establishing the diagnosis of pneumonia when present. Based on several studies, including an autopsy study by Wunderink et al., these useful findings include rapid cavitation of the pulmonary infiltrate, especially if progressive; an air space process abutting a fissure (specificity, 96%); and an air bronchogram, especially if single (specificity, 96%). Unfortunately, such radiographic abnormalities are uncommon (216).

Microbiologic Diagnosis

Blood and pleural fluid cultures. Although VAP spreads to the blood or pleural space in <10% of cases, if an organism known to cause pneumonia is cultured in the setting of clinically suspected pneumonia, treatment is warranted. Consequently, most experts recommend that two sets of blood cultures and a thoracentesis for nonloculated pleural effusions of ≥10 mm in diameter on a lateral decubitus chest radiograph should be part of the evaluation of suspected VAP (30). If the effusion is loculated, ultrasound guidance may be required. However, it is important to keep in mind not only that the sensitivity of blood cultures for the diagnosis of VAP is less than 25% but also that when positive, the organisms may originate from an extrapulmonary site of infection in as many as 64% of cases and even when VAP is present (23, 124).

Nonquantitative or semiquantitative airway sampling. Gram staining and nonquantitative and semiquantitative cultures of tracheal secretions have the advantages of reproducibility and of requiring little technical expertise and no specialized equipment or technique. However, these studies add little to the sensitivity and specificity of the clinical diagnosis of VAP, as the upper respiratory tract is rapidly, within hours of intubation, colonized by potential pulmonary pathogens, even when pneumonia is not present (57, 91). Thus, if an organism is cultured or noted on Gram stain, one does not know if it is the cause of the pneumonia or simply colonization. In a study of 48 patients with respiratory failure, concordance between tracheal nonquantitative cultures and cultures of lung tissue from open lung biopsy was only 40% (82). In that study, of those patients with pneumonia on lung histology, endotracheal aspirate (ETA) had a sensitivity of 82% but a specificity of only 27%. In addition, routine surveillance cultures of ETAs to anticipate the etiology of a subsequent pneumonia can be misleading in a significant percentage of patients, though recent data indicate that quantitative ETAs may be helpful (see below) (78, 146).

Only 15% of ETAs are adequate specimens when strict definitional criteria (organisms on Gram staining and fewer

than 10 squamous epithelial cells per low-power field [magnification, ×100]) are followed (153). Furthermore, the number of polymorphonuclear leukocytes is not predictive of an interpretable specimen in patients with VAP (153). Nonquantitative and semiquantitative cultures of ETAs for the diagnosis of VAP are most useful if the specimen is adequate and antimicrobial therapy has not been added or changed in the prior 72 h. The negative predictive value of these cultures in this setting is high (94%) (15). Alternative causes for the patient's presentation, including nonpulmonary sites of infection, should be investigated. In addition, the absence of growth of multidrug-resistant organisms in this circumstance provides strong evidence that these bacteria are not causative. Antibiotics should be adjusted accordingly. Overall, the presence of prior antibiotics results in a false-negative rate of 10 to 40% (200).

Because of the poor specificity of the clinical diagnosis of VAP and of qualitative evaluation of ETAs, Pugin et al. developed a composite clinical score, called the clinical pulmonary infection score (CPIS), based on six variables: temperature, blood leukocyte count, volume and purulence of tracheal secretions, oxygenation, pulmonary radiography, and semiquantitative culture of tracheal aspirate. The score varied from 0 to 12. A CPIS of >6 had a sensitivity of 93% and a specificity of 100% (164). However, there were several limitations of that investigation, including that only 28 patients with 40 episodes of pneumonia were studied and that the diagnosis was based upon a "bacterial index" that has not been a well-accepted reference test for pulmonary infection. The "bacterial index" is the sum of the logarithm of the number of bacteria cultured per milliliter of bronchoalveolar lavage (BAL) fluid. Two subsequent studies evaluated the accuracy of the CPIS by using both histology and lung tissue cultures as the reference tests (60, 162). In these investigations, the sensitivity was 72% to 77%, and the specificity was 42% to 85%. However, the study with the greater diagnostic accuracy used the tracheal aspirate culture recorded within the 48 to 72 h preceding the investigation, information that may not be available routinely. Moreover, with a sensitivity of 72 to 77%, a CPIS of ≤6 is still insufficient to withhold antibiotic therapy safely in patients with suspected VAP.

Using quantitative culture of BAL fluid as the diagnostic criteria for VAP and a CPIS of >5 as the diagnostic cutoff, the sensitivity and specificity of the CPIS were 83% and 17%, respectively. The addition of Gram staining via blind or bronchoscopically directed BAL or PTC (see below) did improve the overall sensitivity and specificity of the CPIS (65). However, the false-negative rate was still 16 to 25% (65).

Due to poor specificity and poor positive predictive value, reliance on clinical parameters, chest X-ray findings, and non- and semiquantitative sputum analysis will result in overdiagnosis and therefore overtreatment of VAP. Such an approach will result in excess antibiotic use with its attendant cost, potential toxicity, and selection of drug-resistant organisms. A recent decision analysis suggested that more deaths occurred if patients were treated with antibiotics on the basis of only clinical suspicion of VAP than if antibiotics were withheld (190).

Overreliance on the clinical diagnosis of VAP may also result in undertreating alternative infectious and noninfectious causes of fever and pulmonary infiltrates in mechanically ventilated patients. Meduri et al. prospectively studied 50 patients with clinically suspected VAP (139). Twenty-two patients had ARDS. Based on quantitative cultures of bronchoscopic protected specimen brush (PSB) and bronchoalveolar lavage, pneumonia was diagnosed in 42%. Of the infectious causes of fever and pulmonary infiltrates on chest radiography, 84% were pneumonia, sinusitis, urinary tract infection, or catheter-related infection. Less frequent infectious causes included intra-abdominal abscess, peritonitis, acalculous cholecystitis, *Clostridium difficile* colitis, empyema, wound infection, primary bacteremia, and candidemia. Twenty-four percent of fevers were secondary to noninfectious causes, including deep venous thrombosis, pulmonary embolism, pancreatitis, chemical aspiration, fibroproliferative stage of ARDS, and drugs. Fifty-six percent of the chest X-ray abnormalities were due to noninfectious causes. Concomitant infections were found in 62% of cases, with 60% of these being caused by a different pathogen. On average, there were 1.7 causes of fever per patient.

Quantitative cultures of airway specimens. To potentially improve the specificity of the diagnosis of VAP and the consequent unnecessary antibiotic use and its associated problems, numerous studies have investigated the role of quantitative cultures of respiratory secretions. These have included nonbronchoscopic methods such as quantitative cultures of ETAs (QEAs) and sampling of secretions from distal airways "blindly" via an endobronchial catheter. Blind bronchial sampling (BBS), PSB, protected telescoping catheter (PTC), BAL, and protected BAL (mini-BAL) samples can be obtained via the latter method. Bronchoscopic sampling methods permit quantitative cultures of PSB, PTC, and protected and nonprotected BAL specimens.

The PSB and PTC are double-sheathed catheters with a biodegradable plug occluding the distal end of the inner catheter to minimize bacterial contamination. The PSB and PTC procedures involve placing the tip of the bronchoscope or "blindly placed" catheter next to an involved bronchial segmental orifice. With bronchoscopy, direct visualization is possible. With a "blind" procedure, the catheter is advanced until resistance is met and then retracted a few centimeters. The inner catheter is then advanced 2 or 3 cm beyond the outer catheter, ejecting the plug. With PSB, a brush is further advanced and rotated several times; with PTC, a 10-ml syringe is used to perform three brief aspirations of secretions. BAL involves the infusion and aspiration of sterile saline through a flexible fiber-optic bronchoscope or "blindly placed" catheter wedged into a bronchial segmental orifice. Protected BAL involves a specialized balloon-tipped catheter with a distal ejectable plug. When performing a BAL to diagnose VAP, instillation of at least 140 ml of saline is required to maximize diagnostic yield (70, 138, 145).

If a bronchoscopically directed quantitative culture is chosen, the patient should receive adequate sedation, with consideration of a short-acting paralytic agent to prevent coughing during the procedure. The endotracheal tube must be ≥1.5 mm larger than the external diameter of the flexible bronchoscope. The patient should receive a fraction of inspired oxygen (FiO_2) of 100%, and positive-end expiratory pressure should be reduced as much as tolerated. To maximize ventilation and minimize air trapping, the peak inspiratory flow should be

TABLE 1. Diagnostic accuracy of quantitative culturing techniques

Technique	Sensitivity (%)	Specificity (%)	Positive predictive value (%)	Negative predictive value (%)	Reference(s)
Bronchoscopic					
PSB	89 (95% CI, 0.87–0.93)	94 (95% CI, 0.92–0.97)			30
	82	77	74	85	31
BAL	73 ± 18 (range, 42–93)	82 ± 19 (range, 45–100)			199
	91	78	83	87	31
ICOs	69 ± 20	75 ± 28			199
	91	89	91	89	31
Nonbronchoscopic					
BBS	74–97	74–100			26
Mini-BAL	63–100	66–96			26
PSB	58–86	71–100			26
	86	85	80	90	128, 133
QEA					
$\geq 10^6$ CFU/ml	76 ± 9 (range, 38–82)	75 ± 28 (range, 72–85)			38
$\geq 10^6$ CFU/ml	68	84			95, 133
$\geq 10^5$ CFU/ml	63	55			130
$\geq 10^6$ CFU/ml	75	85			130

decreased to ≤60 liters/min, the respiratory rate set between 10 and 20 breaths/min, and the peak inspiratory pressure alarm increased. The patient should be carefully monitored throughout the procedure, with particular attention to exhaled tidal volume, peak inspiratory pressure, oxygen saturation, the electrocardiogram, and vital signs. Secondary hypotension should be anticipated, and appropriate intravenous fluids and vasopressors should be available for immediate administration (70).

The sampling area should be chosen based on the location of the infiltrate on chest X ray or CT scan. This typically corresponds to the bronchial segment with purulent secretions and/or where endobronchial abnormalities are maximal, which can be clues in the setting of diffuse pulmonary infiltrates or minimal changes in a previously abnormal chest X ray (137). When in doubt, sample the posterior right lower lobe, since autopsy studies have indicated that VAP frequently involves this area (61, 92, 130, 173). Multiple specimens are no more accurate than single specimens (136).

As with nonquantitative and semiquantitative cultures, only adequate specimens should be processed. The presence of more than 1% epithelial cells or 10 epithelial cells per low-power field (magnification, ×100) in bronchoscopic or "blind" BAL, PSB, PTC, or bronchial sampling suggests heavy oropharyngeal colonization. Returns of <10% of the instilled BAL fluid are probably not representative of the lower respiratory tract (70). Since interpretation of such specimens is unreliable, they should not be cultured. For QEAs, the same criteria mentioned above for nonquantitative and semiquantitative cultures of an ETA should be utilized.

For each of the quantitative culturing methods, threshold values have been derived and are expressed in CFU per milliliter. If the number of CFU/ml is equal to or exceeds the threshold values for the particular technique, a diagnosis of pneumonia is made. Threshold values often employed for diagnosing pneumonia by quantitative cultures are $\geq 10^5$ to 10^6, $\geq 10^4$, and $\geq 10^3$ CFU/ml for QEA, bronchoscopic BAL, and PSB, respectively, with $\geq 10^5$ CFU/ml being the most widely accepted value for QEA (12, 30). For "blind" distal sampling, the thresholds are $\geq 10^3$ CFU/ml for PSB and mini-BAL and $\geq 10^4$ CFU/ml for cultures obtained with BBS and unprotected BAL (Table 1) (30).

These "cutoff" values for diagnosing VAP are based in part on the findings of quantitative cultures obtained from infected lung tissue and the volume and dilution of the respiratory secretions retrieved by the technique. For instance, BAL collects approximately 1 ml of secretions in 10 to 100 ml of effluent. This corresponds to a dilution factor of 1/10 to 1/100. Several investigators have confirmed that with pneumonia, pathogens are present in lower respiratory tract inflammatory secretions at concentrations of at least 10^5 to 10^6 CFU/ml; contaminants are generally present at less than 10^4 CFU/ml. Consequently, for BAL, the threshold value of 10^4 CFU/ml corresponds to 10^5 to 10^6 CFU/ml in the pneumonia (30).

Numerous factors can influence the results of quantitative cultures, including the timing of the pneumonia, the skill and experience of the operator, the adequacy of the specimen, technical aspects such as appropriate processing and delays in transport to the laboratory, special populations such as those with chronic obstructive pulmonary disease (who may have relatively high bacterial counts without pneumonia), and prior or concurrent antibiotic therapy (149).

Because of these potential limitations, it is important to bear in mind that a quantitative culture that exceeds a threshold value is not diagnostic of VAP by itself (9). False-positive quantitative cultures could be secondary to bronchiolitis, colonization, or oropharyngeal contamination (9). Likewise, a result below these threshold values does not rule out the presence of pneumonia, particularly in the setting of prior antibiotic therapy (see below). While higher bacterial counts correlate with a higher likelihood of VAP, lower counts are associated with a lower probability. Consequently, rather than interpreting a quantitative culture as either "positive" or "negative," it is clinically more useful to utilize the exact number of CFU/ml (see below) (9).

(i) Diagnostic accuracy. Before discussing and comparing the diagnostic accuracies of the different quantitative culturing methods and their advantages and disadvantages, it is important to understand that there exists a significant amount of controversy in the medical literature regarding the use of quantitative cultures in general as well as the use of bronchoscopic (invasive) versus nonbronchoscopic (noninvasive) methods. At least part of the reason for this controversy is that the studies evaluating the accuracies of ETA and of bronchoscopic and nonbronchoscopic PSB, PTC, and BAL to diagnose VAP have shown a significant degree of variability in sensitivity, specificity, and positive and negative predictive values for each of the techniques. This variability has resulted from the use of different "gold standards" for the diagnosis of VAP, the use of different cutoff thresholds for quantitative cultures, differences in equipment and protocols, and differences between the populations studied, in particular, the use of antibiotics. Even the most accepted "gold standard," histopathologic examination and culture of lung tissue obtained by biopsy or at autopsy, has inherent problems. Among other things, patients included in autopsy studies may not be representative of most patients with VAP. Moreover, the recognition of histologic pneumonia varies among pathologists. In a study by Corley et al., the prevalence of pneumonia in postmortem open lung biopsies determined by each of four pathologists varied from 18% to 38% (40). Nonetheless, histopathology and lung tissue culture remain our best "gold standard" for the diagnosis of VAP.

Numerous studies have demonstrated that prior and concurrent antibiotic therapy decrease the accuracy, sensitivity, and negative predictive value of Gram staining, including the percentage of cells containing intracellular organisms (ICOs), as well as quantitative, semiquantitative, and nonquantitative cultures (184). In a study of 76 patients with VAP by Montravers et al., PSB quantitative cultures obtained after the administration of effective antibiotic therapy showed complete eradication of the causative organisms after only 3 days of treatment in 67% of patients (150). Even 24 h of administration of an antibiotic can affect culture results (189). This effect of prior antibiotics on the false-negative rate of microbiologic studies is of great concern, particularly since VAP is a potentially lethal disorder. However, if antibiotics have not been changed in the last 72 h, the diagnostic yield of any culture technique is unaffected (189, 197).

(ii) Bronchoscopic protected specimen brush and BAL. Chastre and Fagon pooled the results of 18 studies that evaluated the bronchoscopically directed PSB technique for diagnosing VAP (30). A total of 795 critically ill patients were included in the analysis. The overall diagnostic accuracy of this method was very good, with a sensitivity of 89% (95% confidence interval [CI], 87 to 93%) and a specificity of 94% (95% CI, 92 to 97%). However, studies investigating the reproducibility and variability of bronchoscopic PSB have raised concerns about this technique. Timsit et al. and Marquette et al. repeated PSB sampling in the same lung subsegment and noted that results of quantitative cultures were on each side of the 10^3-CFU/ml threshold in 16.7% to 13.6% of cases, respectively, with 59 to 67% of samples having CFU/ml counts varying by more than 10-fold (131, 196). These investigators concluded that, as with all quantitative culturing techniques, borderline PSB quantitative culture results should be interpreted with caution. In such a circumstance, one should consider repeating the test if suspicion of VAP persists and antibiotics have not yet been started.

Torres and El-Ebiary reviewed 23 studies that evaluated the accuracy of bronchoscopic BAL in diagnosing VAP. A total of 957 patients were included in the analysis. Sensitivity ranged from 42 to 93%, with a mean ± standard deviation of 73% ± 18%. The specificity ranged from 45 to 100%, with a mean specificity ± standard deviation of 82% ± 19% (199). In 12 studies, the detection of ICOs in 2 to 5% of recovered cells had a sensitivity of 69% ± 20% and a specificity of 75% ± 28% for diagnosing VAP (199). Reproducibility of BAL is excellent when the culture is sterile. However, for positive cultures, the quantitative repeatability was only 53% in one study (73).

Chastre et al. compared PSB and BAL to the "gold standard" histopathologic findings and quantitative tissue culture results from the same areas of lungs of patients in the terminal phase of their illness. Patients were included in the study only if they never had pneumonia or had acquired it during the terminal phase of their illness. Antibiotics had not been changed or added in the 3 days prior to the sampling. In this investigation, PSB had a sensitivity of 82%, a specificity of 77%, a positive predictive value of 74%, and a negative predictive value of 85%; BAL had a sensitivity of 91%, a specificity of 78%, a positive predictive value of 83%, and a negative predictive value of 87%; and the presence of ≥5% ICOs had a sensitivity, specificity, positive predictive value, and negative predictive value of 91%, 89%, 91%, and 89%, respectively (31).

