Invited Commentary

Strategies in the Prevention and Management of Ventilator-Associated Pneumonia

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Ventilator-associated pneumonia (VAP) is a leading cause of morbidity and mortality in the intensive care unit. Prevention of VAP is possible through the use of several evidence-based strategies intended to minimize intubation, the duration of mechanical ventilation, and the risk of aspiration of oropharyngeal pathogens. Current data favor the quantitative analysis of lower respiratory tract cultures for the diagnosis of VAP, accompanied by the initiation of broad-spectrum empiric antimicrobial therapy based on patient risk factors for infection with multi-drug-resistant pathogens and data from unit-specific antibiograms. Eventual choice of antibiotic and duration of therapy are selected based on culture results and patient stability, with an emphasis on minimization of unnecessary antibiotic use.

VENTILATOR-ASSOCIATED PNEUMONIA (VAP), defined as pneumonia occurring 48 to 72 hours after endotracheal intubation, remains the most common intensive care unit (ICU) infection among mechanically ventilated patients and a major source of health care resource consumption. Unfortunately, the emergence of VAP as an ICU epidemic is partially iatrogenic. Nonspecific diagnostic criteria, indiscriminate antibiotic use, and unclear therapeutic endpoints have all contributed to increased episodes of VAP caused by multidrug-resistant (MDR) pathogens. In turn, MDR pathogens increase the likelihood of inadequate initial antimicrobial therapy, which exerts further selection pressure for these pathogens, and results in higher mortality. Many aspects of the prevention, diagnosis, and treatment of VAP remain controversial. However, several evidence-based strategies, reviewed herein, can effectively curtail the burden of VAP.

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Classification

Pneumonia is defined as inflammation of the lung parenchyma caused by infection, and has traditionally been dichotomized into nosocomial- (acquired in an inpatient setting) and community-acquired (acquired in an outpatient setting).[1] However, it is now recognized that pneumonia in outpatients with recent health care contacts, termed healthcare-associated pneumonia (HCAP), is distinct clinically and microbiologically from community-acquired pneumonia (CAP). Compared with CAP, patients with HCAP have significantly higher rates of infection with MDR pathogens, increased mortality, and incur a prolonged hospitalization and greater hospital charges.[2] Instead, HCAP behaves similar to hospital-acquired pneumonia (HAP). Patients with VAP, a subset of HAP and the focus of this review, incur especially poor outcomes.[2] The current classification scheme for pneumonia, as outlined in the recent American Thoracic Society Guidelines for the Management of Adults with HAP, VAP, and HCAP,[3] is summarized in Table 1.

Further distinction is made between early-onset VAP (occurring <5 days after intubation) and late-onset VAP (occurring ≥5 days after intubation). Early-onset VAP is often consequential to aspiration of gastric contents, and is caused by predominantly antibiotic-sensitive bacteria such as methicillin-sensitive *Staphylococcus aureus* (MSSA), *Streptococcus pneumoniae*, and *Haemophilus influenzae*.[2–5] Conversely, patients with late-onset VAP are at increased risk for infection with MDR pathogens (*e.g.*,

TABLE 1. *Classification Scheme for Pneumonia*

Classification	Definition
HCAP	Pneumonia that occurs in patients who were hospitalized in an acute care hospital for 2 or more days within 90 days of the infection; resided in a nursing home or long-term care facility; received recent intravenous antibiotic therapy, chemotherapy, or wound care within the past 30 days of the current infection; or attended a hospital or hemodialysis clinic.
HAP	Pneumonia that occurs >48 hours from the time of admission.
VAP	Pneumonia that occurs more than 48–72 hours after endotracheal intubation and mechanical intubation.
CAP	All other.

Adapted from American Thoracic Society Guidelines for the Management of Adults with Hospital-Acquired, Ventilator-Associated, and Healthcare-Associated Pneumonia.[3]

methicillin-resistant *S. aureus* [MRSA], *Pseudomonas aeruginosa*, or *Acinetobacter* species).

Epidemiology

VAP comprises nearly one-third of all ICU infections.[4–7] The incidence of VAP depends upon the diagnostic criteria used, and thus varies markedly in published reports. Clinical criteria alone overestimate the incidence of VAP compared with microbiologic or histologic data.[8, 9] Safdar et al.[10] performed a systematic review of 89 studies in which the incidence of VAP among mechanically ventilated patients was reported. Despite substantial heterogeneity of diagnostic criteria, the authors reported a pooled incidence of VAP of 22.8 per cent (95% confidence interval [CI] 18.8–26.9%). The National Nosocomial Infection Surveillance system reported recently that VAP occurred at a rate of 7.5 cases per 1000 ventilator days in medical ICUs and 13.6 per 1000 ventilator days in surgical ICUs.[11] The incidence of VAP varies with the duration of mechanical ventilation, increasing at a rate of 3 per cent per day during the first 5 days, 2 per cent per day during days 5–10, and 1 per cent per day after that.[12]

Risk factors for VAP are summarized in Table 2. Perhaps most important is airway intubation itself. The risk of HAP increases 6- to 20-fold in mechanically ventilated patients;[6, 13, 14] patients with respiratory failure managed with noninvasive, positive-pressure ventilation have a lower incidence of pneumonia.[15–17] VAP is especially common in patients with ARDS, owing to prolonged mechanical ventilation and devastated local airway host defenses.[18–20]

Whether VAP is an independent risk factor for mortality is controversial.[21] Most recent series have reported a crude mortality rate in patients with VAP of 9 per cent to 27 per cent,[5, 22–25] although rates can exceed 75 per cent in high-risk patients infected with MDR organisms.[18, 26] Assignment of attributable mortality in patients with VAP has been problematic because compared with non-VAP patients, patients who develop VAP are systemically more ill upon intubation. Several authors have addressed this issue through a matched cohort study design. Heyland et al.[27] matched 177 patients who developed VAP to controls by age, admission diagnosis, location before ICU, and admission Acute Physiology and Chronic Health Evaluation II score. Patients who developed VAP had a significantly longer ICU length of stay (LOS), but no increase in mortality (23.7% *vs* 17.7%, $P = 0.19$). Furthermore, attributable mortality was highest for patients infected with high-risk organisms, defined as MRSA, *Pseudomonas*, *Acinetobacter*, and *Stenotrophomonas*. However, appropriate initial empiric therapy may mitigate adverse outcomes.[28]

TABLE 2. *Risk Factors for VAP*

Age ≥60 years
Acute respiratory distresss syndrome (ARDS)
Chronic obstructive pulmonary disease or other underlying pulmonary disease
Coma or impaired consciousness
Serum albumin <2.2 g/dL
Burns, trauma
Blood transfusion
Organ failure
Supine position
Large-volume gastric aspiration
Sinusitis
Immunosuppression

Hugonnet et al.[29] matched patients with and without VAP by age, severity of illness, and duration of mechanical ventilation before the development of VAP. Compared with non-VAP patients, patients with VAP suffered an increased ICU LOS, duration of mechanical ventilation, ICU costs, but again, not mortality (32.0% *vs* 24.7%, $P = 0.26$). However, when these and other matched cohort studies were pooled by meta-analysis, patients with VAP were more than twice as likely to die compared with those without VAP (odds ratio [OR] 2.03, 95% CI 1.16–3.56, $P = 0.03$) and incurred a longer ICU LOS and a mean increased ICU cost of $10,019.[10]

Pathogenesis

Impaired host immunity and displacement of normal oropharyngeal flora by pathogens predispose the critically ill, mechanically ventilated patient to VAP. Normal nonspecific host defenses, such as the epiglottis, vocal cords, cough reflex, and ciliated epithelium and mucus of the upper airways are bypassed or ren-

dered ineffective during intubation. Bacteria gain access to the lower respiratory tract via aspiration through the endotracheal tube (where they may establish colonies impervious to the effects of antibiotics in the glycocalyx biofilm that coats the lumen of artificial airway devices), migration around it (particularly if cuff inflation pressure is not maintained), or, in rare instances, hematogenous spread from blood stream infections. Displacement of normal flora by pathogens is also necessary for the development of VAP.[30–32] The facial sinuses and stomach may serve as potential pathogen reservoirs, but measures to minimize passage of pathogens from these sources into the lower airways have provided mixed results (see below).

Currently, the most common pathogens isolated from patients with VAP are MRSA (15%), *Pseudomonas* (14%), *Enterobacter* (3%), *E. coli* (3%), and *Acinetobacter* (2%).[5, 23] Because of indiscriminant use of broad-spectrum antibiotics, MDR pathogens are increasingly implicated in VAP.[33–36] Infection with MRSA is particularly common in patients with diabetes mellitus and after traumatic brain injury.[36–38] *P. aeruginosa*, the most common gram-negative pathogen in VAP, is increasingly common with an MDR phenotype, especially to fluoroquinolones[34, 39] and third-generation cephalosporins.[40]

Anaerobic bacteria are isolated infrequently from patients with VAP, although this finding may represent an inability to culture these organisms effectively from the oxygen-enriched environment of the mechanically ventilated airway.[41] Although isolation of fungi such as *Candida* spp. and *Aspergillus fumigatus* from endotracheal aspirates is common, it nearly always represents colonization of the immunocompetent host.[42–45] However, when fungi are isolated from two or more normally sterile sites (*e.g.*, urine and lower respiratory tract) in an immunocompromised patient, systemic antifungal therapy should be considered.

Prevention

Prevention of VAP requires a thorough understanding of modifiable risk factors. Strict infection control, including hand hygiene with alcohol-based hand disinfectants, gowning, and gloving, minimizes person-to-person transmission of pathogens and is paramount to deterring all ICU infections.[46, 47] Prevention of VAP begins with minimization of endotracheal intubation and the duration of mechanical ventilation. Noninvasive, positive-pressure ventilation should always be considered in lieu of intubation, as patients with respiratory failure managed with noninvasive, positive-pressure ventilation have a lower incidence of VAP.[15–17, 48] Evidence-based strategies to decrease the duration of mechanical ventilation include daily interruption of sedation,[49] standardized weaning protocols, and adequate ICU staffing.[50]

If endotracheal intubation is mandated, the orotracheal compared with the nasotracheal route may decrease the risk of developing VAP. Holzapfel et al.[51] found that the incidence of VAP in patients who were randomized to orotracheal intubation was nearly one-half that of patients intubated nasotracheally (6% *vs* 11%). In light of these data and the association between nasotracheal intubation and the development of nosocomial sinusitis,[52] orotracheal intubation is preferred.