(iii) Quantitative endotracheal aspirate. Using a threshold value of $\geq 10^6$ CFU/ml, the sensitivity and specificity of QEA have varied widely from study to study. Sensitivity ranged from 38% to 82% with a mean of 76% ± 9%; specificity ranged from 72% to 85% with a mean of 75% ± 28%. When the diagnosis of VAP was based on postmortem lung examination, the sensitivity/specificity for 10^5-CFU/ml and 10^6-CFU/ml thresholds were 63%/75% and 55%/85%, respectively (130). Patients on antibiotics were included in that study, which may have decreased the sensitivity of the procedure.

Jourdain et al. found the QEA to have a sensitivity and a specificity of as high as 68% and 84%, respectively, and a false-negative rate of as high as 32% compared to bronchoscopic quantitative PSB and BAL (95, 133). The diagnostic thresholds for QEA, PSB, and BAL in that study were $\geq 10^6$ CFU/ml, $\geq 10^3$ CFU/ml and ≥5% ICOs, respectively. In addition, only 40% of the organisms isolated from QEAs were concomitantly isolated from PSB specimens. Strengths of this study included a well-defined "gold standard," which is as close as one can get to the "true gold standard" of histopathology and lung tissue culture, and the absence of an addition to or change in antibiotics in the 3 days prior to the appearance of the new pulmonary infiltrate.

(iv) Blind BBS, PSB, and BAL. Campbell reviewed 15 studies evaluating the accuracy of blinded sampling methods (26). A total of 654 episodes of pneumonia were included in the analysis. Sensitivities for BBS, mini-BAL, and PSB were 74 to 97%, 63 to 100%, and 58 to 86%, respectively. Specificities ranged from 74 to 100% for BBS, from 66 to 96% for mini-BAL, and from 71 to 100% for PSB. Marik and Brown compared blind PSB to PSB performed by bronchoscopy. In that

study both diagnostic techniques were performed in the absence of antibiotic therapy and blind PSB preceded bronchoscopy, to minimize contamination of the lower respiratory tract. In addition, the study used a well-defined and reasonable "gold standard" for the diagnosis of VAP, though not histopathologic and lung tissue culture. In that investigation, blind PSB had a sensitivity of 86%, a specificity of 85%, a positive predictive value of 80%, and a negative predictive value of 90% (128, 133).

(v) Comparisons among the different quantitative culturing techniques: bronchoscopic versus nonbronchoscopic techniques. Inherent advantages of nonbronchoscopic techniques include less invasiveness; less compromise of oxygenation, ventilation, and respiratory mechanics during the procedure; less likelihood of increasing intracranial pressure; less likelihood of inducing arrhythmias; availability where there is no bronchoscopist; lack of contamination presented by the bronchoscopic channel; availability to patients with small endotracheal tubes; and lower cost. Of the quantitative techniques, QEA is least invasive, most readily available, and least expensive, and it requires the least experience and is easily repeatable.

Where comparisons have been made, the authors of most studies have concluded that the diagnostic accuracies of nonbronchoscopic and bronchoscopic techniques are similar. Nonetheless, and although not noted by all studies, certain generalizations regarding the overall medical literature can be made.

(i) In some studies, the concordance between the sensitivity of bronchoscopic versus nonbronchoscopic quantitative cultures has been only approximately 80% (30, 94, 140). Consequently in some patients, particularly if the pneumonia is not diffuse and involves the left lung or upper lobes, the diagnosis of VAP could be missed by blind sampling.

(ii) Compared to nonbronchoscopic sampling methods, bronchoscopic quantitative cultures have greater specificity (104, 162).

(iii) Because BAL samples larger areas of lung, it as at least as sensitive as PSB and PTC (135). The sensitivity and negative predictive value of a culture for pneumonia are affected by the size of the sampling area and the amount of retrieved secretions. Bronchoalveolar lavage, which samples approximately 1 million alveoli, is estimated to recover 5 to 10 times the number of organisms obtained by PSB. Quantitative endotracheal aspirates would likewise be expected to provide more representative samples than PSB and PTC. Combining the results of PSB and BAL may increase sensitivity (187).

(iv) Other "technical" advantages of BAL over PSB are that the technique of smear preparation for direct microscopic examination of BAL is better established and that BAL is less likely to cause bleeding (28).

(v) Protected sampling methods such as PSB, PTC, and protected BAL, because they "bypass" the oropharyngeal and upper airway bacterial contamination/colonization, have superior specificity and positive predictive values (135).

(vi) Protected specimen brush is more specific than sensitive for the diagnosis of VAP. Consequently, a positive result increases the likelihood of pneumonia being present (199).

(vii) Direct visualization of the airways by bronchoscopy permits sampling from the airway that corresponds to the abnormal region on chest X ray or CT scan, to purulent secretions, and/or to maximal endobronchial abnormalities. Consequently, bronchoscopy should theoretically improve the sensitivity of the procedure, particularly for pneumonias involving the upper lobes and the left lung (94, 115).

(a) Timsit et al. reported that the presence of two or more of the following had a sensitivity of 78% and a specificity of 89% for diagnosing VAP: a decrease in the partial pressure of arterial oxygen (PaO_2)/FiO_2 ratio of $\geq$50 mmHg, distal purulent secretions, or persistence of distal secretions surging from distal bronchi during exhalation (195).

(b) In a study with autopsy serving as the gold standard to diagnose VAP, a bronchoscopic BAL with $<$50% neutrophil differential had a 100% negative predictive value for the diagnosis of VAP (98).

(viii) Compared to QEA and BBS, blind and bronchoscopic PSB, PTC, and BAL provide additional information that may be clinically useful.

(a) In one study of PSB, having fewer than 10% neutrophils on direct examination was uniformly associated with negative cultures, a finding that would contribute significantly to the specificity and positive predictive value of the procedure (142).

(b) Immediate performance of a direct microscopic examination, BAL, PBC, and PTC also enable a search for ICOs. If $\geq$2 to 5% of recovered cells contain ICOs, this result can potentially serve as a guide for the initial selection of empirical therapy. Unfortunately, as indicated above, the accuracy of this procedure is too low to be clinically useful in most circumstances. Not surprisingly, concomitant antibiotic administration increases the likelihood of false-negative results (53, 205). Moreover in one study, one-third of episodes of VAP caused by *Pseudomonas aeruginosa* were associated with negative direct stainings (205). Consequently, in the majority of cases, a negative direct staining still requires initial broad-spectrum antibiotics until culture results are returned.

(c) In a recent study by Michel et al., QEAs performed twice a week anticipated the etiology of a subsequent pneumonia in 83% of cases (146). This contrasts with the results of similar studies utilizing nonquantitative cultures of ETAs (78).

The key question, however, is not which quantitative culturing technique is more accurate but whether these techniques affect outcomes from VAP. Four studies have prospectively evaluated the impact of an invasive diagnostic strategy on the morbidity of, the use of antimicrobial drugs in, and the mortality of VAP. Unfortunately, the four studies had different designs as well as methodological flaws, including an inappropriate selection of diagnostic techniques for comparison, insufficient control for previous antimicrobial treatment, inconsistent ways of managing antibiotic treatment in patients who had negative microbiologic assays, and insufficient power to detect clinically important differences among alternative strategies.

In the three, randomized, controlled Spanish studies, no differences in mortality and morbidity were found when either invasive (PSB and/or BAL) or QEA techniques were used to diagnose VAP (175, 176, 186). However, these studies contained relatively few patients (51, 76, and 88 patients) and therefore were not powered sufficiently to demonstrate a difference in mortality. Moreover, antibiotics were continued in all patients, thereby negating one of the major potential advantages of any diagnostic test in patients clinically suspected

TABLE 2. CPIS

Day	Parameter	Value for score of:	
		1 point	2 points
1	Temp (°C)	38.5 to 38.9	≥39 or ≤36
	White blood cells/mm^3	<4,000 or >11,000	<4,000 or >11,000 and ≥50% bands
	Secretions	Nonpurulent	Purulent
	PaO_2/FiO_2		≤240 and no ARDS
	Chest X-ray infiltrates	Diffuse or patchy	Localized
3	Temp (°C)	38.5 to 38.9	≥39 or ≤36
	White blood cells/mm^3	<4,000 or >11,000	<4,000 or >11,000 and ≥50% bands
	Secretions	Nonpurulent	Purulent
	PaO_2/FiO_2		≤240 and no ARDS
	Chest X-ray infiltrates	Diffuse or patchy	Localized
	Progression of chest X-ray infiltrates		Yes (no ARDS or congestive heart failure)
	Sputum	Culture >1+	Culture >1+ and same organism on Gram staining

of having VAP. In other studies, it has been shown that antibiotics can be safely stopped in patients with negative quantitative cultures (30). Although these studies did not demonstrate any difference in clinical outcomes, they did confirm that invasive tools are associated with a greater ability to narrow or discontinue antibiotics.

In a large, multicenter, randomized, unblinded French study of 413 critically ill patients with a clinical suspicion of pneumonia, bronchoscopy with quantitative cultures of PSB or BAL was compared to nonquantitative endotracheal aspirates (64). Patients with recent changes in antibiotic therapy were excluded, limiting the ability to generalize the results. Patients in the invasive diagnostic group had more antibiotic-free days in a 28-day period (11.4 versus 7.5 days), fewer antibiotics per day (1.0 versus 1.3), and less organ dysfunction at day 3 and 7. The mortality rate at 14 days was significantly lower in the invasive diagnostic group (16.2% versus 25.8%; $P = 0.022$); there was no difference at 28 days. However, when a multivariate analysis was performed, there was an improvement in mortality at 28 days (hazard ratio, 1.54; 95% confidence interval, 1.10 to 2.16; $P = 0.01$).

One problem with this study that could have confounded results was that the invasive diagnostic group had a much lower rate of inappropriate initial antibiotics (1 patient [0.5%] versus 24 patients [13%]; $P < 0.001$). Of the cohort that received inappropriate antibiotics, 33% died, including all in the noninvasive diagnostic group before day 14. Numerous studies have documented the importance of appropriate and early antimicrobial therapy for VAP (2, 90, 125). Therefore, the improved outcome at 14 days in the invasive diagnostic group may have been secondary to higher use of inappropriate antibiotics in the noninvasive diagnostic group and not to the actual invasive procedures.

A recent meta-analysis of the impact of invasive approaches on the diagnosis of VAP concluded that invasive lower airway sampling does not alter hospital mortality but consistently results in changes to the antibiotic regimen (182). In that study, the odds ratio for change in antibiotic management after invasive testing was 2.85 (95% CI, 1.45 to 5.59). In another outcomes study, the invasive bronchoscopic evaluation of VAP was also shown to allow de-escalation or narrowing of antibiotics to occur once organisms and their susceptibilities were identified (169). In contrast, in a decision analysis of antibiotic and diagnostic strategies for VAP, Ost et al. concluded that from the perspective of minimizing cost, minimizing antibiotic use, and maximizing survival, the best strategy was employing mini-BAL and treating with three antibiotics (160). While mini-BAL did not improve survival, it did decrease cost and antibiotic use (160).

At the present time, based on the available data, the optimal strategy for diagnosing VAP remains to be defined. The American Thoracic Society (ATS)/Infectious Disease Society of America guidelines do provide expert opinion supporting quantitative or semiquantitative cultures of respiratory specimens, although the panel favors invasive quantitative techniques (5). However, a large, better matched, multicenter, randomized study comparing quantitative cultures of endotracheal aspirates to quantitative cultures of bronchoscopic specimens to a clinical strategy using scoring systems and nonquantitative and semiquantitative cultures is still needed. Potential confounding variables such as antibiotic regimens and antibiotic discontinuation protocols must be controlled. Until such evidence exists, the use of invasive bronchoscopic techniques cannot be required for the routine diagnosis of VAP. Therefore, which diagnostic approach for VAP should be undertaken is up to the discretion of the clinician. Factors to consider include local experience, expertise, availability, and cost.

TREATMENT

Principles to apply when choosing appropriate therapy for VAP include knowledge of organisms likely to be present, local resistance patterns within the ICU, a rational antibiotic regimen, and a rationale for antibiotic de-escalation or stoppage. Although the clinician could know the organisms and sensitivities prior to the development of VAP (see "Antibiotic Management" below), this is often not the case. In the latter situation, empirical choices that provide adequate coverage are critical. Early effective therapy for VAP is associated with reduced mortality. Luna et al. demonstrated that inadequate therapy during the initial 48 h, despite provision of adequate therapy after BAL results, was associated with a mortality rate of 91% (125). When empirical therapy was appropriate, mor-

TABLE 3. Routine care of patients suspected of having ventilator-associated pneumonia

Action
Blood cultures, 2 sets
Urine analysis with culture
Thoracentesis, if pleural effusion present
Consider antiatelectatic measures (increase of positive-end expiratory pressure and/or tidal vol, bronchodilators, chest physical therapy [including suctioning])

tality rates were much lower (38%). Delays in the administration of appropriate antibiotic therapy for VAP have been associated with excess mortality (2, 90, 125). In one study, a delay in appropriate therapy for 24 h or more was associated with a 69.7% mortality, compared to 28.4% in patients treated without the delay ($P < 0.001$) (90). Consequently, once VAP is considered, cultures must be obtained quickly and treatment initiated without delay. VAP should be considered with a CPIS score of >6, as illustrated in Table 2, or alternatively, with a new pulmonary infiltrate and at least two of the following: fever, leukocytosis, and purulent secretions.

As multiple etiologies may explain why patients develop a fever and pulmonary infiltrates while receiving mechanical ventilation, we often search for other infectious and noninfectious etiologies concurrently with evaluation for VAP. The extent of this investigation is dictated by the clinical circumstances, including physical examination, laboratory findings, and the severity of illness (Tables 3 and 4). In patients with sepsis, a definite site of infection cannot be found in 20 to 30% (212). As delays in treating severe sepsis significantly increase mortality, we are very hesitant to discontinue antibiotics in patients with severe sepsis, even if initial respiratory and other cultures are negative. In such critically ill individuals, we usually continue broad-spectrum antibiotics as we continue to aggressively pursue other infectious and noninfectious causes of the patient's presentation (Tables 3 and 4). However, because VAP is rarely occult, we direct our antibiotic coverage and diagnostic efforts at non-VAP causes of sepsis.

There is a general consensus that VAP is very likely in certain situations. These circumstances are outlined in Table 5 (198, 215). However, either such scenarios are uncommon or the procedures required are undesirable or contraindicated in critically ill patients on mechanical ventilators. Therefore, in most cases the clinician has a choice of two strategies for managing suspected VAP (Table 6). One strategy is based on clinical criteria and nonquantitative or semiquantitative cultures of tracheal aspirates. The other strategy utilizes quantitative cultures of respiratory specimens. The quantitative culture approach can be further divided into bronchoscopic (invasive) and nonbronchoscopic (noninvasive) strategies. As outlined above, each strategy has its own advantages and disadvantages.

TABLE 4. Evaluation for infectious (other than VAP) and noninfectious causes of fever

Action to be considered
Changing and/or culturing intravenous lines
CT scan of sinuses, with fine needle aspirate if abnormal
Evaluation for venous thromboembolism
Clostridium difficile evaluation if diarrhea present
Abdominal ultrasound and/or CT scan (especially in the case of abnormal abdominal physical examination, abnormal liver function tests, elevated lipase/amylase, or presence of predisposing factors (abdominal surgery, pancreatitis, gastrointestinal bleed or malignancy, or high-dose corticosteroids)
Lumbar puncture (especially in the case of a predisposing factor such as head trauma or neurosurgical procedure)
Drug fever

TABLE 5. High probability of VAP

Finding
Radiographic evidence of cavitation or necrosis of the pulmonary infiltrate, particularly if rapid and progressive
An empyema with an adjacent pulmonary infiltrate
Simultaneous recovery of the same microorganism from respiratory secretions and pleural fluid
Simultaneous recovery of the same microorganism from respiratory secretions and blood, with no other source of the bacteremia
Consistent histology on lung biopsy
Positive Gram stain/culture on transthoracic needle aspirate
Chest X ray demonstrating an air space process abutting a fissure
Chest X ray demonstrating an air bronchogram, especially if single

Bronchoscopy allows the direct examination of respiratory secretions from BAL, PSB, and PTC to determine the percentage of cells containing ICOs. Some experts cite this potential for early guidance of antibiotic management as a factor favoring the bronchoscopic approach to the management of VAP over other strategies (29, 30). However, and as outlined above, the false-negative rate of direct staining is alarmingly high, particularly with concomitant antibiotic use and with VAP caused by *Pseudomonas*. Consequently, we contend that a negative direct staining still requires initial broad-spectrum antibiotics until culture results are returned, particularly if antibiotics have been added or changed in the previous 72 h.

Quantitative Culture Strategy

Although there is no definitive evidence that quantitative cultures clearly improve patient outcomes, we favor a quantitative culture strategy for the management of suspected VAP. The superior specificity of quantitative compared to nonquantitative and semiquantitative culture techniques permits us to more confidently discontinue antibiotics and thereby avoid the attendant complications, including the potential for increased bacterial resistance. In addition, a negative quantitative culture compels us to more aggressively search for other noninfectious and nonpulmonary infectious causes of the patient's presentation.