Once intubation has occurred, the majority of preventive measures against VAP decrease the risk of aspiration. Maintenance of endotracheal cuff pressure >20 cm H_2O[53] and continuous aspiration of subglottic secretions achieved through the use of a endotracheal tube equipped with a dorsal lumen significantly reduce the incidence of VAP.[54–59] Furthermore, strong evidence exists that semirecumbent positioning (30°–45° head-up) is protective compared with supine positioning, especially during enteral feeding.[60–62]

Compared with postpyloric feeding, intragastric feeding results in more episodes of gastroesophageal reflux and aspiration.[63] However, recent randomized, controlled trials (RCTs) comparing rates of VAP have produced variable results.[64, 65] Heyland et al.[66] performed a meta-analysis of 11 RCTs and reported a relative risk of 0.77 (95% CI [0.60–1.00], $P = 0.05$) for VAP with postpyloric compared with gastric feedings. Based on these data, most expert recommendations do not differentiate between gastric and postpyloric feeding.[3, 66, 67] Promotility agents such as erythromycin may facilitate safe intragastric feeding, should this route be used.[68]

The timing of onset of enteral feedings may influence the risk of developing VAP. Initiation of enteral feeds on Day 1 compared with Day 5 resulted in significantly more episodes of VAP (49.3% *vs* 30.7%, $P = 0.02$) and a longer ICU LOS in one prospective trial of 150 patients.[69] More recently, Schorr et al.[70] reported that enteral nutrition begun ≤48 hours after the initiation of mechanical ventilation was independently associated with the development of VAP (OR 2.65, 95% CI 1[0.93–3.63], $P < 0.0001$).

Pharmacologic strategies intended to minimize the risk of aspiration of pathogenic bacteria include selective decontamination of the digestive tract (SDD) with topical or systemic antibiotics or antiseptics, and minimization of stress ulcer prophylaxis. Myriad clinical trials have addressed SDD, most of which have reported a significant decrease in the incidence of VAP.[71–76] However, the evidence in favor of SDD has been limited by questionable study methodology,[77] the use of narrow patient subsets from ICUs in which

MDR pathogens were rare, and an increased number of infections caused by MDR bacteria observed in the SSD groups.[78–80] For these reasons, the use of SDD is currently not recommended for the routine prevention of VAP.

Alternatively, oropharyngeal decontamination can be accomplished with a topical antiseptic such as chlorhexidine. Recent RCTs have provided evidence for[81] and against[82] the efficacy of chlorhexidine in the prevention of VAP, but a recent meta-analysis suggests that topical chlorhexidine may be effective for prevention of VAP.[82A]

Stress ulcer prophylaxis is a known risk factor for the development of VAP;[32, 83] its use should be reserved for patients at high risk for gastrointestinal mucosal hemorrhage (*e.g.*, prolonged mechanical ventilation, intracranial hemorrhage, coagulopathy, and glucocorticoid therapy). Randomized controlled trials comparing histamine type-2 antagonists, sucralfate, and antacids have yielded conflicting results;[84–89] no agent is preferred for prophylaxis based solely on efficacy for prevention of VAP.

Ample data document the relationship between blood transfusion and infection risk in surgical,[90–92] trauma,[93] and critically ill patients.[94] Shorr et al.[70] found red blood cell transfusion to be independently associated with the development of VAP (OR 1.89, 95% CI [1.33–2.68], $P = 0.0004$). Early et al.[95] documented a decreased incidence of VAP in a surgical ICU after implementation of an anemia management protocol. After implementation of the protocol, fewer blood transfusions were administered despite equivalent outcomes, and the incidence of VAP decreased from 8.1 per cent to 0.8 per cent ($P = 0.002$).

Several antibiotic administration strategies, including "de-escalation" and antibiotic rotation or "cycling," have been suggested to prevent VAP caused by MDR pathogens. De-escalation refers to the process of tailoring empiric broad-spectrum antimicrobial coverage to specific pathogens once microbiologic data from lower respiratory tract samples become available. Discontinuation of unnecessary antibiotics at this point curtails not only the emergence of MDR organisms, but also the risk of drug toxicity. Antibiotic cycling offers the potential for antibiotic classes to be used on a scheduled basis to preserve overall activity against predominant pathogens.[96, 97] Several prospective trials have documented a decreased incidence of VAP,[98, 99] improved initial adequacy of therapy,[28] and decreased mortality[100] after the implementation of scheduled antibiotic rotation. However, these studies have been limited by the use of historical controls, and thus possibly confounded by other changes in care. Furthermore, recent data have challenged the efficacy of antibiotic cycling.[101] Pending further research, cycling of antibiotics may be considered if multiple classes of antibiotics are cycled frequently in conjunction with other strategies to prevent the emergence of MDR organisms.[102]

Finally, staff education programs concerning modifiable risk factors may be cost-effective in preventing VAP. Zazk et al.[103] demonstrated that an education program administered to respiratory care practitioners and intensive care nurses that highlighted correct practices for the prevention of VAP resulted in a significantly decreased incidence of VAP and increased cost savings. Strategies to prevent VAP are listed in Table 3.

Diagnosis

The goals in diagnosing VAP are to determine if the patient has pneumonia and to determine the etiologic pathogen. Poor specificity is particularly problematic in the diagnosis of VAP because it not only exposes individual patients to unnecessary risk from overtreatment with antibiotics, but also increases selection pressure and thus the emergence of MDR bacteria within the ICU.[34, 104] Conversely, inadequate initial therapy in patients with VAP (poor sensitivity) has been associated consistently with increased mortality that cannot be reduced by subsequent changes in antibiotics.[105]

TABLE 3. *Strategies to Prevent VAP*

Strategy	Recommended	Insufficient Evidence	Reference(s)
Universal infection control precautions	+		46, 47
Orotracheal intubation	+		51, 52
Maintenance of endotracheal cuff pressure >20 cm H_2O	+		53
Continuous aspiration of subglottic secretions	+		54–59
Semirecumbent positioning	+		60–62
Postpyloric feeding		+	64–67
Postponement of enteral feeding for at least 48 hours after inbubation	+		69, 70
Selective decontamination of the digestive tract		+	71–80
Topical antiseptics		+	81, 82
Transfusion restriction	+		70, 95
Antibiotic cycling		+	28, 98–102

The diagnosis of VAP should be considered in the presence of one or more of the following: fever, leukocytosis or leukopenia, purulent sputum, hypoxemia, or a new or evolving infiltrate viewed on chest radiography (CXR). However, several noninfectious respiratory disease processes may mimic these signs, such as congestive heart failure, atelectasis, pulmonary thromboembolism, pulmonary hemorrhage, and ARDS, making clinical criteria alone nonspecific. Fabregas et al.[106] found the presence of a new infiltrate on CXR, along with two of the three aforementioned clinical criteria, to be 69 per cent sensitive and 75 per cent specific for the diagnosis of VAP when compared with *post mortem* histology. Several subsequent reports have confirmed the low specificity of clinical acumen in the diagnosis of VAP,[107–109] and clinically diagnosed VAP is confirmed microbiologically in fewer than 50 per cent of cases.[9, 110, 111]

Pugin et al.[112] standardized clinical, radiographic, and microbiologic criteria into the Clinical Pulmonary Infection Score (CPIS). Temperature, leukocyte count, CXR infiltrates, the appearance and volume of tracheal secretions, P_aO_2:F_IO_2, and culture and gram stain of tracheal aspirate (0–2 points each) yield a maximum CPIS score of 12 points; a score of >6 points indicates a high probability of VAP. Despite favorable test performance of the CPIS in its initial description, and its subsequent modification to include radiological progression of pulmonary infiltrate,[113] the specificity of CPIS is no better than clinical acumen alone when compared with lower respiratory tract cultures obtained via bronchoscopic bronchoalveolar lavage (BAL) or protected specimen brush (PSB).[114–116] The National Nosocomial Infection Surveillance system diagnostic criteria for nosocomial pneumonia,[117] which include similar combinations of clinical and radiographic parameters, performs equivalently to the CPIS when compared with quantitative lower respiratory tract cultures.[118] Incorporation of results from gram-stained lower respiratory tract samples into the CPIS improves specificity only marginally.[114] However, the negative predictive value of a gram stain showing no organisms in a clinically stable patient approaches 100 per cent.[119]

Because of the low specificity of clinical signs, radiographic criteria, and microscopic examination of lower respiratory tract samples, culture of lower respiratory tract samples before any manipulation of antibiotics is mandatory for a workup of suspected VAP to minimize false-negative results. Two fundamental issues regarding lower respiratory tract samples are debated: The method of specimen collection (invasive *vs* noninvasive) and the method of specimen analysis (semiquantitative *vs* quantitative).

Noninvasive techniques include sampling of the lower respiratory tract via endotracheal aspirates (EAs), blinded plugged telescoping catheter, blinded PSB, and mini-BAL. Endotracheal aspirates are less specific because of an increased likelihood of contamination by oropharyngeal flora (indicated by the presence of squamous epithelial cells on gram stain) and a decreased likelihood that the presence of organisms indicates infection rather than colonization.

Invasive techniques (BAL or PSB) collect lower respiratory tract samples using fiberoptic bronchoscopy. The main theoretical advantage of bronchoscopy is direct visualization of the airways. However, invasive techniques are more expensive and resource-intensive than their noninvasive counterparts, and may not be available readily. Furthermore, although bronchoscopy is generally well-tolerated, a significant reduction in arterial oxygen saturation has been observed for up to 24 hours after the procedure, possibly related to alveolar flooding caused by residual lavage fluid. However, this transient desaturation is of unclear importance, not having been correlated with poorer outcomes.[120]