Our ICU practice is to rely on QEAs, as most studies have concluded that the sensitivities of nonbronchoscopic and bronchoscopic quantitative techniques are comparable. However, the overall concordance in some studies has been only approximately 80% (30, 94, 140). That is, in some patients, the diagnosis of VAP could be missed by blind, nonbronchoscopic sampling, particularly if the pneumonia involves the left lung or upper lobes. Moreover, the additional information obtained from direct visualization of the airways, percentage of neutro-

TABLE 6. Evaluation of fever in patients suspected of having ventilator-associated pneumonia

Clinical circumstance	Management recommendation
Initial evaluation; clinically suspect VAP[a]	Calculate day 1 CPIS (see Table 2); routine care for suspected VAP (see Table 3); if febrile, consider other etiologies (see Table 4)[b]; immediate institution of antimicrobial treatment after cultures performed[c]
Reevaluation at 48–72 h	Calculate day 3 CPIS (see Table 2)
(i) High likelihood of VAP (see Table 5) or (ii) nonpulmonary site of infection identified or (iii) unexplained severe sepsis[d]	Continue antibiotics; adjust regimen based on culture results and probable site(s) of infection[b]
Chest X-ray infiltrates no longer present[e]; severe sepsis absent now and initially; no nonpulmonary site of infection identified	Discontinue antibiotics and follow patient; if still febrile, search for etiology[b]
Non- or semiquantitative culture strategy	
(i) Day 1 CPIS of >6 and ETA culture positive or (ii) day 1 CPIS of ≤6 and day 3 CPIS of >6	Continue antibiotics; adjust regimen based on culture results
Day 1 CPIS of ≤6 and day 3 CPIS of ≤6 and:	
Cultures negative and antibiotics have not been changed or added in the 72 h prior to obtaining cultures (VAP unlikely)	Discontinue antibiotics and follow patient; if still febrile, search for etiology[b]
(i) Cultures negative and antibiotics have been changed or added in the 72 h prior to obtaining cultures or (ii) cultures positive	No firm recommendation; consider discontinuing antibiotics and following patient[f] (favored); if still febrile, search for etiology[b]
Day 1 CPIS of >6 and ETA culture negative	No firm recommendation; consider discontinuing antibiotics and following if antibiotics have not been changed in the 72 h prior to obtaining cultures, particularly if alternative, noninfectious diagnosis confirmed; otherwise, continue antibiotics; if still febrile, search for etiology[b]
Quantitative culture strategy	
Colony count exceeds threshold (VAP likely)[g]	Continue antibiotics; adjust regimen based on culture results
Colony count below threshold and:	
Antibiotics have not been changed or added in the 72 h prior to obtaining cultures (VAP unlikely)[h]	Discontinue antibiotics and follow patient; if still febrile, search for etiology[b]
Antibiotics have been changed or added in the 72 h prior to obtaining cultures	No firm recommendations; if still febrile, search for etiology[b]
Day 1 CPIS of ≤6 and day 3 CPIS of ≤6	Consider discontinuing antibiotics and following patient[f] (favored)
Factors increasing probability of true-negative result are present[h]	Consider discontinuing antibiotics and following patient

[a] CPIS on day 1 of >6 (see Table 2) and in the setting of ARDS, one or more of the following clinical parameters: new and persistent (>48 h) or progressive radiographic infiltrate, temperature of >38°C or <36°C, blood leukocyte count of >10,000 cells/ml or <5,000 cells/ml, purulent tracheal secretions, unexplained hemodynamic instability, or unexplained deterioration in oxygenation status.

[b] Consider that patient may have more than one explanation for fever.

[c] Rationale: delayed treatment of VAP increases mortality.

[d] Rationale: a definite site of infection cannot be found in 20 to 30% of patients with sepsis; delayed treatment of severe sepsis increases mortality.

[e] Rationale: infiltrates secondary to pneumonia do not improve in 72 h; consider atelectasis, congestive heart failure, hemorrhage, or chemical pneumonitis as the cause of pulmonary infiltrates.

[f] Rationale: based on reference 183.

[g] Factors increasing probability of a true-positive result: colony count more than 10^1 CFU/ml above threshold, presence of distal purulent secretions or persistence of distal secretions surging from distal bronchi during exhalation after bronchoscopic aspiration, >50% neutrophils on BAL, and >10% neutrophils and <1% epithelial cells on direct examination of BAL, PSB, or PTC.

[h] Factors increasing probability of a true-negative result: colony count more than 10^1 CFU/ml below threshold, absence of distal purulent secretions or persistence of distal secretions surging from distal bronchi during exhalation, <50% neutrophils on BAL differential, and <10% neutrophils and <1% epithelial cells on direct examination of BAL, PSB, or PTC.

phils on BAL, and percentage of epithelial cells and neutrophils on direct staining of PSB and BAL aid in our decision making. When we utilize bronchoscopy, we favor BAL over PSB because of its better safety profile and because it samples a greater area of the lung, which should theoretically improve sensitivity and negative predictive value. Performing both BAL and PSB may increase sensitivity further (see above).

If the quantitative culture strategy is employed, it is essential to interpret quantitative culture results in the clinical context. Consider a quantitative BAL culture yield of 10^3 CFU/ml from

a mechanically ventilated patient obtained 48 h after administration of broad-spectrum antibiotics. This is below the 10^4-CFU/ml threshold, but antibiotics given or changed within the 72 h prior to obtaining a quantitative culture can decrease the bacterial burden and result in a false-negative quantitative culture. In the appropriate clinical context, such a result can be interpreted as consistent with the presence of VAP. In contrast, the same culture result obtained for an individual on no antibiotics or without a change in the previous 72 h would be less indicative of VAP. Moreover, if available, the percentage of neutrophils on BAL differential, the percentage of neutrophils and epithelial cells on direct staining of BAL and PSB, the percentage of organisms containing ICOs, and visual inspection of the airways can also be useful in individual cases (see above).

Clinical Strategy

The primary advantage of a clinical strategy for diagnosing VAP is that it does not require specific expertise or specialized equipment or techniques and is noninvasive. Therefore, such an approach can be utilized anywhere. However, because of the poor specificity of clinical signs and symptoms of VAP and of nonquantitative or semiquantitative cultures of tracheal secretions, relying on the clinical approach would be expected to result in treating noninfectious processes with broad-spectrum antibiotics as well as potentially failing to recognize and pursue noninfectious mimics of VAP and nonpulmonary infections.

Antibiotic Management

The ATS has recently published guidelines to guide empirical antibiotic choices (5). These guidelines are divided into those for patients at risk for VAP caused by multidrug-resistant organisms and those for patients without such risk. Risk factors for multidrug-resistant organisms include prior antimicrobial therapy in the preceding 90 days, current hospitalization exceeding 5 days (not necessarily ICU days), high frequency of resistance in the community or local hospital unit, and immunosuppressive disease and/or therapy. In addition, the clinician must consider risk factors for health care-associated pneumonia, as such a pneumonia may present with multidrug-resistant organisms even upon hospital admission (5). Such risk factors for the intubated patient include a hospitalization for >2 days within the preceding 90 days, residence in a long-term care facility, chronic dialysis within 30 days, home wound care, home infusion therapy (inclusive of antibiotics), and a family member with a multidrug-resistant pathogen.

In the absence of risk factors for multidrug-resistant bacteria, the clinician should choose empirical therapy for *Streptococcus pneumoniae*, *Haemophilus influenzae*, methicillin-sensitive *Staphylococcus aureus*, and antibiotic-sensitive gram-negative enteric organisms. Antibiotic choices include ceftriaxone, quinolones (levofloxacin, moxifloxacin, or ciprofloxacin), ampicillin/sulbactam, or ertapenem (Fig. 1). When risk factors for multidrug-resistant organisms are present, the clinician must consider not only the organisms listed above but also *Pseudomonas aeruginosa*, *Klebsiella*, *Enterobacter*, *Serratia*, *Acinetobacter*, *Stenotrophomonas maltophilia*, *Burkholderia cepacia*, and methicillin-resistant *S. aureus*. Empirical therapy is broadened to include (i) either an antipseudomonal cephalosporin (cefepime or ceftazadime), an antipseudomonal carbepenem (imipenem or meropenem), or a β-lactam/β-lactamase inhibitor (pipercacillin-tazobactam) plus (ii) an antipseudomonal fluoroquinolone (ciprofloxacin or levofloxacin) or an aminoglycoside (amikacin, gentamicin, or tobramycin) plus linezolid or vancomycin.

While the complex regimen outlined above is appropriate, creating a milieu of further resistant organism must be a concern, as it will lead to fewer opportunities to choose effective empirical therapy. As noted in "DIAGNOSIS" above, there is considerable controversy over the use of quantitative cultures and which quantitative culturing technique to use. Michel et al. applied QEA as a surveillance tool and routinely obtained samples twice weekly (146). Sensitivities were determined for microorganisms present at a concentration of $\geq 10^3$ CFU/ml. When VAP occurred, the most recent QEA preceding VAP was used to direct antibiotic therapy, and a BAL was obtained to assess the appropriateness of the antibiotic regimen. Those authors also compared results of BAL to empirical regimens that would have been chosen by the classification of Trouillet et al. and the 1996 ATS consensus guidelines (6, 203). The antibiotic regimen as guided by QEA was appropriate in 95% of cases. This was not statistically different from the appropriateness of the empirical regimens chosen by the strategy of Trouillet et al. (83% appropriate) but was superior to that of the empirical choices suggested by the 1996 ATS guidelines (68% appropriate). This approach is very new, and the cost is that of culturing and determining sensitivities (if the threshold is exceeded). The benefit is that it appears to provide a high likelihood for appropriate initial therapy. Furthermore, it will likely reduce the application of overly broad antibiotic regimens, hence reducing the likelihood of inducing more multidrug-resistant organisms.

Considerable controversy surrounds monotherapy versus combination therapy for patients with VAP. The primary reasons for combination therapy are to prevent the development of resistance, improve outcomes, provide synergy, and provide sufficient antibiotic coverage should the pathogen be resistant to the agent that would have been chosen as single therapy. The former two arguments, while logical, have yet to be proven (36, 209). In fact, a meta-analysis suggested that clinical failure was more common with combination therapy, as was nephrotoxicity; aminoglycosides were the second agent, and combination therapy did not prevent new resistance patterns (209). However, given that mortality is higher when therapy is inappropriate during the first 48 h, we favor initiating combination therapy for patients at risk for multidrug-resistant organisms until sensitivities are known. This is consistent with an approach suggested by Gruson et al. (75).

Commonly employed methods to reduce the development of resistance include de-escalation therapy, truncated courses of antibiotics, dosing regimens that account for patient-antibiotic pharmacokinetics and pharmacodynamics (PK/PD), antibiotic cycling, and surveillance cultures. Most intensivists have embraced the former two; however, the latter two remain controversial. The ATS has put forth a management strategy to address de-escalation and early stoppage of antibiotics (5). Upon suspicion of VAP, empirical antibiotics are initiated and lower respiratory tract cultures obtained. At 48 to 72 h, if the patient is improving and cultures are negative, strong consideration

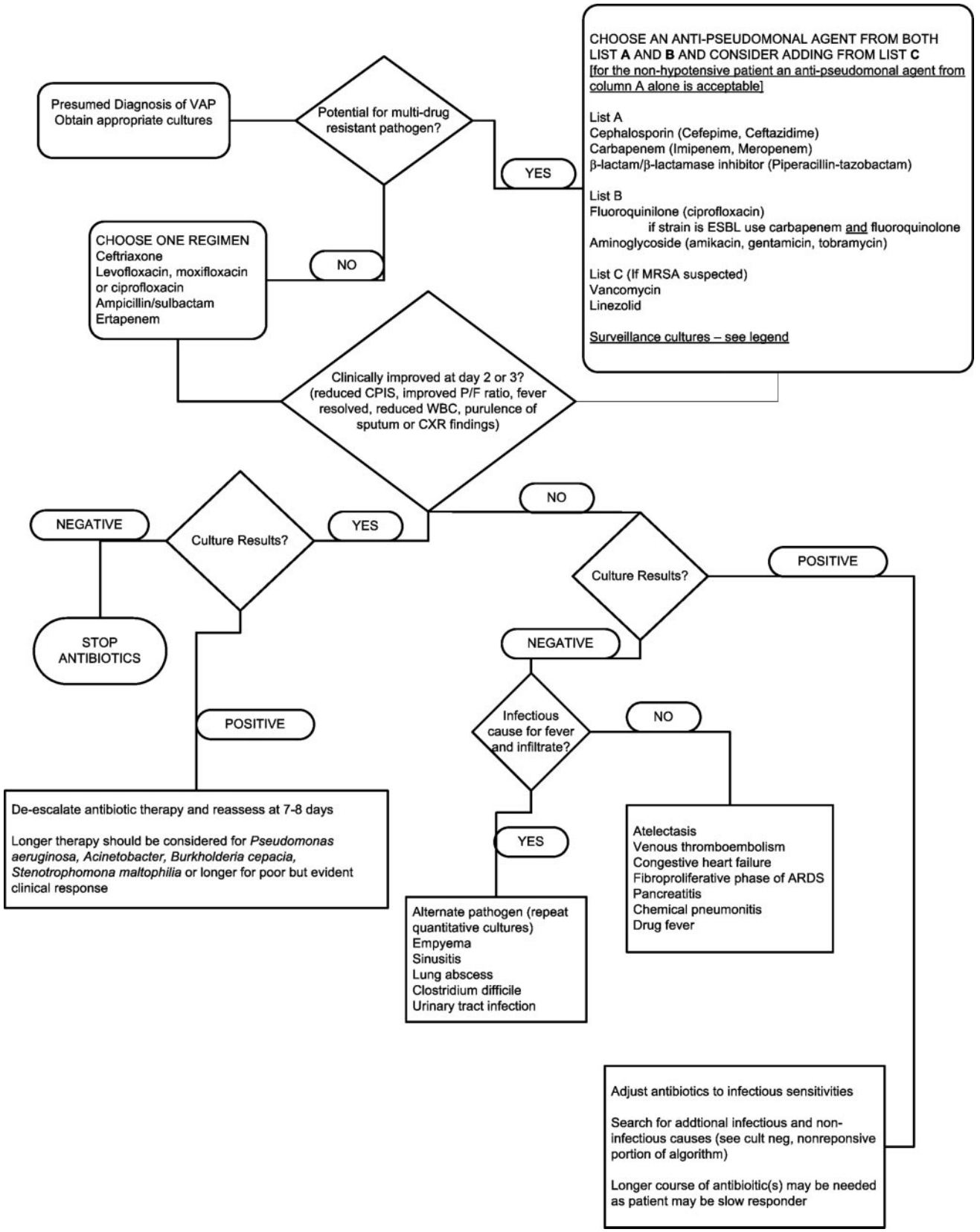

FIG. 1. Algorithm for diagnosis and treatment of VAP. (©American Thoracic Society. Adapted from the *American Journal of Respiratory and Critical Care Medicine* [5] with permission.) Antibiotic choice can be tailored to the pathogens' last sensitivity report should QEA surveillance cultures be obtained twice weekly and should the growth level exceed 100,000 CFU/ml (146.)

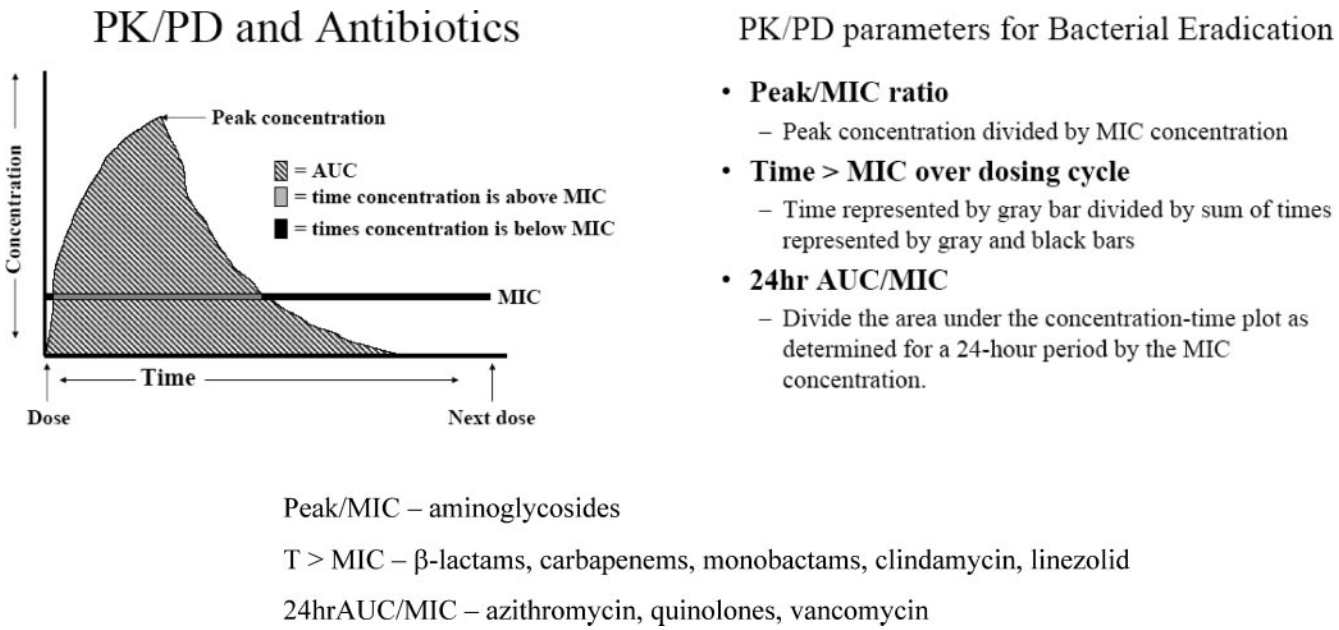

FIG. 2. Pharmacodynamic and pharmokinetic approach to antibiotic therapy.

should be given to stopping antibiotics. Rello et al. have suggested truncating the course at <5 days provided the patient has been afebrile for >48 h (169). Should the culture results be positive and the patient has improved at 48 to 72 h, then the ATS guidelines suggest de-escalation (reduction in antibiotics to be administered, including potential for monotherapy) and treating patients without *P. aeruginosa*, *Acinetobacter*, or *Stenotrophomonas maltophilia* for 7 to 8 days. A longer course is indicated for *P. aeruginosa*, *Acinetobacter*, and *Stenotrophomonas maltophilia*.

The antibiotic regimen (choice and dosing) should be reevaluated for change or prolongation in patients with poor clinical responses, which may be assessed by a rising CPIS. A rising CPIS has been associated with higher mortality (183). These recommendations are based on the results from studies by Dennesen et al., Luna et al., Singh et al., and Ibrahim et al. (49, 88, 122, 183). Such strategies are dependent upon clear evidence of patient improvement as defined by reduction in serial CPISs or improvement of the PaO_2/FiO_2 ratio at days 3 to 5 (122). The technique chosen in obtaining microbiologic data may indeed affect the clinical decision to de-escalate therapy. Heyland et al. reported that the choice of bronchoscopic BAL and PSB resulted in increased physician confidence in the diagnosis and management of VAP; this resulted in a greater tendency to limit or discontinue antibiotics, an outcome that was echoed in a recent meta-analysis (79, 182).

Singh et al. proposed another potential clinical strategy to minimize unnecessary antibiotic use for VAP and the potential consequences (183). In this study, patients with a modified CPIS of ≤6 on day 1 (Table 2) were randomized to receive either standard antimicrobial therapy or ciprofloxacin monotherapy, with reevaluation at 3 days. In the ciprofloxacin monotherapy group, if the CPIS remained at ≤6 at day 3, antibiotics were discontinued. Continuation of antibiotics in the standard therapy group was left up to the discretion of the attending physician but occurred in 96% of patients. Despite monotherapy with ciprofloxacin, a shorter duration of treatment ($P = 0.0001$) and lower cost ($P = 0.003$), mortality, and length of ICU stay did not differ. In addition, antimicrobial resistance, superinfections, or both were less in the experimental group than in the standard therapy group (15% versus 36%; $P = 0.017$). Such an approach recognizes that a gold standard for diagnosing VAP does not exist, and consequently the approach does not attempt to discern whether the patient did or did not have pneumonia. Rather, the goal was to identify patients for whom a shorter course of antibiotic therapy would suffice. In a subsequent study that incorporated the modified CPIS, 41% of patients with a score of ≤6 did not have pneumonia by quantitative BAL culture (65). Therefore, one potential explanation for the good outcome in the study by Singh and colleagues is that many of the patients did not have pneumonia.

The antibiotic regimen may be appropriate but the dose or frequency not appropriate. This is important not only in treating resistant organisms but in preventing the development of resistance, by means of eradications. Three tools to predict antibiotic efficacy are to assess the peak concentration achieved, the time the antibiotic exceeds the MIC, and the extent to which the area under a concentration-time plot exceeds the MIC (Fig. 2). Coupling an understanding of the mechanisms of how bacteria are eradicated and PK/PD parameters results in reduced mortality and morbidity (3, 4, 18, 84, 120, 151, 152, 177, 217).

The ATS guidelines also address the nonresponding patient with negative and positive cultures (5). A change in antibiotic coverage is warranted should the culture results indicate that empirical therapy was inappropriate. However, if culture results are negative or appropriate antibiotic regimens were chosen and the patient has not improved, then the clinician should consider other organisms, other diagnoses, or a complication of the disease or therapy (Fig. 1). Such a decision is generally made after 72 h of therapy, as most patients respond within this

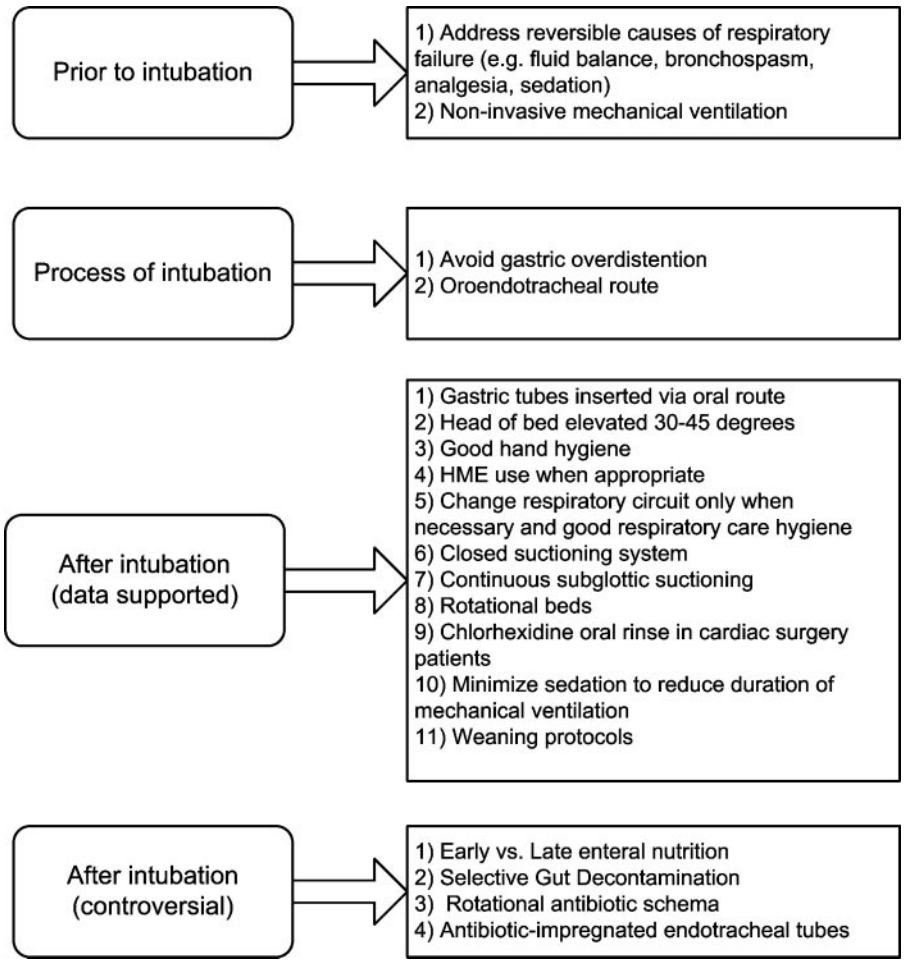

FIG. 3. Potential strategies to prevent VAP.

time frame (122, 123). At this juncture, quantitative cultures are warranted. Montravers et al. have demonstrated that clinical failure rarely occurred when protected brush samples recovered organisms at $<10^3$ CFU/ml (7% failure rate). Conversely, higher failure rates were seen when culture results exceeded 10^3 CFU/ml (55.8% failure rate) (150). Persistent fever or failure to improve with antibiotic therapy may indicate that the inciting process is noninfectious. Other diagnoses include atelectasis, congestive heart failure, venous thromboembolic disease, pancreatitis, chemical pneumonitis from aspiration, proliferative phase of acute respiratory distress syndrome, drug fever, or pulmonary hemorrhage (5). Alternatively, the process may be infectious but not VAP. The clinician should consider empyema, lung abscess, *Clostridium difficile* colitis, urinary tract infection, and sinusitis (139, 172) (Table 4).

Candida species, while commonly cultured from patients, rarely cause invasive pulmonary disease, even when quantitative thresholds are exceeded (58, 166, 210). However, *Candida* may be a marker that the patient is more likely to develop VAP with *P. aeruginosa* (a causal relationship has not been demonstrated) (8). Azoulay et al., in a surveillance study, noted that patients colonized with *Candida* species were 1.58 times more likely to develop VAP and 2.22 times more likely to develop *P. aeruginosa* (8). The three most common *Candida* species recovered were *C. albicans* (2/3), *C. glabrata* (1/5), and *C. tropicalis* (1/8). Those colonized were older and were more likely to have respiratory failure as a reason for ICU admission. These patients had longer courses of mechanical ventilation, received more antibiotics, and experienced higher hospital mortality. However, there are no data to support the routine administration of antifungal therapy when *Candida* species are found in pulmonary secretions of mechanically ventilated patients.

After considering VAP, the clinician should promptly institute therapy. Choosing an appropriate antibiotic regimen, defined by sensitivities of the organism cultured and by dosing regimen ordered, is paramount, as the first 48 h is critical to patient survival. Surveillance cultures may provide better guidance than empirical strategies. Truncated courses of antibiotics are indicated for culture-negative improving patients and for VAP not caused by *P. aeruginosa*, *Acinetobacter*, and *Stenotrophomonas maltophilia*. Such a practice may reduce the likelihood of colonization with multidrug-resistant organisms or creating a local environment of resistant organisms.

PREVENTION

Clinicians must focus on eliminating or minimizing the incidence of VAP through preventive techniques (Fig. 3). While

little has affected the incidence of late-onset VAP, the occurrence of early-onset VAP can be reduced by simple measures. Data have accumulated to support interventions and establish guidelines, yet translation into practice is lacking. Health care team compliance rates vary between 30 and 64% (39). The focus should be addressing modifiable risk factors such as endotracheal and nasogastric tubes, tracheotomy, reintubation, enteral nutrition, corticosteroid administration, gastric pH-modifying agents, supine positioning, prior antibiotic usage, poor infection control practice, and contaminated respiratory equipment, medications, or water (24, 42, 100, 102, 155, 191).

Noninvasive mechanical ventilation (NIV) has been associated with more favorable outcomes (mortality and morbidity) in comparison to endotracheal tube placement in patients with acute exacerbations of chronic obstructive pulmonary disease or acute pulmonary edema (7, 21, 117, 118). The incidence of nosocomial pneumonia was reduced in the group randomized to NIV (7, 27, 74, 76, 157). Furthermore, immunocompromised patients with bilateral infiltrates also benefited from NIV over invasive mechanical ventilation (IMV) with regard to both mortality and morbidity (81). Yet clinicians have significant reluctance to initiate NIV, perhaps because of patient intolerance or increased resource consumption (nursing and respiratory therapy).

Once the decision to intubate is made, the practice of VAP prevention should be directed at reducing colonization and aspiration (volume of organisms presented to the lungs). This begins with choosing the oral route of intubation and focusing on minimizing the duration of mechanical ventilation (DOMV). Oral intubation is preferred over nasal intubation, as the latter has been associated with both VAP and sinusitis, with the same bacteria identified in both. Rouby et al., demonstrated a significant reduction in nosocomial sinusitis when patients are orally cannulated with endotracheal and gastric tubes (172). Holzapfel et al. have linked the reduction in nosocomial sinusitis to a reduction in VAP (83). Furthermore, the clinician must give careful attention to the mundane and seemingly small interventions, such as regularly assessing endotracheal cuff pressure, performing endotracheal suctioning, draining ventilator tube condensate, avoiding gastric overdistention, avoiding the supine position, avoiding unnecessary ventilator circuit changes, application of heat and moisture exchangers (HMEs) when appropriate, minimizing out-of-ICU transports, and regular hand cleaning with soap or alcohol disinfectant. Maintaining cuff pressure of endotracheal tubes at $\geq$20 mm Hg reduces nosocomial pneumonia, presumably by minimizing the passage of oropharyngeal contents into the trachea (192).

The duration of intubation directly affects the likelihood of VAP, which is more evident in patients with ICU LOS exceeding 5 days. Fagon et al. suggested that the incidence of VAP increases by 1% per day of IMV (62). However, Cook et al. found that the incidence per day varies over time, with 3% per day during first 5 days of IMV, 2% for the second 5 days, and 1% for the subsequent 5-day period (39). This observation is supported by Ibrahim et al., who identified an incidence rate of VAP of 11.5%, 56% of which were early onset ($\leq$5 day) (87). Hence, the greatest attack rates appear to be during the initial days of mechanical ventilation. Additionally, significant risk factors for early-onset VAP include cardiopulmonary resuscitation and continuous sedation (167).

Continuous sedation is more often administered in the acute phase of an illness. In addition to treating the primary cause of respiratory failure, the DOMV can be reduced through judicious use of sedatives and analgesics. Studies by Brook et al. and Kress et al. have demonstrated that protocols for sedative and analgesic administration with the goal of minimizing constant infusions led to reduced DOMV (22, 113). Furthermore, daily interruption of sedation results in a reduced incidence of intensive care unit complications, in which VAP was included (127, 180). Weaning protocols have also resulted in reduced DOMV, whether respiratory therapist initiated or not (59, 67).

Patients should be cared for in the semirecumbent position to reduce the extent of aspiration, especially when receiving enteral feeds. Radionuclide studies reveal increased tracheal penetration of gastric contents when intubated patients are supine (85, 159, 201). Drakulovic et al. found that the simple elevation of the head of bed to 45° results in dramatic reductions in VAP incidence and a trend toward reduced mortality (54). Nonetheless, a recent survey by the University Hospital Consortium revealed that compliance with the simple and no-cost intervention of elevating the head is woefully low, and a study by Heyland et al. revealed that the head of bed is on average elevated to 29° and not 45° (80). Kinetic bed therapy has also led to a reduction in the incidence of VAP (46, 48, 69, 72, 97, 202, 213). However, this is costly and has not been directly compared to head-of-bed elevation, a no-cost option.

Some VAP is contracted from inhalation of bacteria through the ventilator circuit and may be a result of contaminated aerosols, condensate, or suction catheters. Traditionally, ventilator circuit changes have been on a regular schedule and often daily. However, the data examining this practice reveal that there is no benefit to changing the circuit on a regular basis, and the present recommendations are to change the circuit when soiled (56, 108, 121). Such a practice would likely reduce the rate of accidental spillage of condensate into the airway. As heated humidifiers enhance the amount of condensate, attention has been focused on HMEs. These devices have led to a reduction in VAP, albeit small, and should be used in patients without significant secretions or concern over the risk of obstruction (17, 55, 99, 107, 132, 141, 174). While changing the HME less frequently than every 48 h may lead to further reductions in VAP, care must be taken to carefully monitor for trapped secretions and subsequent airway obstruction or increments in the work of breathing (45, 193).

Endotracheal suctioning of intubated patients can be performed through an open or closed system. In theory the closed system could reduce the incidence of VAP, but in practice this has not been demonstrated (35, 50, 93, 106, 219). Cost analysis favors the closed system, as the enveloped catheter can be reused for suctioning and needs to be changed only when dysfunctional (52). However, respiratory therapists have voiced concerns over residue buildup within the lumen of the endotracheal tube.

As most VAP follows from aspiration of oropharyngeal secretions, attention to proper cuff inflation pressures and endotracheal suctioning can affect the volume presented to the

trachea. The application of continuous suction of subglottic secretions through specialized endotracheal tubes will reduce the incidence of VAP (110, 126, 181, 185, 204). Surprisingly, this was not associated a reduction in mortality, ICU LOS, or duration of mechanical ventilation. While studying the application of continuous subglottic suctioning, Rello et al. noted a trend of increased VAP in patients with endotracheal cuff pressures of <20 cm H_2O (168). Hence, it is recommended not only to assess cuff pressure for tracheal ischemia (which occurs when pressure exceeds 30 cm H_2O) but also to ensure that adequate cuff pressure (>20 mm Hg) is present.

The endotracheal tube itself is a reservoir for gram-negative bacteria. The buildup of a biofilm within endotracheal tubes occurs frequently. One study demonstrated that 84% of endotracheal tubes examined had a biofilm (188). As documented by Inglis et al., this biofilm is heavily laden with bacteria, usually gram-negative organisms (66, 89). At present, ongoing studies are directed at either eliminating this biofilm or reducing the bacterial load associated with it.

Oral decontamination with chlorhexidine has been shown to reduce the incidence of VAP in patients undergoing cardiac surgery, presumably by reducing oropharyngeal colonization (51). Furthermore, numerous studies with oral decontamination antibiotic pastes alone or coadministered with systemic antibiotics have shown a reduction in early VAP (1, 13, 47, 163, 171). Two meta-analyses have suggested better results with oral decontamination alone than with the combination of oral and systemic prophylaxis (44, 154). With either approach, however, concern over the emergence of antibiotic-resistant organisms has tempered use, as has the labor intensity required to apply these regimens at the bedside. This is particularly true in ICUs housing organisms with high antibiotic resistance rates (68, 71, 77, 119, 147, 148, 208, 214). While often recommended, it appears not to be routinely practiced. Two recent studies will further the debate, as they demonstrated significant reductions in VAP and mortality with selective decontamination of the digestive tract (47, 114). These two studies were performed under conditions where selective decontamination of the digestive tract is most effective, i.e., surgical intensive care units housing patients less likely to be colonized with resistant bacteria.