Irrespective of collection method, respiratory tract cultures may be analyzed using semiquantitative or quantitative microbiology. The crucial issue is distinction of colonization from infection.[121] Whereas semiquantitative microbiology reports growth in terms of ordinal categories (*e.g.*, light, moderate, or heavy), quantitative microbiology reports growth in number of colony forming units (CFUs) per milliliter of aliquot. In the latter case, a threshold value is selected to distinguish colonization from infection. Commonly used thresholds are 10^3 CFU/mL for PSB, 10^4 CFU/mL for BAL, and 10^5 CFU/mL for EA. It is generally recommended that any threshold be lowered at least one order of magnitude if antibiotics have been changed recently or started before sample acquisition.[122]

Endotracheal aspirates possess inferior specificity when compared with blinded PTC[123] and bronchoscopic BAL or PSB.[124–127] Two systematic reviews, one of bronchoscopic BAL[120] and one of blinded invasive techniques,[128] reported similar test characteristics for the two techniques. However, methodologic variability is rampant. Sixteen of 23 studies (70%) in the former review used histology as a reference standard compared with only 4 of 15 studies (27%) analyzed in the latter review. Furthermore, the remainder of studies analyzed in the review of blinded invasive techniques used bronchoscopic BAL or PSB as the reference category. Both reviews reported substantial interstudy variability in sampling technique as well as threshold values. A recent study reported that compared with a reference standard of bronchoscopic BAL (threshold 10^4 CFU/mL), blinded plugged telescoping catheter was 77 per cent sensitive and 94 per

cent specific.[126] Thus, despite these limitations, it is likely that bronchoscopic techniques are more specific than blinded techniques, and that both techniques are superior to EAs.

Evidence-based recommendations for the diagnosis of VAP have been difficult to formulate because many RCTs have compared various permutations of collection and analytical methodology, threshold values, and reference categories. The largest RCT of this type compared an invasive, quantitative approach with a noninvasive, semiquantitative approach.[9] A total of 413 patients suspected of VAP were randomized to evaluation with bronchoscopic BAL or PSB with quantitative cultures, or "clinical" management consisting of semiquantitative analysis of EAs. Antibiotic therapy was discontinued in clinically stable patients with negative culture results, regardless of study arm. Compared with the clinical strategy, patients in the invasive group demonstrated decreased 14-day mortality (16% *vs* 25%, $P = 0.02$), less antibiotic use (11.9 *vs* 7.7 antibiotic-free days), decreased sepsis-related organ failure, and decreased 28-day mortality after adjustment for severity of illness. The clinical strategy also resulted in more and broader-spectrum antibiotic therapy compared with the invasive strategy, and increased emergence of fungi. It is unclear whether these improved outcomes resulted from the use of an invasive *versus* a noninvasive strategy or a quantitative *versus* a semiquantitative strategy.

Two RCTs have compared outcomes of patients with suspected VAP managed with an invasive *versus* a noninvasive approach when both samples were cultured quantitatively. Sanchez-Nieto et al.[127] randomized 51 patients with suspected VAP to EA *versus* bronchoscopic BAL or PSB. Initial antibiotic therapy was modified in a significantly higher percentage of invasive patients compared with noninvasive (42% *vs* 16%, $P < 0.05$), but there was no difference in severity-adjusted mortality, ICU LOS, or duration of mechanical ventilation. Ruiz et al.[129] randomized 76 patients with suspected VAP to EAs *versus* bronchoscopic BAL or PSB, and found no difference in incidence of antibiotic modification, duration of mechanical ventilation, ICU length of stay, crude mortality, or adjusted mortality. In both studies, antibiotics were continued in all patients with negative cultures.

Shorr et al.[130] performed a meta-analysis of the aforementioned trials comparing EAs (quantitative or semiquantitative) to bronchoscopic quantitative cultures. Although the pooled OR suggested a survival advantage to the invasive approach (OR = 0.62), the result was not significant ($P = 0.62$). However, patients in the invasive group were more likely to undergo changes in antimicrobial regimen.

Recently, the Canadian Critical Care Trials Group reported the results of analysis of a secondary endpoint of an antibiotic therapy trial of VAP (carbapenem *versus* carbapenem/fluoroquinolone), showing in 740 patients that sputum sampling by BAL with quantitative microbiology was not different than routine suctioning and laboratory analysis in terms of mortality and antibiotic use.[130A] However, the study was underpowered (anticipated mortality 40%; observed rate 19%), and patients with *Pseudomonas* and MRSA were excluded, making the study difficult to interpret.

In conclusion, samples obtained via bronchoscopic BAL or PSB and then analyzed quantitatively have the highest specificity in diagnosing VAP. Data reporting outcomes in patients managed with an invasive *versus* a "clinical" strategy are conflicting, although the largest such trial showed a significant survival advantage for patients managed with the invasive/quantitative approach. Several trials demonstrate that patients so managed are also more likely to undergo antibiotic changes (de-escalation). Trials rebutting the use of the invasive/quantitative strategy are limited because patients with negative cultures continued to receive antibiotics, which negates the putative benefit (the ability to discontinue antimicrobial therapy). This last point is of considerable importance because the value of invasive, quantitative specimens lies not with their impact upon the decision to initiate therapy (these cultures will not become available for 48–72 hours), but rather with their effect upon alteration or discontinuation of antibiotic therapy based on final results.