Gastric volumes and acidity affect the incidence of VAP. Reducing the acidity of gastric secretions and feeding will reduce bacterial overgrowth. However, in high-risk patients (ventilated for >48 h and coagulopathic), the risk of bleeding outweighs the risk of VAP from pH-modifying agents (52). Hence, it is difficult to recommend against H_2 blockers or proton pump inhibitors. Sucralafate may indeed be superior from the viewpoint of VAP, but it is less effective with regard to prophylaxis of gastrointestinal bleeding, and thus it use is not warranted over H_2 blockers or proton pump inhibitors (16, 37, 143).

Multiple studies have examined postpyloric versus gastric feedings with regard to incidence of aspiration and development of VAP. These studies were small and inconclusive. In a meta-analysis, postpyloric feedings reduce the incidence of VAP and increased the nutrition delivered (80). However, no single trial demonstrated that postpyloric tube feedings prevent VAP. The improved delivery of nutrition was likely the result of decreased gastric residual assessments and consequently fewer stoppages in continuous tube feedings. A recent publication favored a delay of greater than 5 days before initiating tube feedings, as the incidence of VAP was reduced (86). Further data are needed to unconditionally embrace this practice.

Preventing Multidrug Resistance

Antibiotic cycling remains controversial. Employing a rotational schedule for empirical antibiotic administration for suspected VAP may indeed lead to a reduced incidence of resistant organisms (75, 111, 165). While such a strategy may not reduce the incidence of VAP, reductions in mortality may be seen (165). This is likely a result of changes in resistance patterns resulting in a higher likelihood of choosing appropriate antibiotic regimens (112). Because rotational schedules have primarily targeted reducing the resistance of gram-negative organisms, we do not know the impact of rotating antibiotics against gram-positive organisms, such as methicillin-resistant *S. aureus*. Furthermore, the frequency with which to rotate antibiotics remains unclear, as monthly and quarterly regimens have been assessed with documented successes (75, 165). Furthermore, the probability of antibiotic cycling leading to a reduction in antimicrobial resistance is low as determined through mathematical modeling (14). At this juncture, it is premature to recommend rotating antibiotics or a rotational schema.

Multidrug resistance can also be reduced when patient-antibiotic PK/PD characteristics are accounted for. Early eradication minimizes the opportunity for a population of organisms to develop resistance. Peak concentrations for aminoglycosides 10-fold greater than MIC appear to inhibit the emergence of resistant organisms (178, 207). When choosing fluoroquinolones, resistant organisms are less likely to be seen when the 24-h area-under-the-curve/MIC levels are >100 for gram-negative bacteria and >40 for gram-positive bacteria (177, 179, 194). Changes in medication frequency or infusion rates can increase the time that the antibiotic concentration exceeds the MIC. For β-lactams, monobactams, glycopeptides, and cabapenems this can be important in enhancing bactericidal activity, again reducing opportunities for resistant organisms to emerge (18, 19, 105, 120, 217).

In summary, several opportunities to reduce the incidence of VAP are available to the clinician. Many are no-cost or minimal-cost interventions and should be implemented as part of routine care protocols. Care of the critically ill should be directed at applying interventions that reduce mortality, minimize morbidity, shorten the length of stay, and reduce cost. Reducing VAP through the simple measures outlined does exactly that. We recommend that the clinician's practice include noninvasive mechanical ventilation over intubation when appropriate, oral intubation when an endotracheal tube is necessary, orogastric over nasogastric tubes, elevation of the head to at least 30°, minimization of sedation, administration of a proton pump inhibitor when prophylaxis is indicated, a frequency of ventilator tubing changes at 7 days or when soiled, avoidance or elimination of endotracheal tube leak, good technique in removal of condensate, and of course excellent hand hygiene. At this time we do not support the routine use of endotracheal tubes with subglottic suction capabilities, rota-

tional beds, in-line suction systems, rotational antibiotic schemes, or selective gut decontamination.

Strategies and a more thorough discussion on prevention are within the ATS/Infectious Disease Society of America statement and papers by Kollef and by Dodek et al. (5, 52, 101). Zack et al. have demonstrated that a multifaceted and multidisciplinary approach to VAP prevention can indeed reduce the incidence (218). Success is dependent upon persistent attention to detail, high compliance rates, and a champion.

CONCLUSION

A low threshold for suspicion of VAP is needed when a patient's clinical course deteriorates. The day 1 CPIS can be useful, especially when combined with quantitative cultures. The choice of which quantitative culture methodology to use is an open debate. However, diagnostic cost favors QEA, which can also be implemented as a surveillance technique. However, the clinician is more likely to stop antibiotics with a more invasive quantitative culture, resulting in increased savings.

Antibiotic administration should be promptly initiated when VAP is suspected and quantitative cultures obtained and should be broad in coverage. Knowledge of local antibiograms should guide the choice of antibiotics, in addition to likelihood of organisms (early- or late-onset VAP). For patients already on antibiotics at the time of suspected VAP, the clinician should choose antibiotics from different classes, as it is likely that resistance to "in-use" antibiotics has developed.

Assessment of the likelihood of VAP by day 3 is needed to decide whether antibiotics should be continued. The assessment should include a repeat CPIS, as the change in CPIS can guide clinical decisions, even stoppage of antibiotics. Assessment of quantitative culture results and sensitivities at this juncture is prudent, as it may permit early antibiotic de-escalation by choosing a more narrowly focused agent(s). Monotherapy may be appropriate in many instances of VAP and should reduce the incidence of drug resistance. A change to monotherapy may be possible in a responding patient where organism sensitivity results permit. A short course (6 to 8 days) can be administered to patients with VAP but is dependent on the patient physiologic response to treatment along with which organisms have been recovered (see above) (32, 144).

Simple and effective preventive measures can be instituted easily and at minimal costs. Such measures might include NIV, diligent respiratory care, hand hygiene, elevation of head, oral and not nasal cannulation, minimization of sedation, institution of weaning protocols, judicious use of antibiotics, de-escalation, and leveraging PK/PD characteristics for antibiotics administered. More costly interventions should be reserved for appropriate situations.

Utilizing the preventive, diagnostic, and treatment recommendations outlined in this paper should allow for improved outcomes for a common and serious medical complication seen in ICU mechanically ventilated patients.

REFERENCES

1. **Abele-Horn, M., A. Dauber, A. Bauernfeind, W. Russwurm, I. Seyfarth-Metzger, P. Gleich, and G. Ruckdeschel.** 1997. Decrease in nosocomial pneumonia in ventilated patients by selective oropharyngeal decontamination (SOD). Intensive Care Med. **23:**187–195.
2. **Alvarez-Lerma, F., et al.** 1996. Modification of empiric antibiotic treatment in patients with pneumonia acquired in the intensive care unit. Intensive Care Med. **22:**387–394.
3. **Ambrose, P. G., D. M. Grasela, T. H. Grasela, J. Passarell, H. B. Mayer, and P. F. Pierce.** 2001. Pharmacodynamics of fluoroquinolones against *Streptococcus pneumoniae* in patients with community-acquired respiratory tract infections. Antimicrob. Agents Chemother. **45:**2793–2797.
4. **Ambrose, P. G., R. C. Owens, Jr., M. J. Garvey, and R. N. Jones.** 2002. Pharmacodynamic considerations in the treatment of moderate to severe pseudomonal infections with cefepime. J. Antimicrob. Chemother. **49:**445–453.
5. **American Thoracic Society.** 2005. Guidelines for the management of adults with hospital-acquired, ventilator-associated, and healthcare-associated pneumonia. Am. J. Respir. Crit. Care Med. **171:**388–416.
6. **American Thoracic Society.** 1996. Hospital-acquired pneumonia in adults: diagnosis, assessment of severity, initial antimicrobial therapy, and preventive strategies. A consensus statement, American Thoracic Society, November 1995. Am. J. Respir. Crit. Care Med. **153:**1711–1725.
7. **Antonelli, M., G. Conti, M. Rocco, M. Bufi, R. A. De Blasi, G. Vivino, A. Gasparetto, and G. U. Meduri.** 1998. A comparison of noninvasive positive-pressure ventilation and conventional mechanical ventilation in patients with acute respiratory failure. N. Engl. J. Med. **339:**429–435.
8. **Azoulay, E., J. F. Timsit, M. Tafflet, A. de Lassence, M. Darmon, J. R. Zahar, C. Adrie, M. Garrouste-Orgeas, Y. Cohen, B. Mourvillier, and B. Schlemmer.** 2006. Candida colonization of the respiratory tract and subsequent Pseudomonas ventilator-associated pneumonia. Chest **129:**110–117.
9. **Baker, A. M., D. L. Bowton, and E. F. Haponik.** 1995. Decision making in nosocomial pneumonia. An analytic approach to the interpretation of quantitative bronchoscopic cultures. Chest **107:**85–95.
10. **Baker, A. M., J. W. Meredith, and E. F. Haponik.** 1996. Pneumonia in intubated trauma patients. Microbiology and outcomes. Am. J. Respir. Crit. Care Med. **153:**343–349.
11. **Bell, R. C., J. J. Coalson, J. D. Smith, and W. G. Johanson, Jr.** 1983. Multiple organ system failure and infection in adult respiratory distress syndrome. Ann. Intern. Med. **99:**293–298.
12. **Bergmans, D. C., M. J. Bonten, P. W. De Leeuw, and E. E. Stobberingh.** 1997. Reproducibility of quantitative cultures of endotracheal aspirates from mechanically ventilated patients. J. Clin. Microbiol. **35:**796–798.
13. **Bergmans, D. C., M. J. Bonten, C. A. Gaillard, J. C. Paling, S. van der Geest, F. H. van Tiel, A. J. Beysens, P. W. de Leeuw, and E. E. Stobberingh.** 2001. Prevention of ventilator-associated pneumonia by oral decontamination: a prospective, randomized, double-blind, placebo-controlled study. Am. J. Respir. Crit. Care Med. **164:**382–388.
14. **Bergstrom, C. T., M. Lo, and M. Lipsitch.** 2004. Ecological theory suggests that antimicrobial cycling will not reduce antimicrobial resistance in hospitals. Proc. Natl. Acad. Sci. USA **101:**13285–13290.
15. **Blot, F., B. Raynard, E. Chachaty, C. Tancrede, S. Antoun, and G. Nitenberg.** 2000. Value of gram stain examination of lower respiratory tract secretions for early diagnosis of nosocomial pneumonia. Am. J. Respir. Crit. Care Med. **162:**1731–1737.
16. **Bonten, M. J., C. A. Gaillard, S. van der Geest, F. H. van Tiel, A. J. Beysens, H. G. Smeets, and E. E. Stobberingh.** 1995. The role of intragastric acidity and stress ulcus prophylaxis on colonization and infection in mechanically ventilated ICU patients. A stratified, randomized, double-blind study of sucralfate versus antacids. Am. J. Respir. Crit. Care Med. **152:**1825–1834.
17. **Boots, R. J., S. Howe, N. George, F. M. Harris, and J. Faoagali.** 1997. Clinical utility of hygroscopic heat and moisture exchangers in intensive care patients. Crit. Care Med. **25:**1707–1712.
18. **Boselli, E., D. Breilh, M. Cannesson, F. Xuereb, T. Rimmele, D. Chassard, M. C. Saux, and B. Allaouchiche.** 2004. Steady-state plasma and intrapulmonary concentrations of piperacillin/tazobactam 4 g/0.5 g administered to critically ill patients with severe nosocomial pneumonia. Intensive Care Med. **30:**976–979.
19. **Boselli, E., D. Breilh, T. Rimmele, J. C. Poupelin, M. C. Saux, D. Chassard, and B. Allaouchiche.** 2004. Plasma and lung concentrations of ceftazidime administered in continuous infusion to critically ill patients with severe nosocomial pneumonia. Intensive Care Med. **30:**989–991.
20. **Boyce, J. M., G. Potter-Bynoe, L. Dziobek, and S. L. Solomon.** 1991. Nosocomial pneumonia in Medicare patients. Hospital costs and reimbursement patterns under the prospective payment system. Arch. Intern. Med. **151:**1109–1114.
21. **Brochard, L., J. Mancebo, M. Wysocki, F. Lofaso, G. Conti, A. Rauss, G. Simonneau, S. Benito, A. Gasparetto, F. Lemaire, et al.** 1995. Noninvasive ventilation for acute exacerbations of chronic obstructive pulmonary disease. N. Engl. J. Med. **333:**817–822.
22. **Brook, A. D., T. S. Ahrens, R. Schaiff, D. Prentice, G. Sherman, W. Shannon, and M. H. Kollef.** 1999. Effect of a nursing-implemented sedation protocol on the duration of mechanical ventilation. Crit. Care Med. **27:**2609–2615.
23. **Bryan, C. S.** 1999. Nosocomial pneumonia: blood cultures remain useful. Chest **116:**859–860.
24. **Bryan, C. S., and K. L. Reynolds.** 1984. Bacteremic nosocomial pneumonia. Analysis of 172 episodes from a single metropolitan area. Am. Rev. Respir. Dis. **129:**668–671.

25. **Butler, K. L., K. E. Sinclair, V. J. Henderson, G. McKinney, D. A. Mesidor, I. Katon-Benitez, and W. L. Weaver.** 1999. The chest radiograph in critically ill surgical patients is inaccurate in predicting ventilator-associated pneumonia. Am. Surg. **65:**805–810.
26. **Campbell, G. D., Jr.** 2000. Blinded invasive diagnostic procedures in ventilator-associated pneumonia. Chest **117:**207S–211S.
27. **Carlucci, A., J. C. Richard, M. Wysocki, E. Lepage, and L. Brochard.** 2001. Noninvasive versus conventional mechanical ventilation. An epidemiologic survey. Am. J. Respir. Crit. Care Med. **163:**874–880.
28. **Chastre, J.** 2005. Conference summary: ventilator-associated pneumonia. Respir. Care **50:**975–983.
29. **Chastre, J., A. Combes, and C. E. Luyt.** 2005. The invasive (quantitative) diagnosis of ventilator-associated pneumonia. Respir. Care **50:**797–812.
30. **Chastre, J., and J. Y. Fagon.** 2002. Ventilator-associated pneumonia. Am. J. Respir. Crit. Care Med. **165:**867–903.
31. **Chastre, J., J. Y. Fagon, M. Bornet-Lecso, S. Calvat, M. C. Dombret, R. al Khani, F. Basset, and C. Gibert.** 1995. Evaluation of bronchoscopic techniques for the diagnosis of nosocomial pneumonia. Am. J. Respir. Crit. Care Med. **152:**231–240.
32. **Chastre, J., M. Wolff, J. Y. Fagon, S. Chevret, F. Thomas, D. Wermert, E. Clementi, J. Gonzalez, D. Jusserand, P. Asfar, D. Perrin, F. Fieux, and S. Aubas.** 2003. Comparison of 8 vs 15 days of antibiotic therapy for ventilator-associated pneumonia in adults: a randomized trial. JAMA **290:**2588–2598.
33. **Chollet-Martin, S., P. Montravers, C. Gibert, C. Elbim, J. M. Desmonts, J. Y. Fagon, and M. A. Gougerot-Pocidalo.** 1993. High levels of interleukin-8 in the blood and alveolar spaces of patients with pneumonia and adult respiratory distress syndrome. Infect. Immun. **61:**4553–4559.
34. **Chollet-Martin, S., P. Montravers, C. Gibert, C. Elbim, J. M. Desmonts, J. Y. Fagon, and M. A. Gougerot-Pocidalo.** 1992. Subpopulation of hyperresponsive polymorphonuclear neutrophils in patients with adult respiratory distress syndrome. Role of cytokine production. Am. Rev. Respir. Dis. **146:**990–996.
35. **Combes, P., B. Fauvage, and C. Oleyer.** 2000. Nosocomial pneumonia in mechanically ventilated patients, a prospective randomised evaluation of the Stericath closed suctioning system. Intensive Care Med. **26:**878–882.
36. **Cometta, A., J. D. Baumgartner, D. Lew, W. Zimmerli, D. Pittet, P. Chopart, U. Schaad, C. Herter, P. Eggimann, O. Huber, et al.** 1994. Prospective randomized comparison of imipenem monotherapy with imipenem plus netilmicin for treatment of severe infections in nonneutropenic patients. Antimicrob. Agents Chemother. **38:**1309–1313.
37. **Cook, D., G. Guyatt, J. Marshall, D. Leasa, H. Fuller, R. Hall, S. Peters, F. Rutledge, L. Griffith, A. McLellan, G. Wood, A. Kirby, et al.** 1998. A comparison of sucralfate and ranitidine for the prevention of upper gastrointestinal bleeding in patients requiring mechanical ventilation. N. Engl. J. Med. **338:**791–797.
38. **Cook, D., and L. Mandell.** 2000. Endotracheal aspiration in the diagnosis of ventilator-associated pneumonia. Chest **117:**195S–197S.
39. **Cook, D. J., S. D. Walter, R. J. Cook, L. E. Griffith, G. H. Guyatt, D. Leasa, R. Z. Jaeschke, and C. Brun-Buisson.** 1998. Incidence of and risk factors for ventilator-associated pneumonia in critically ill patients. Ann. Intern. Med. **129:**433–440.
40. **Corley, D. E., S. H. Kirtland, R. H. Winterbauer, S. P. Hammar, D. H. Dail, D. E. Bauermeister, and J. W. Bolen.** 1997. Reproducibility of the histologic diagnosis of pneumonia among a panel of four pathologists: analysis of a gold standard. Chest **112:**458–465.
41. **Craig, C. P., and S. Connelly.** 1984. Effect of intensive care unit nosocomial pneumonia on duration of stay and mortality. Am. J. Infect Control **12:** 233–238.
42. **Craven, D. E., L. M. Kunches, V. Kilinsky, D. A. Lichtenberg, B. J. Make, and W. R. McCabe.** 1986. Risk factors for pneumonia and fatality in patients receiving continuous mechanical ventilation. Am. Rev. Respir. Dis. **133:**792–796.
43. **Cunnion, K. M., D. J. Weber, W. E. Broadhead, L. C. Hanson, C. F. Pieper, and W. A. Rutala.** 1996. Risk factors for nosocomial pneumonia: comparing adult critical-care populations. Am. J. Respir. Crit. Care Med. **153:**158–162.
44. **D'Amico, R., S. Pifferi, C. Leonetti, V. Torri, A. Tinazzi, and A. Liberati.** 1998. Effectiveness of antibiotic prophylaxis in critically ill adult patients: systematic review of randomised controlled trials. Br. Med J. **316:**1275–1285.
45. **Davis, K., Jr., S. L. Evans, R. S. Campbell, J. A. Johannigman, F. A. Luchette, D. T. Porembka, and R. D. Branson.** 2000. Prolonged use of heat and moisture exchangers does not affect device efficiency or frequency rate of nosocomial pneumonia. Crit. Care Med. **28:**1412–1418.
46. **deBoisblanc, B. P., M. Castro, B. Everret, J. Grender, C. D. Walker, and W. R. Summer.** 1993. Effect of air-supported, continuous, postural oscillation on the risk of early ICU pneumonia in nontraumatic critical illness. Chest **103:**1543–1547.
47. **de Jonge, E., M. J. Schultz, L. Spanjaard, P. M. Bossuyt, M. B. Vroom, J. Dankert, and J. Kesecioglu.** 2003. Effects of selective decontamination of digestive tract on mortality and acquisition of resistant bacteria in intensive care: a randomised controlled trial. Lancet **362:**1011–1016.
48. **Demarest, G. B., W. W. Schmidt-Nowara, L. W. Vance, and A. R. Altman.** 1989. Use of the kinetic treatment table to prevent the pulmonary complications of multiple trauma. West. J. Med. **150:**35–38.
49. **Dennesen, P. J., A. J. van der Ven, A. G. Kessels, G. Ramsay, and M. J. Bonten.** 2001. Resolution of infectious parameters after antimicrobial therapy in patients with ventilator-associated pneumonia. Am. J. Respir. Crit. Care Med. **163:**1371–1375.
50. **Deppe, S. A., J. W. Kelly, L. L. Thoi, J. H. Chudy, R. N. Longfield, J. P. Ducey, C. L. Truwit, and M. R. Antopol.** 1990. Incidence of colonization, nosocomial pneumonia, and mortality in critically ill patients using a Trach Care closed-suction system versus an open-suction system: prospective, randomized study. Crit. Care Med. **18:**1389–1393.
51. **DeRiso, A. J., II, J. S. Ladowski, T. A. Dillon, J. W. Justice, and A. C. Peterson.** 1996. Chlorhexidine gluconate 0.12% oral rinse reduces the incidence of total nosocomial respiratory infection and nonprophylactic systemic antibiotic use in patients undergoing heart surgery. Chest **109:** 1556–1561.
52. **Dodek, P., S. Keenan, D. Cook, D. Heyland, M. Jacka, L. Hand, J. Muscedere, D. Foster, N. Mehta, R. Hall, and C. Brun-Buisson.** 2004. Evidence-based clinical practice guideline for the prevention of ventilator-associated pneumonia. Ann. Intern. Med. **141:**305–313.
53. **Dotson, R. G., and S. K. Pingleton.** 1993. The effect of antibiotic therapy on recovery of intracellular bacteria from bronchoalveolar lavage in suspected ventilator-associated nosocomial pneumonia. Chest **103:**541–546.
54. **Drakulovic, M. B., A. Torres, T. T. Bauer, J. M. Nicolas, S. Nogue, and M. Ferrer.** 1999. Supine body position as a risk factor for nosocomial pneumonia in mechanically ventilated patients: a randomised trial. Lancet **354:** 1851–1858.
55. **Dreyfuss, D., K. Djedaini, I. Gros, L. Mier, G. Le Bourdelles, Y. Cohen, P. Estagnasie, F. Coste, and Y. Boussougant.** 1995. Mechanical ventilation with heated humidifiers or heat and moisture exchangers: effects on patient colonization and incidence of nosocomial pneumonia. Am. J. Respir. Crit. Care Med. **151:**986–992.
56. **Dreyfuss, D., K. Djedaini, P. Weber, P. Brun, J. J. Lanore, J. Rahmani, Y. Boussougant, and F. Coste.** 1991. Prospective study of nosocomial pneumonia and of patient and circuit colonization during mechanical ventilation with circuit changes every 48 hours versus no change. Am. Rev. Respir. Dis. **143:**738–743.
57. **du Moulin, G. C., D. G. Paterson, J. Hedley-Whyte, and A. Lisbon.** 1982. Aspiration of gastric bacteria in antacid-treated patients: a frequent cause of postoperative colonisation of the airway. Lancet **i:**242–245.
58. **el-Ebiary, M., A. Torres, N. Fabregas, J. P. de la Bellacasa, J. Gonzalez, J. Ramirez, D. del Bano, C. Hernandez, and M. T. Jimenez de Anta.** 1997. Significance of the isolation of Candida species from respiratory samples in critically ill, non-neutropenic patients. An immediate postmortem histologic study. Am. J. Respir. Crit. Care Med. **156:**583–590.
59. **Ely, E. W., M. O. Meade, E. F. Haponik, M. H. Kollef, D. J. Cook, G. H. Guyatt, and J. K. Stoller.** 2001. Mechanical ventilator weaning protocols driven by nonphysician health-care professionals: evidence-based clinical practice guidelines. Chest **120:**454S–463S.
60. **Fabregas, N., S. Ewig, A. Torres, M. El-Ebiary, J. Ramirez, J. P. de La Bellacasaqq, T. Bauer, and H. Cabello.** 1999. Clinical diagnosis of ventilator associated pneumonia revisited: comparative validation using immediate post-mortem lung biopsies. Thorax **54:**867–873.
61. **Fabregas, N., A. Torres, M. El-Ebiary, J. Ramirez, C. Hernandez, J. Gonzalez, J. P. de la Bellacasa, J. de Anta, and R. Rodriguez-Roisin.** 1996. Histopathologic and microbiologic aspects of ventilator-associated pneumonia. Anesthesiology **84:**760–771.
62. **Fagon, J. Y., J. Chastre, Y. Domart, J. L. Trouillet, J. Pierre, C. Darne, and C. Gibert.** 1989. Nosocomial pneumonia in patients receiving continuous mechanical ventilation. Prospective analysis of 52 episodes with use of a protected specimen brush and quantitative culture techniques. Am. Rev. Respir. Dis. **139:**877–884.
63. **Fagon, J. Y., J. Chastre, A. J. Hance, M. Guiguet, J. L. Trouillet, Y. Domart, J. Pierre, and C. Gibert.** 1988. Detection of nosocomial lung infection in ventilated patients. Use of a protected specimen brush and quantitative culture techniques in 147 patients. Am. Rev. Respir. Dis. **138:**110–116.
64. **Fagon, J. Y., J. Chastre, M. Wolff, C. Gervais, S. Parer-Aubas, F. Stephan, T. Similowski, A. Mercat, J. L. Diehl, J. P. Sollet, and A. Tenaillon.** 2000. Invasive and noninvasive strategies for management of suspected ventilator-associated pneumonia. A randomized trial. Ann. Intern. Med. **132:**621–630.
65. **Fartoukh, M., B. Maitre, S. Honore, C. Cerf, J. R. Zahar, and C. Brun-Buisson.** 2003. Diagnosing pneumonia during mechanical ventilation: the clinical pulmonary infection score revisited. Am. J. Respir. Crit. Care Med. **168:**173–179.
66. **Feldman, C., M. Kassel, J. Cantrell, S. Kaka, R. Morar, A. Goolam Mahomed, and J. I. Philips.** 1999. The presence and sequence of endotracheal tube colonization in patients undergoing mechanical ventilation. Eur. Respir. J. **13:**546–551.
67. **Ferrer, M., A. Esquinas, F. Arancibia, T. T. Bauer, G. Gonzalez, A. Carrillo, R. Rodriguez-Roisin, and A. Torres.** 2003. Noninvasive ventilation during

persistent weaning failure: a randomized controlled trial. Am. J. Respir. Crit. Care Med. **168:**70–76.

68. **Ferrer, M., A. Torres, J. Gonzalez, J. Puig de la Bellacasa, M. el-Ebiary, M. Roca, J. M. Gatell, and R. Rodriguez-Roisin.** 1994. Utility of selective digestive decontamination in mechanically ventilated patients. Ann. Intern. Med. **120:**389–395.
69. **Fink, M. P., C. M. Helsmoortel, K. L. Stein, P. C. Lee, and S. M. Cohn.** 1990. The efficacy of an oscillating bed in the prevention of lower respiratory tract infection in critically ill victims of blunt trauma. A prospective study. Chest **97:**132–137.
70. **Gallego, M., and J. Rello.** 1999. Diagnostic testing for ventilator-associated pneumonia. Clin. Chest Med. **20:**671–679.
71. **Gastinne, H., M. Wolff, F. Delatour, F. Faurisson, S. Chevret, et al.** 1992. A controlled trial in intensive care units of selective decontamination of the digestive tract with nonabsorbable antibiotics. N. Engl. J. Med. **326:**594–599.
72. **Gentilello, L., D. A. Thompson, A. S. Tonnesen, D. Hernandez, A. S. Kapadia, S. J. Allen, B. A. Houtchens, and M. E. Miner.** 1988. Effect of a rotating bed on the incidence of pulmonary complications in critically ill patients. Crit. Care Med. **16:**783–786.
73. **Gerbeaux, P., V. Ledoray, A. Boussuges, F. Molenat, P. Jean, and J. M. Sainty.** 1998. Diagnosis of nosocomial pneumonia in mechanically ventilated patients: repeatability of the bronchoalveolar lavage. Am. J. Respir. Crit. Care Med. **157:**76–80.
74. **Girou, E., F. Schortgen, C. Delclaux, C. Brun-Buisson, F. Blot, Y. Lefort, F. Lemaire, and L. Brochard.** 2000. Association of noninvasive ventilation with nosocomial infections and survival in critically ill patients. JAMA **284:**2361–2367.
75. **Gruson, D., G. Hilbert, F. Vargas, R. Valentino, C. Bebear, A. Allery, C. Bebear, G. Gbikpi-Benissan, and J. P. Cardinaud.** 2000. Rotation and restricted use of antibiotics in a medical intensive care unit. Impact on the incidence of ventilator-associated pneumonia caused by antibiotic-resistant gram-negative bacteria. Am. J. Respir. Crit. Care Med. **162:**837–843.
76. **Guerin, C., R. Girard, C. Chemorin, R. De Varax, and G. Fournier.** 1997. Facial mask noninvasive mechanical ventilation reduces the incidence of nosocomial pneumonia. A prospective epidemiological survey from a single ICU. Intensive Care Med. **23:**1024–1032.
77. **Hammond, J. M., P. D. Potgieter, G. L. Saunders, and A. A. Forder.** 1992. Double-blind study of selective decontamination of the digestive tract in intensive care. Lancet **340:**5–9.
78. **Hayon, J., C. Figliolini, A. Combes, J. L. Trouillet, N. Kassis, M. C. Dombret, C. Gibert, and J. Chastre.** 2002. Role of serial routine microbiologic culture results in the initial management of ventilator-associated pneumonia. Am. J. Respir. Crit. Care Med. **165:**41–46.
79. **Heyland, D. K., D. J. Cook, J. Marshall, M. Heule, B. Guslits, J. Lang, R. Jaeschke, et al.** 1999. The clinical utility of invasive diagnostic techniques in the setting of ventilator-associated pneumonia. Chest **115:**1076–1084.
80. **Heyland, D. K., J. W. Drover, R. Dhaliwal, and J. Greenwood.** 2002. Optimizing the benefits and minimizing the risks of enteral nutrition in the critically ill: role of small bowel feeding. J Parenter. Enteral. Nutr. **26:**S51–S57.
81. **Hilbert, G., D. Gruson, F. Vargas, R. Valentino, G. Gbikpi-Benissan, M. Dupon, J. Reiffers, and J. P. Cardinaud.** 2001. Noninvasive ventilation in immunosuppressed patients with pulmonary infiltrates, fever, and acute respiratory failure. N. Engl. J. Med. **344:**481–487.
82. **Hill, J. D., J. L. Ratliff, J. C. Parrott, M. Lamy, R. J. Fallat, E. Koeniger, E. M. Yaeger, and G. Whitmer.** 1976. Pulmonary pathology in acute respiratory insufficiency: lung biopsy as a diagnostic tool. J. Thoracic Cardiovasc. Surg. **71:**64–71.
83. **Holzapfel, L., S. Chevret, G. Madinier, F. Ohen, G. Demingeon, A. Coupry, and M. Chaudet.** 1993. Influence of long-term oro- or nasotracheal intubation on nosocomial maxillary sinusitis and pneumonia: results of a prospective, randomized, clinical trial. Crit. Care Med. **21:**1132–1138.
84. **Hyatt, J. M., P. S. McKinnon, G. S. Zimmer, and J. J. Schentag.** 1995. The importance of pharmacokinetic/pharmacodynamic surrogate markers to outcome. Focus on antibacterial agents. Clin. Pharmacokinet. **28:**143–160.
85. **Ibanez, J., A. Penafiel, J. M. Raurich, P. Marse, R. Jorda, and F. Mata.** 1992. Gastroesophageal reflux in intubated patients receiving enteral nutrition: effect of supine and semirecumbent positions. J. Parenter. Enteral. Nutr. **16:**419–422.
86. **Ibrahim, E. H., L. Mehringer, D. Prentice, G. Sherman, R. Schaiff, V. Fraser, and M. H. Kollef.** 2002. Early versus late enteral feeding of mechanically ventilated patients: results of a clinical trial. J. Parenter. Enteral. Nutr. **26:**174–181.
87. **Ibrahim, E. H., S. Ward, G. Sherman, and M. H. Kollef.** 2000. A comparative analysis of patients with early-onset vs late-onset nosocomial pneumonia in the ICU setting. Chest **117:**1434–1442.
88. **Ibrahim, E. H., S. Ward, G. Sherman, R. Schaiff, V. J. Fraser, and M. H. Kollef.** 2001. Experience with a clinical guideline for the treatment of ventilator-associated pneumonia. Crit. Care Med. **29:**1109–1115.
89. **Inglis, T. J., M. R. Millar, J. G. Jones, and D. A. Robinson.** 1989. Tracheal tube biofilm as a source of bacterial colonization of the lung. J. Clin. Microbiol. **27:**2014–2018.
90. **Iregui, M., S. Ward, G. Sherman, V. J. Fraser, and M. H. Kollef.** 2002. Clinical importance of delays in the initiation of appropriate antibiotic treatment for ventilator-associated pneumonia. Chest **122:**262–268.
91. **Johanson, W. G., Jr., A. K. Pierce, J. P. Sanford, and G. D. Thomas.** 1972. Nosocomial respiratory infections with gram-negative bacilli. The significance of colonization of the respiratory tract. Ann. Intern. Med. **77:**701–706.
92. **Johanson, W. G., Jr., J. J. Seidenfeld, R. de los Santos, J. J. Coalson, and P. Gomez.** 1988. Prevention of nosocomial pneumonia using topical and parenteral antimicrobial agents. Am. Rev. Respir. Dis. **137:**265–272.
93. **Johnson, K. L., P. A. Kearney, S. B. Johnson, J. B. Niblett, N. L. MacMillan, and R. E. McClain.** 1994. Closed versus open endotracheal suctioning: costs and physiologic consequences. Crit. Care Med. **22:**658–666.
94. **Jorda, R., F. Parras, J. Ibanez, J. Reina, J. Bergada, and J. M. Raurich.** 1993. Diagnosis of nosocomial pneumonia in mechanically ventilated patients by the blind protected telescoping catheter. Intensive Care Med. **19:**377–382.
95. **Jourdain, B., A. Novara, M. L. Joly-Guillou, M. C. Dombret, S. Calvat, J. L. Trouillet, C. Gibert, and J. Chastre.** 1995. Role of quantitative cultures of endotracheal aspirates in the diagnosis of nosocomial pneumonia. Am. J. Respir. Crit. Care Med. **152:**241–246.
96. **Kappstein, I., G. Schulgen, U. Beyer, K. Geiger, M. Schumacher, and F. D. Daschner.** 1992. Prolongation of hospital stay and extra costs due to ventilator-associated pneumonia in an intensive care unit. Eur. J. Clin. Microbiol. Infect. Dis. **11:**504–508.
97. **Kirschenbaum, L., E. Azzi, T. Sfeir, P. Tietjen, and M. Astiz.** 2002. Effect of continuous lateral rotational therapy on the prevalence of ventilator-associated pneumonia in patients requiring long-term ventilatory care. Crit. Care Med. **30:**1983–1986.
98. **Kirtland, S. H., D. E. Corley, R. H. Winterbauer, S. C. Springmeyer, K. R. Casey, N. B. Hampson, and D. F. Dreis.** 1997. The diagnosis of ventilator-associated pneumonia: a comparison of histologic, microbiologic, and clinical criteria. Chest **112:**445–457.
99. **Kirton, O. C., B. DeHaven, J. Morgan, O. Morejon, and J. Civetta.** 1997. A prospective, randomized comparison of an in-line heat moisture exchange filter and heated wire humidifiers: rates of ventilator-associated early-onset (community-acquired) or late-onset (hospital-acquired) pneumonia and incidence of endotracheal tube occlusion. Chest **112:**1055–1059.
100. **Koerner, R. J.** 1997. Contribution of endotracheal tubes to the pathogenesis of ventilator-associated pneumonia. J. Hosp. Infect **35:**83–89.
101. **Kollef, M. H.** 2004. Prevention of hospital-associated pneumonia and ventilator-associated pneumonia. Crit. Care Med. **32:**1396–1405.
102. **Kollef, M. H.** 1993. Ventilator-associated pneumonia. A multivariate analysis. JAMA **270:**1965–1970.
103. **Kollef, M. H.** 2005. What is ventilator-associated pneumonia and why is it important? Respir. Care **50:**714–724.
104. **Kollef, M. H., K. R. Bock, R. D. Richards, and M. L. Hearns.** 1995. The safety and diagnostic accuracy of minibronchoalveolar lavage in patients with suspected ventilator-associated pneumonia. Ann. Intern. Med. **122:**743–748.
105. **Kollef, M. H., and S. T. Micek.** 2005. Strategies to prevent antimicrobial resistance in the intensive care unit. Crit. Care Med. **33:**1845–1853.
106. **Kollef, M. H., D. Prentice, S. D. Shapiro, V. J. Fraser, P. Silver, E. Trovillion, P. Weilitz, B. von Harz, and R. St. John.** 1997. Mechanical ventilation with or without daily changes of in-line suction catheters. Am. J. Respir. Crit. Care Med. **156:**466–472.
107. **Kollef, M. H., S. D. Shapiro, V. Boyd, P. Silver, B. Von Harz, E. Trovillion, and D. Prentice.** 1998. A randomized clinical trial comparing an extended-use hygroscopic condenser humidifier with heated-water humidification in mechanically ventilated patients. Chest **113:**759–767.
108. **Kollef, M. H., S. D. Shapiro, V. J. Fraser, P. Silver, D. M. Murphy, E. Trovillion, M. L. Hearns, R. D. Richards, L. Cracchilo, and L. Hossin.** 1995. Mechanical ventilation with or without 7-day circuit changes. A randomized controlled trial. Ann. Intern. Med. **123:**168–174.
109. **Kollef, M. H., P. Silver, D. M. Murphy, and E. Trovillion.** 1995. The effect of late-onset ventilator-associated pneumonia in determining patient mortality. Chest **108:**1655–1662.
110. **Kollef, M. H., N. J. Skubas, and T. M. Sundt.** 1999. A randomized clinical trial of continuous aspiration of subglottic secretions in cardiac surgery patients. Chest **116:**1339–1346.
111. **Kollef, M. H., J. Vlasnik, L. Sharpless, C. Pasque, D. Murphy, and V. Fraser.** 1997. Scheduled change of antibiotic classes: a strategy to decrease the incidence of ventilator-associated pneumonia. Am. J. Respir. Crit. Care Med. **156:**1040–1048.
112. **Kollef, M. H., S. Ward, G. Sherman, D. Prentice, R. Schaiff, W. Huey, and V. J. Fraser.** 2000. Inadequate treatment of nosocomial infections is associated with certain empiric antibiotic choices. Crit. Care Med. **28:**3456–3464.
113. **Kress, J. P., A. S. Pohlman, M. F. O'Connor, and J. B. Hall.** 2000. Daily