Therapy

Neither the decision to initiate antimicrobial therapy nor the choice of specific agents involves interpretation of lower respiratory tract cultures, which will not become available for 48 to 72 hours. Rather, the decision to initiate therapy is based on clinical suspicion and microscopic examination of gram-stained lower respiratory samples (Fig. 1). Furthermore, choice of agent is based on individual patient risk factors for infection with MDR organisms (Table 4) and data from institutional antibiograms. The majority of data indicate that antimicrobial therapy may be withheld safely if a gram-stained lower respiratory tract sample reveals no organisms and the patient has no signs of severe sepsis.[130–133] Clinical signs of infection along with a negative gram stain suggest an extrapulmonary source of infection or sterile inflammation (*e.g.*, intracerebral hemorrhage).

Patients with microorganisms visualized on gram stain, or clinical instability, should receive empiric therapy for VAP until the results of lower respiratory tract cultures become available. The primary concern when treating VAP is the administration of "adequate

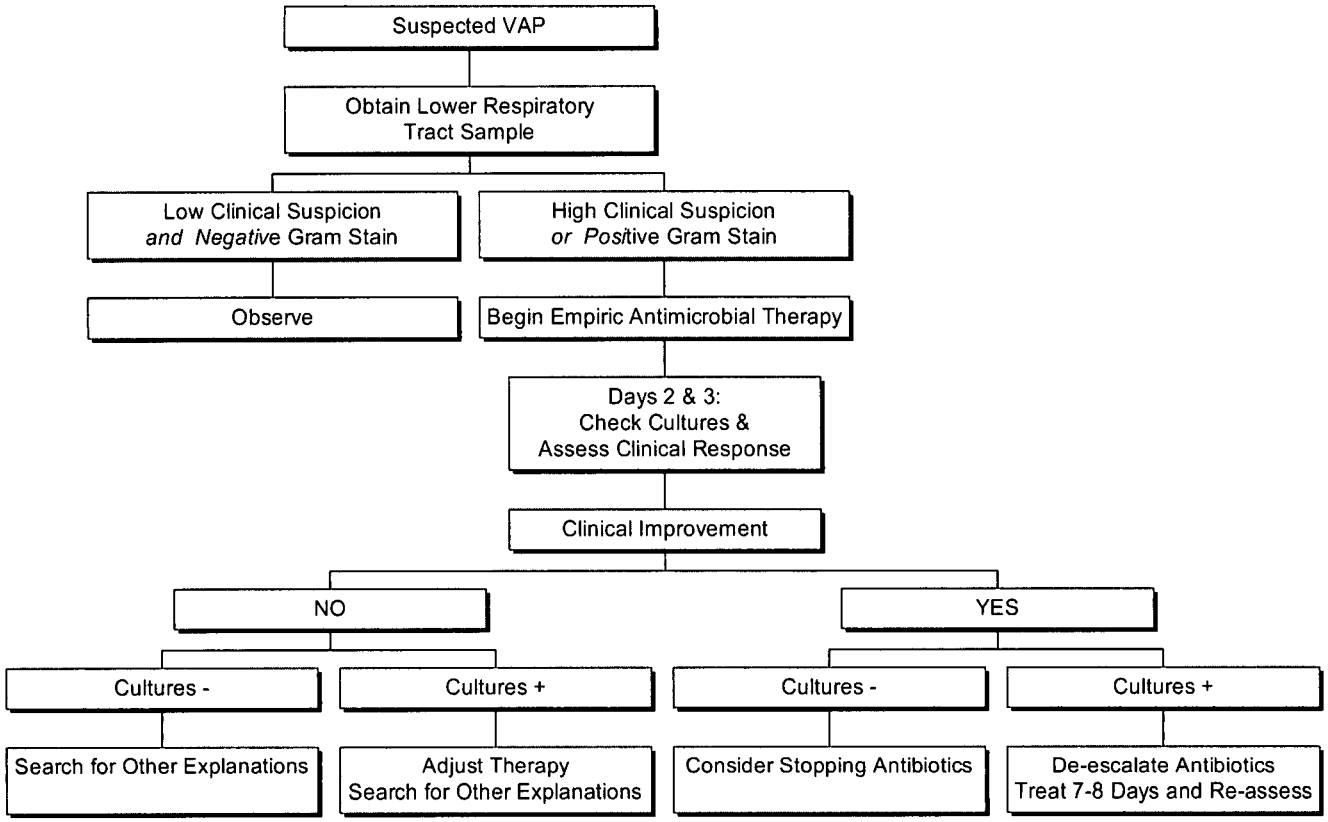

FIG. 1. VAP management algorithm. VAP, ventilator-associated pneumonia.

TABLE 4. *Risk Factors for VAP with MDR Organisms*

Late-onset VAP
Antibiotics within previous 90 days
Hospitalization within previous 90 days
Current hospitalization >5 days
Admission from a long-term care/hemodialysis facility
High frequency of antibiotic resistance in the community
Immunosuppressive disease or therapy

therapy," being collectively at least one antimicrobial agent to which the pathogen is sensitive, in the correct dose, via the correct route of administration, and in a timely manner. A second crucial aspect of VAP therapy involves serial reevaluation and interpretation of initial microbiology so that therapy may be discontinued if no organism is isolated and the patient has not deteriorated clinically; therapy is de-escalated to treat only the specific etiologic pathogen; and an endpoint of therapy may be identified in prospect and adhered to.