interruption of sedative infusions in critically ill patients undergoing mechanical ventilation. N. Engl. J. Med. **342:**1471–1477.
114. **Krueger, W. A., F. P. Lenhart, G. Neeser, G. Ruckdeschel, H. Schreckhase, H. J. Eissner, H. Forst, J. Eckart, K. Peter, and K. E. Unertl.** 2002. Influence of combined intravenous and topical antibiotic prophylaxis on the incidence of infections, organ dysfunctions, and mortality in critically ill surgical patients: a prospective, stratified, randomized, double-blind, placebo-controlled clinical trial. Am. J. Respir. Crit. Care Med. **166:**1029–1037.
115. **Leal-Noval, S. R., E. Alfaro-Rodriguez, F. Murillo-Cabeza, J. Garnacho-Montero, J. Rey-Perez, and M. A. Munoz-Sanchez.** 1992. Diagnostic value of the blind brush in mechanically ventilated patients with nosocomial pneumonia. Intensive Care Med. **18:**410–414.
116. **Lefcoe, M. S., G. A. Fox, D. J. Leasa, R. K. Sparrow, and D. G. McCormack.** 1994. Accuracy of portable chest radiography in the critical care setting. Diagnosis of pneumonia based on quantitative cultures obtained from protected brush catheter. Chest **105:**885–887.
117. **Liesching, T., H. Kwok, and N. S. Hill.** 2003. Acute applications of noninvasive positive pressure ventilation. Chest **124:**699–713.
118. **Lightowler, J. V., J. A. Wedzicha, M. W. Elliott, and F. S. Ram.** 2003. Non-invasive positive pressure ventilation to treat respiratory failure resulting from exacerbations of chronic obstructive pulmonary disease: Cochrane systematic review and meta-analysis. Br. Med. J. **326:**185.
119. **Lingnau, W., J. Berger, F. Javorsky, M. Fille, F. Allerberger, and H. Benzer.** 1998. Changing bacterial ecology during a five-year period of selective intestinal decontamination. J. Hosp. Infect. **39:**195–206.
120. **Lipman, J., S. C. Wallis, and C. Rickard.** 1999. Low plasma cefepime levels in critically ill septic patients: pharmacokinetic modeling indicates improved troughs with revised dosing. Antimicrob. Agents Chemother. **43:**2559–2561.
121. **Long, M. N., G. Wickstrom, A. Grimes, C. F. Benton, B. Belcher, and A. M. Stamm.** 1996. Prospective, randomized study of ventilator-associated pneumonia in patients with one versus three ventilator circuit changes per week. Infect. Control Hosp. Epidemiol. **17:**14–19.
122. **Luna, C. M., D. Blanzaco, M. S. Niederman, W. Matarucco, N. C. Baredes, P. Desmery, F. Palizas, G. Menga, F. Rios, and C. Apezteguia.** 2003. Resolution of ventilator-associated pneumonia: prospective evaluation of the clinical pulmonary infection score as an early clinical predictor of outcome. Crit. Care Med. **31:**676–682.
123. **Luna, C. M., and M. S. Niederman.** 2002. What is the natural history of resolution of nosocomial pneumonia? Semin. Respir. Crit. Care Med. **23:**471–480.
124. **Luna, C. M., A. Videla, J. Mattera, C. Vay, A. Famiglietti, P. Vujacich, and M. S. Niederman.** 1999. Blood cultures have limited value in predicting severity of illness and as a diagnostic tool in ventilator-associated pneumonia. Chest **116:**1075–1084.
125. **Luna, C. M., P. Vujacich, M. S. Niederman, C. Vay, C. Gherardi, J. Matera, and E. C. Jolly.** 1997. Impact of BAL data on the therapy and outcome of ventilator-associated pneumonia. Chest **111:**676–685.
126. **Mahul, P., C. Auboyer, R. Jospe, A. Ros, C. Guerin, Z. el Khouri, M. Galliez, A. Dumont, and O. Gaudin.** 1992. Prevention of nosocomial pneumonia in intubated patients: respective role of mechanical subglottic secretions drainage and stress ulcer prophylaxis. Intensive Care Med. **18:**20–25.
127. **Marelich, G. P., S. Murin, F. Battistella, J. Inciardi, T. Vierra, and M. Roby.** 2000. Protocol weaning of mechanical ventilation in medical and surgical patients by respiratory care practitioners and nurses: effect on weaning time and incidence of ventilator-associated pneumonia. Chest **118:**459–467.
128. **Marik, P. E., and W. J. Brown.** 1995. A comparison of bronchoscopic vs blind protected specimen brush sampling in patients with suspected ventilator-associated pneumonia. Chest **108:**203–207.
129. **Markowicz, P., M. Wolff, K. Djedaini, Y. Cohen, J. Chastre, C. Delclaux, J. Merrer, B. Herman, B. Veber, A. Fontaine, D. Dreyfuss, et al.** 2000. Multicenter prospective study of ventilator-associated pneumonia during acute respiratory distress syndrome. Incidence, prognosis, and risk factors. Am. J. Respir. Crit. Care Med. **161:**1942–1948.
130. **Marquette, C. H., M. C. Copin, F. Wallet, R. Neviere, F. Saulnier, D. Mathieu, A. Durocher, P. Ramon, and A. B. Tonnel.** 1995. Diagnostic tests for pneumonia in ventilated patients: prospective evaluation of diagnostic accuracy using histology as a diagnostic gold standard. Am. J. Respir. Crit. Care Med. **151:**1878–1888.
131. **Marquette, C. H., F. Herengt, D. Mathieu, F. Saulnier, R. Courcol, and P. Ramon.** 1993. Diagnosis of pneumonia in mechanically ventilated patients. Repeatability of the protected specimen brush. Am. Rev. Respir. Dis. **147:**211–214.
132. **Martin, C., G. Perrin, M. J. Gevaudan, P. Saux, and F. Gouin.** 1990. Heat and moisture exchangers and vaporizing humidifiers in the intensive care unit. Chest **97:**144–149.
133. **Mayhall, C. G.** 1997. Nosocomial pneumonia. Diagnosis and prevention. Infect. Dis. Clin. N. Am. **11:**427–457.
134. **McEachern, R., and G. D. Campbell, Jr.** 1998. Hospital-acquired pneumonia: epidemiology, etiology, and treatment. Infect. Dis. Clin. N. Am. **12:**761–779.
135. **Meduri, G. U.** 1995. Diagnosis and differential diagnosis of ventilator-associated pneumonia. Clin. Chest Med. **16:**61–93.
136. **Meduri, G. U., J. M. Belenchia, R. J. Estes, R. G. Wunderink, M. el Torky, and K. V. Leeper, Jr.** 1991. Fibroproliferative phase of ARDS. Clinical findings and effects of corticosteroids. Chest **100:**943–952.
137. **Meduri, G. U., and J. Chastre.** 1992. The standardization of bronchoscopic techniques for ventilator-associated pneumonia. Chest **102:**557S–564S.
138. **Meduri, G. U., and W. G. Johanson, Jr.** 1992. International Consensus Conference: clinical investigation of ventilator-associated pneumonia. Introduction. Chest **102:**551S–552S.
139. **Meduri, G. U., G. L. Mauldin, R. G. Wunderink, K. V. Leeper, Jr., C. B. Jones, E. Tolley, and G. Mayhall.** 1994. Causes of fever and pulmonary densities in patients with clinical manifestations of ventilator-associated pneumonia. Chest **106:**221–235.
140. **Meduri, G. U., R. C. Reddy, T. Stanley, and F. El-Zeky.** 1998. Pneumonia in acute respiratory distress syndrome. A prospective evaluation of bilateral bronchoscopic sampling. Am. J. Respir. Crit. Care Med. **158:**870–875.
141. **Memish, Z. A., G. A. Oni, W. Djazmati, G. Cunningham, and M. W. Mah.** 2001. A randomized clinical trial to compare the effects of a heat and moisture exchanger with a heated humidifying system on the occurrence rate of ventilator-associated pneumonia. Am. J. Infect. Control **29:**301–305.
142. **Mertens, A. H., J. M. Nagler, D. I. Galdermans, H. R. Slabbynck, B. Weise, and D. Coolen.** 1998. Quality assessment of protected specimen brush samples by microscopic cell count. Am. J. Respir. Crit. Care Med. **157:**1240–1243.
143. **Messori, A., S. Trippoli, M. Vaiani, M. Gorini, and A. Corrado.** 2000. Bleeding and pneumonia in intensive care patients given ranitidine and sucralfate for prevention of stress ulcer: meta-analysis of randomised controlled trials. Br. Med. J. **321:**1103–1106.
144. **Micek, S. T., S. Ward, V. J. Fraser, and M. H. Kollef.** 2004. A randomized controlled trial of an antibiotic discontinuation policy for clinically suspected ventilator-associated pneumonia. Chest **125:**1791–1799.
145. **Michaud, S., S. Suzuki, and S. Harbarth.** 2002. Effect of design-related bias in studies of diagnostic tests for ventilator-associated pneumonia. Am. J. Respir. Crit. Care Med. **166:**1320–1325.
146. **Michel, F., B. Franceschini, P. Berger, J. M. Arnal, M. Gainnier, J. M. Sainty, and L. Papazian.** 2005. Early antibiotic treatment for BAL-confirmed ventilator-associated pneumonia: a role for routine endotracheal aspirate cultures. Chest **127:**589–597.
147. **Misset, B., M. D. Kitzis, G. Conscience, F. Goldstein, A. Fourrier, and J. Carlet.** 1994. Mechanisms of failure to decontaminate the gut with polymixin E, gentamicin and amphotericin B in patients in intensive care. Eur. J. Clin. Microbiol. Infect. Dis. **13:**165–170.
148. **Misset, B., M. D. Kitzis, P. Mahe, G. Conscience, F. W. Goldstein, A. Fourrier, and J. Carlet.** 1993. Bacteriological side effects of gut decontamination with polymyxin E, gentamicin, and amphotericin B. Infect. Control Hosp. Epidemiol. **14:**62–64.
149. **Monso, E., J. Ruiz, A. Rosell, J. Manterola, J. Fiz, J. Morera, and V. Ausina.** 1995. Bacterial infection in chronic obstructive pulmonary disease. A study of stable and exacerbated outpatients using the protected specimen brush. Am. J. Respir. Crit. Care Med. **152:**1316–1320.
150. **Montravers, P., J. Y. Fagon, J. Chastre, M. Lecso, M. C. Dombret, J. L. Trouillet, and C. Gibert.** 1993. Follow-up protected specimen brushes to assess treatment in nosocomial pneumonia. Am. Rev. Respir. Dis. **147:**38–44.
151. **Moore, R. D., P. S. Lietman, and C. R. Smith.** 1987. Clinical response to aminoglycoside therapy: importance of the ratio of peak concentration to minimal inhibitory concentration. J. Infect. Dis. **155:**93–99.
152. **Moore, R. D., C. R. Smith, and P. S. Lietman.** 1984. The association of aminoglycoside plasma levels with mortality in patients with gram-negative bacteremia. J. Infect. Dis. **149:**443–448.
153. **Morris, A. J., D. C. Tanner, and L. B. Reller.** 1993. Rejection criteria for endotracheal aspirates from adults. J. Clin. Microbiol. **31:**1027–1029.
154. **Nathens, A. B., and J. C. Marshall.** 1999. Selective decontamination of the digestive tract in surgical patients: a systematic review of the evidence. Arch. Surg. **134:**170–176.
155. **Niederman, M. S., D. E. Craven, A. M. Fein, and D. E. Schultz.** 1990. Pneumonia in the critically ill hospitalized patient. Chest **97:**170–181.
156. **Nouira, S., S. Marghli, M. Belghith, L. Besbes, S. Elatrous, and F. Abroug.** 2001. Once daily oral ofloxacin in chronic obstructive pulmonary disease exacerbation requiring mechanical ventilation: a randomised placebo-controlled trial. Lancet **358:**2020–2025.
157. **Nourdine, K., P. Combes, M. J. Carton, P. Beuret, A. Cannamela, and J. C. Ducreux.** 1999. Does noninvasive ventilation reduce the ICU nosocomial infection risk? A prospective clinical survey. Intensive Care Med. **25:**567–573.
158. **Nseir, S., C. Di Pompeo, P. Pronnier, S. Beague, T. Onimus, F. Saulnier, B. Grandbastien, D. Mathieu, M. Delvallez-Roussel, and A. Durocher.** 2002. Nosocomial tracheobronchitis in mechanically ventilated patients: incidence, aetiology and outcome. Eur. Respir. J. **20:**1483–1489.