Ample data exist detailing the increased mortality associated with inadequate initial antimicrobial therapy in patients with VAP. Iregui et al.[134] showed that delayed therapy (defined as initial antibiotic treatment administered ≥24 hours after meeting diagnostic criteria for VAP) was independently associated with hospital mortality (OR 7.68, 95% CI [4.50–13.09], $P < 0.001$). The mean difference in time to antibiotic administration between groups was 16 hours. Similarly, Kollef et al.[28] reported that inadequate initial antimicrobial therapy was an independent risk factor for ICU mortality in patients with gram-negative infections (OR 4.22, 95% CI [3.57–4.98], $P < 0.001$). Alvarez-Lerma et al.[105] demonstrated that attributable mortality from VAP was significantly lower among patients receiving initial appropriate antibiotic treatment compared with receipt of inappropriate treatment (16.2% *vs* 24.7%; $P = 0.03$). That appropriate initial therapy is essential is underscored by the fact that Alvarez-Lerma et al. demonstrated that switching to appropriate therapy once culture results became available did not ameliorate the excess mortality associated with inadequate initial therapy.

The choice of initial antimicrobial therapy depends on patient risk factors for MDR pathogens and local microbiologic data that may be obtained from the unit-specific antibiogram (Fig. 2). Having a current and frequently updated antibiogram increases the likelihood that appropriate initial antibiotic treatment will be prescribed.[135–137] In general, therapy for patients at risk for infection with a MDR organism should provide coverage against MRSA, *Pseudomonas*, *Acinetobacter*, and extended-spectrum β-lactamase-producing *Klebsiella*. This will likely require at least two drugs,

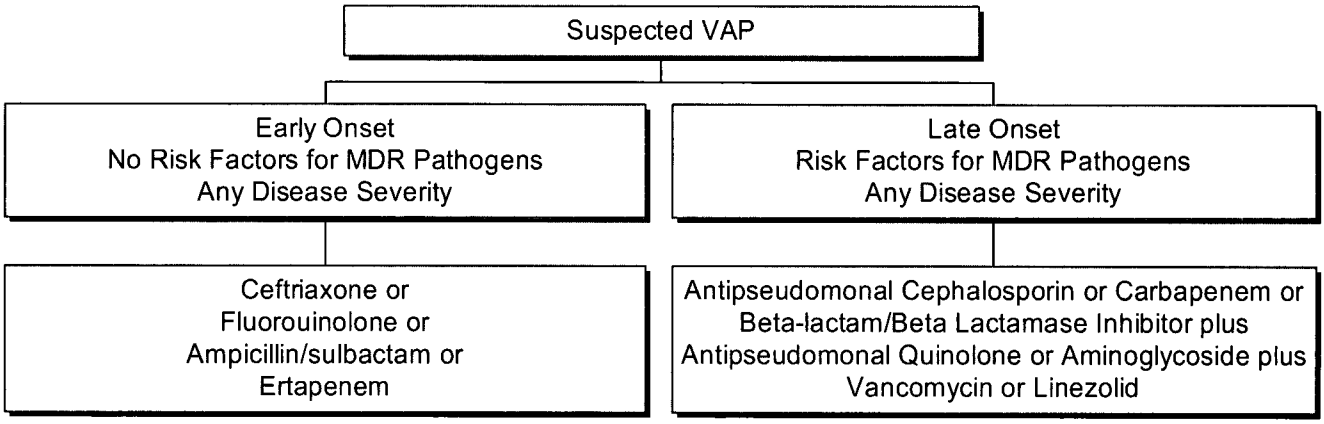

FIG. 2. Algorithm for selection of initial antimicrobial therapy in suspected VAP. VAP, ventilator-associated pneumonia; MDR, multi-drug-resistant.

one effective against MRSA (*e.g.*, vancomycin or linezolid) and one effective against MDR gram-negative bacilli, particularly *Pseudomonas* (*e.g.*, piperacillin-tazobactam or meropenem). Patients with early-onset VAP and none of the aforementioned risk factors may be treated with narrow-spectrum therapy as outlined in Fig. 2. Unfortunately, in most ICUs, such patients are relatively few.

Antimicrobial therapy for VAP should be administered initially via the intravenous (IV) route. Enteral therapy may be considered if patients demonstrate an adequate response to IV therapy, gastrointestinal function is normal, and the antibiotics used possess equivalent bioavailability when administered via this route. Conversion to enteral therapy for VAP using linezolid or a fluoroquinolone is effective, assuming the aforementioned criteria are met.[138] A RCT of the adjunctive use of aerosolized tobramycin showed no difference in clinical outcomes between groups, despite significantly increased microbiologic eradication in the tobramicin group;[139] further research into the use of aerosolized antibiotics is needed.

Inadequate dosing of antibiotics leads to the emergence of MDR bacteria and is associated with poorer outcomes in VAP.[140] Appropriate initial dosing of vancomycin (15 mg/kg every 12 h), aminoglycosides (gentamicin or tobramycin 7 mg/kg daily; or amikacin 20 mg/kg daily) and fluoroquinolones (levofloxacin 750 mg daily or ciprofloxacin 400 mg every 8 h) is paramount to achieving adequate therapy (all doses assume normal renal function).