159. **Orozco-Levi, M., A. Torres, M. Ferrer, C. Piera, M. el-Ebiary, J. P. de la Bellacasa, and R. Rodriguez-Roisin.** 1995. Semirecumbent position protects from pulmonary aspiration but not completely from gastroesophageal reflux in mechanically ventilated patients. Am. J. Respir. Crit. Care Med. **152:**1387–1390.
160. **Ost, D. E., C. S. Hall, G. Joseph, C. Ginocchio, S. Condon, E. Kao, M. LaRusso, R. Itzla, and A. M. Fein.** 2003. Decision analysis of antibiotic and diagnostic strategies in ventilator-associated pneumonia. Am. J. Respir. Crit. Care Med. **168:**1060–1067.
161. **Papazian, L., F. Bregeon, X. Thirion, R. Gregoire, P. Saux, J. P. Denis, G. Perin, J. Charrel, J. F. Dumon, J. P. Affray, and F. Gouin.** 1996. Effect of ventilator-associated pneumonia on mortality and morbidity. Am. J. Respir. Crit. Care Med. **154:**91–97.
162. **Papazian, L., P. Thomas, L. Garbe, I. Guignon, X. Thirion, J. Charrel, C. Bollet, P. Fuentes, and F. Gouin.** 1995. Bronchoscopic or blind sampling techniques for the diagnosis of ventilator-associated pneumonia. Am. J. Respir. Crit. Care Med. **152:**1982–1991.
163. **Pugin, J., R. Auckenthaler, D. P. Lew, and P. M. Suter.** 1991. Oropharyngeal decontamination decreases incidence of ventilator-associated pneumonia. A randomized, placebo-controlled, double-blind clinical trial. JAMA **265:**2704–2710.
164. **Pugin, J., R. Auckenthaler, N. Mili, J. P. Janssens, P. D. Lew, and P. M. Suter.** 1991. Diagnosis of ventilator-associated pneumonia by bacteriologic analysis of bronchoscopic and nonbronchoscopic "blind" bronchoalveolar lavage fluid. Am. Rev. Respir. Dis. **143:**1121–1129.
165. **Raymond, D. P., S. J. Pelletier, T. D. Crabtree, T. G. Gleason, L. L. Hamm, T. L. Pruett, and R. G. Sawyer.** 2001. Impact of a rotating empiric antibiotic schedule on infectious mortality in an intensive care unit. Crit. Care Med. **29:**1101–1108.
166. **Rello, J., M. E. Esandi, E. Diaz, D. Mariscal, M. Gallego, and J. Valles.** 1998. The role of Candida sp isolated from bronchoscopic samples in nonneutropenic patients. Chest **114:**146–149.
167. **Rello, J., J. A. Paiva, J. Baraibar, F. Barcenilla, M. Bodi, D. Castander, H. Correa, E. Diaz, J. Garnacho, M. Llorio, M. Rios, A. Rodriguez, and J. Sole-Violan.** 2001. International Conference for the Development of Consensus on the Diagnosis and Treatment of Ventilator-Associated Pneumonia. Chest **120:**955–970.
168. **Rello, J., R. Sonora, P. Jubert, A. Artigas, M. Rue, and J. Valles.** 1996. Pneumonia in intubated patients: role of respiratory airway care. Am. J. Respir. Crit. Care Med. **154:**111–115.
169. **Rello, J., L. Vidaur, A. Sandiumenge, A. Rodriguez, B. Gualis, C. Boque, and E. Diaz.** 2004. De-escalation therapy in ventilator-associated pneumonia. Crit. Care Med. **32:**2183–2190.
170. **Richards, M. J., J. R. Edwards, D. H. Culver, R. P. Gaynes, et al.** 1999. Nosocomial infections in medical intensive care units in the United States. Crit. Care Med. **27:**887–892.
171. **Rodriguez-Roldan, J. M., A. Altuna-Cuesta, A. Lopez, A. Carrillo, J. Garcia, J. Leon, and A. J. Martinez-Pellus.** 1990. Prevention of nosocomial lung infection in ventilated patients: use of an antimicrobial pharyngeal nonabsorbable paste. Crit. Care Med. **18:**1239–1242.
172. **Rouby, J. J., P. Laurent, M. Gosnach, E. Cambau, G. Lamas, A. Zouaoui, J. L. Leguillou, L. Bodin, T. D. Khac, C. Marsault, et al.** 1994. Risk factors and clinical relevance of nosocomial maxillary sinusitis in the critically ill. Am. J. Respir. Crit. Care Med. **150:**776–783.
173. **Rouby, J. J., E. Martin De Lassale, P. Poete, M. H. Nicolas, L. Bodin, V. Jarlier, Y. Le Charpentier, J. Grosset, and P. Viars.** 1992. Nosocomial bronchopneumonia in the critically ill. Histologic and bacteriologic aspects. Am. Rev. Respir. Dis. **146:**1059–1066.
174. **Roustan, J. P., J. Kienlen, P. Aubas, S. Aubas, and J. du Cailar.** 1992. Comparison of hydrophobic heat and moisture exchangers with heated humidifier during prolonged mechanical ventilation. Intensive Care Med. **18:**97–100.
175. **Ruiz, M., A. Torres, S. Ewig, M. A. Marcos, A. Alcon, R. Lledo, M. A. Asenjo, and A. Maldonaldo.** 2000. Noninvasive versus invasive microbial investigation in ventilator-associated pneumonia: evaluation of outcome. Am. J. Respir. Crit. Care Med. **162:**119–125.
176. **Sanchez-Nieto, J. M., A. Torres, F. Garcia-Cordoba, M. El-Ebiary, A. Carrillo, J. Ruiz, M. L. Nunez, and M. Niederman.** 1998. Impact of invasive and noninvasive quantitative culture sampling on outcome of ventilator-associated pneumonia: a pilot study. Am. J. Respir. Crit. Care Med. **157:**371–376.
177. **Schentag, J. J.** 1999. Antimicrobial action and pharmacokinetics/pharmacodynamics: the use of AUIC to improve efficacy and avoid resistance. J. Chemother. **11:**426–439.
178. **Schentag, J. J., M. C. Birmingham, J. A. Paladino, J. R. Carr, J. M. Hyatt, A. Forrest, G. S. Zimmer, M. H. Adelman, and T. J. Cumbo.** 1997. In nosocomial pneumonia, optimizing antibiotics other than aminoglycosides is a more important determinant of successful clinical outcome, and a better means of avoiding resistance. Semin. Respir. Infect. **12:**278–293.
179. **Schentag, J. J., K. K. Gilliland, and J. A. Paladino.** 2001. What have we learned from pharmacokinetic and pharmacodynamic theories? Clin. Infect. Dis. **32**(Suppl. 1)**:**S39–S46.
180. **Schweickert, W. D., B. K. Gehlbach, A. S. Pohlman, J. B. Hall, and J. P. Kress.** 2004. Daily interruption of sedative infusions and complications of critical illness in mechanically ventilated patients. Crit. Care Med. **32:**1272–1276.
181. **Shorr, A. F., and P. G. O'Malley.** 2001. Continuous subglottic suctioning for the prevention of ventilator-associated pneumonia: potential economic implications. Chest **119:**228–235.
182. **Shorr, A. F., J. H. Sherner, W. L. Jackson, and M. H. Kollef.** 2005. Invasive approaches to the diagnosis of ventilator-associated pneumonia: a meta-analysis. Crit. Care Med. **33:**46–53.
183. **Singh, N., P. Rogers, C. W. Atwood, M. M. Wagener, and V. L. Yu.** 2000. Short-course empiric antibiotic therapy for patients with pulmonary infiltrates in the intensive care unit. A proposed solution for indiscriminate antibiotic prescription. Am. J. Respir. Crit. Care Med. **162:**505–511.
184. **Sirvent, J. M., L. Vidaur, S. Gonzalez, P. Castro, J. de Batlle, A. Castro, and A. Bonet.** 2003. Microscopic examination of intracellular organisms in protected bronchoalveolar mini-lavage fluid for the diagnosis of ventilator-associated pneumonia. Chest **123:**518–523.
185. **Smulders, K., H. van der Hoeven, I. Weers-Pothoff, and C. Vandenbroucke-Grauls.** 2002. A randomized clinical trial of intermittent subglottic secretion drainage in patients receiving mechanical ventilation. Chest **121:**858–862.
186. **Sole Violan, J., J. A. Fernandez, A. B. Benitez, J. A. Cardenosa Cendrero, and F. Rodriguez de Castro.** 2000. Impact of quantitative invasive diagnostic techniques in the management and outcome of mechanically ventilated patients with suspected pneumonia. Crit. Care Med. **28:**2737–2741.
187. **Sole Violan, J., F. Rodriguez de Castro, J. Caminero Luna, A. Bordes Benitez, and J. L. Manzano Alonso.** 1993. Comparative efficacy of bronchoalveolar lavage and telescoping plugged catheter in the diagnosis of pneumonia in mechanically ventilated patients. Chest **103:**386–390.
188. **Sottile, F. D., T. J. Marrie, D. S. Prough, C. D. Hobgood, D. J. Gower, L. X. Webb, J. W. Costerton, and A. G. Gristina.** 1986. Nosocomial pulmonary infection: possible etiologic significance of bacterial adhesion to endotracheal tubes. Crit. Care Med. **14:**265–270.
189. **Souweine, B., B. Veber, J. P. Bedos, B. Gachot, M. C. Dombret, B. Regnier, and M. Wolff.** 1998. Diagnostic accuracy of protected specimen brush and bronchoalveolar lavage in nosocomial pneumonia: impact of previous antimicrobial treatments. Crit. Care Med. **26:**236–244.
190. **Sterling, T. R., E. J. Ho, W. T. Brehm, and M. B. Kirkpatrick.** 1996. Diagnosis and treatment of ventilator-associated pneumonia—impact on survival. A decision analysis. Chest **110:**1025–1034.
191. **Sutherland, K. R., K. P. Steinberg, R. J. Maunder, J. A. Milberg, D. L. Allen, and L. D. Hudson.** 1995. Pulmonary infection during the acute respiratory distress syndrome. Am. J. Respir. Crit. Care Med. **152:**550–556.
192. **Tablan, O. C., L. J. Anderson, N. H. Arden, R. F. Breiman, J. C. Butler, M. M. McNeil, et al.** 1994. Guideline for prevention of nosocomial pneumonia. Am. J. Infect. Control **22:**247–292.
193. **Thomachot, L., M. Leone, K. Razzouk, F. Antonini, R. Vialet, and C. Martin.** 2002. Randomized clinical trial of extended use of a hydrophobic condenser humidifier: 1 vs. 7 days. Crit. Care Med. **30:**232–237.
194. **Thomas, J. K., A. Forrest, S. M. Bhavnani, J. M. Hyatt, A. Cheng, C. H. Ballow, and J. J. Schentag.** 1998. Pharmacodynamic evaluation of factors associated with the development of bacterial resistance in acutely ill patients during therapy. Antimicrob Agents Chemother. **42:**521–527.
195. **Timsit, J. F., B. Misset, E. Azoulay, B. Renaud, M. Garrouste-Orgeas, and J. Carlet.** 1996. Usefulness of airway visualization in the diagnosis of nosocomial pneumonia in ventilated patients. Chest **110:**172–179.
196. **Timsit, J. F., B. Misset, S. Francoual, F. W. Goldstein, P. Vaury, and J. Carlet.** 1993. Is protected specimen brush a reproducible method to diagnose ICU-acquired pneumonia? Chest **104:**104–108.
197. **Timsit, J. F., B. Misset, B. Renaud, F. W. Goldstein, and J. Carlet.** 1995. Effect of previous antimicrobial therapy on the accuracy of the main procedures used to diagnose nosocomial pneumonia in patients who are using ventilation. Chest **108:**1036–1040.
198. **Torres, A., R. Aznar, J. M. Gatell, P. Jimenez, J. Gonzalez, A. Ferrer, R. Celis, and R. Rodriguez-Roisin.** 1990. Incidence, risk, and prognosis factors of nosocomial pneumonia in mechanically ventilated patients. Am. Rev. Respir. Dis. **142:**523–528.
199. **Torres, A., and M. El-Ebiary.** 2000. Bronchoscopic BAL in the diagnosis of ventilator-associated pneumonia. Chest **117:**198S–202S.
200. **Torres, A., and S. Ewig.** 2004. Diagnosing ventilator-associated pneumonia. N. Engl. J. Med. **350:**433–435.
201. **Torres, A., J. Serra-Batlles, E. Ros, C. Piera, J. Puig de la Bellacasa, A. Cobos, F. Lomena, and R. Rodriguez-Roisin.** 1992. Pulmonary aspiration of gastric contents in patients receiving mechanical ventilation: the effect of body position. Ann. Intern. Med. **116:**540–543.
202. **Traver, G. A., M. L. Tyler, L. D. Hudson, D. L. Sherrill, and S. F. Quan.** 1995. Continuous oscillation: outcome in critically ill patients. J. Crit. Care **10:**97–103.
203. **Trouillet, J. L., J. Chastre, A. Vuagnat, M. L. Joly-Guillou, D. Combaux, M. C. Dombret, and C. Gibert.** 1998. Ventilator-associated pneumonia

caused by potentially drug-resistant bacteria. Am. J. Respir. Crit. Care Med. **157:**531–539.

204. **Valles, J., A. Artigas, J. Rello, N. Bonsoms, D. Fontanals, L. Blanch, R. Fernandez, F. Baigorri, and J. Mestre.** 1995. Continuous aspiration of subglottic secretions in preventing ventilator-associated pneumonia. Ann. Intern. Med. **122:**179–186.
205. **Valles, J., J. Rello, R. Fernandez, L. Blanch, F. Baigorri, J. Mestre, L. Matas, A. Marin, and A. Artigas.** 1994. Role of bronchoalveolar lavage in mechanically ventilated patients with suspected pneumonia. Eur. J. Clin. Microbiol. Infect. Dis. **13:**549–558.
206. **van Nieuwenhoven, C. A., E. Buskens, D. C. Bergmans, F. H. van Tiel, G. Ramsay, and M. J. Bonten.** 2004. Oral decontamination is cost-saving in the prevention of ventilator-associated pneumonia in intensive care units. Crit. Care Med. **32:**126–130.
207. **Verpooten, G. A., R. A. Giuliano, L. Verbist, G. Eestermans, and M. E. De Broe.** 1989. Once-daily dosing decreases renal accumulation of gentamicin and netilmicin. Clin. Pharmacol. Ther. **45:**22–27.
208. **Verwaest, C., J. Verhaegen, P. Ferdinande, M. Schetz, G. Van den Berghe, L. Verbist, and P. Lauwers.** 1997. Randomized, controlled trial of selective digestive decontamination in 600 mechanically ventilated patients in a multidisciplinary intensive care unit. Crit. Care Med. **25:**63–71.
209. **Vidal, L., M. Paul, I. Ben-Dor, E. Pokroy, K. Soares-Weiser, and L. Leibovici.** 2004. Oral versus intravenous antibiotic treatment for febrile neutropenia in cancer patients. Cochrane Database Syst. Rev. CD003992.
210. **Vincent, J. L., D. J. Bihari, P. M. Suter, H. A. Bruining, J. White, M. H. Nicolas-Chanoin, M. Wolff, R. C. Spencer, M. Hemmer, et al.** 1995. The prevalence of nosocomial infection in intensive care units in Europe. Results of the European Prevalence of Infection in Intensive Care (EPIC) Study. JAMA **274:**639–644.
211. **Warren, D. K., S. J. Shukla, M. A. Olsen, M. H. Kollef, C. S. Hollenbeak, M. J. Cox, M. M. Cohen, and V. J. Fraser.** 2003. Outcome and attributable cost of ventilator-associated pneumonia among intensive care unit patients in a suburban medical center. Crit. Care Med. **31:**1312–1317.
212. **Wheeler, A. P., and G. R. Bernard.** 1999. Treating patients with severe sepsis. N. Engl. J. Med. **340:**207–214.
213. **Whiteman, K., L. Nachtmann, D. Kramer, S. Sereika, and M. Bierman.** 1995. Effects of continuous lateral rotation therapy on pulmonary complications in liver transplant patients. Am. J. Crit. Care. **4:**133–139.
214. **Wiener, J., G. Itokazu, C. Nathan, S. A. Kabins, and R. A. Weinstein.** 1995. A randomized, double-blind, placebo-controlled trial of selective digestive decontamination in a medical-surgical intensive care unit. Clin. Infect. Dis. **20:**861–867.
215. **Wunderink, R. G., C. G. Mayhall, and C. Gibert.** 1992. Methodology for clinical investigation of ventilator-associated pneumonia. Epidemiology and therapeutic intervention. Chest **102:**580S–588S.
216. **Wunderink, R. G., L. S. Woldenberg, J. Zeiss, C. M. Day, J. Ciemins, and D. A. Lacher.** 1992. The radiologic diagnosis of autopsy-proven ventilator-associated pneumonia. Chest **101:**458–463.
217. **Wysocki, M., F. Delatour, F. Faurisson, A. Rauss, Y. Pean, B. Misset, F. Thomas, J. F. Timsit, T. Similowski, H. Mentec, L. Mier, and D. Dreyfuss.** 2001. Continuous versus intermittent infusion of vancomycin in severe staphylococcal infections: prospective multicenter randomized study. Antimicrob. Agents Chemother. **45:**2460–2467.
218. **Zack, J. E., T. Garrison, E. Trovillion, D. Clinkscale, C. M. Coopersmith, V. J. Fraser, and M. H. Kollef.** 2002. Effect of an education program aimed at reducing the occurrence of ventilator-associated pneumonia. Crit. Care Med. **30:**2407–2412.
219. **Zeitoun, S. S., A. L. de Barros, S. Diccini, and Y. Juliano.** 2001. Incidence of ventilator-associated pneumonia in patients using open-suction systems and closed-suction systems: a prospective study—preliminary data. Rev. Lat. Am. Enfermagem. **9:**46–52.