Certain points regarding specific antibiotics warrant further discussion. Most notably, linezolid has emerged as an effective alternative therapy for VAP caused by gram-positive bacteria, and MRSA in particular. Linezolid is theoretically appealing for the treatment of VAP because achievable concentrations in bronchial secretions exceed those in serum, dosing adjustment is not needed for renal failure, and enteral administration has equivalent bioavailability.[141] Two RCTs demonstrated clinical equivalence of linezolid and vancomycin in the treatment of VAP caused by gram-positive pathogens,[142, 143] and a *post hoc* logistic regression analysis of both studies reported a significantly increased likelihood of clinical cure for linezolid therapy compared with vancomycin.[144] One limitation of these studies involves the possible inadequate initial dosing of vancomycin (1 g every 12 h *vs* the currently recommended 15 mg/kg every 12 h). However, linezolid is at least as effective as vancomycin in the treatment of gram-positive VAP, and specifically, MRSA infections. Recent cost-effectiveness analyses have also demonstrated significant cost savings associated with the use of linezolid compared with vancomycin.[145, 146]

Abundant data now exist documenting the association between fluoroquinolone use and the emergence of VAP caused by MDR pathogens, particularly *Pseudomonas*.[147–149] Therefore, fluoroquinolone use in the treatment of VAP should be judicious, based on frequently updated institutional antibiograms.

Whereas multidrug therapy is usually necessary to achieve adequate empiric coverage in patients with suspected VAP until culture results become available, combination therapy directed against a specific pathogen (*e.g.*, "double-coverage" of *Pseudomonas*) is unlikely to provide benefit and may worsen outcomes. Neither *in vitro* nor *in vivo* synergy of such combination therapy has been demonstrated consistently.[150, 151] A meta-analysis of all trials of β-lactam monotherapy *versus* β-lactam-aminoglycoside combination therapy for immunocompetent patients with sepsis, including 64 trials and 7586 patients, found no difference in mortality (relative risk 0.90, 95% CI [0.77–1.06]) or the development of resistance.[152] In fact, clinical failure was more common with combination therapy.

After initiation of adequate antimicrobial therapy

for suspected VAP, results of lower respiratory tract cultures may reveal no growth or insignificant growth (below a predetermined threshold value); significant (above threshold) growth of a pathogen sensitive to a narrow-spectrum agent; or significant growth of a pathogen sensitive only to a broad-spectrum agent. Regarding the first scenario, data indicate that antimicrobial therapy may be discontinued safely as long as the patient has not deteriorated clinically.[130–133] In the second scenario, therapy is de-escalated to a narrow-spectrum agent with activity against the pathogen isolated. In the last scenario, the initial broad-spectrum agent to which the pathogen is susceptible is continued.

The goal of adequate empiric therapy is to initiate a combination of antibiotics likely to cover all possible etiologic pathogens, followed by tailored therapy if possible. The ideal treatment of suspected VAP thus involves an initial period of perfect sensitivity followed by a period of perfect specificity, once microbiology results are available. In this fashion, no patient with VAP is untreated, and no patient without VAP is treated after microbiologic data are available.

Once pathogen-specific therapy has been initiated, its duration must be determined such that prolonged and unnecessary periods of antibiotic administration are avoided. Resolution of clinical and radiographic parameters typically lags the eradication of infection.[153] Vidaur et al.[122] found that improved oxygenation and normalization of temperature occurred within 3 days in VAP patients without ARDS. Dennesen et al.[154] observed a clinical response to therapy of VAP, defined as normalization of temperature, white blood cell count, arterial oxygen saturation, and quality of tracheal aspirates, within 6 days of therapy.

A randomized, multicenter trial of 401 patients with microbiologically proven VAP assigned subjects to receive eight or 14 days of antibiotic therapy.[155] All patients received adequate initial therapy after invasive/quantitative specimen collection, and patients whose therapy ended at 8 days were stable clinically at that time. Patients treated for 8 days had equivalent mortality, ICU LOS, duration of mechanical ventilation, and recurrence of infection despite significantly fewer antibiotic-free days. Recurrent infections were less likely to be caused by MDR pathogens in patients treated for 8 days. However, patients with VAP caused by nonfermenting gram-negative bacilli (*e.g.*, *Pseudomonas*, *Acinetobacter*, and *Stenotrophomonas*) were more likely to develop recurrent pneumonia if treated for 8 days only. Thus, an 8-day course of initially appropriate antimicrobial therapy appears safe and effective provided that the patient has not deteriorated and the pathogen is not a nonfermenting gram-negative bacillus.

In select patients, a shorter course of therapy may be effective for the treatment of VAP. Singh et al.[113] randomized patients with suspected VAP and a CPIS score ≤ 6 points to receive standard therapy (physician discretion) *versus* ciprofloxacin monotherapy, with re-evaluation at Day 3 and discontinuation of antibiotics if the CPIS remained ≤ 6. If the CPIS remained ≤ 6 at the 3-day evaluation point, antibiotics were continued in 96 per cent (24/25) of patients in the standard therapy group, but in none of the patients in the experimental therapy group ($P = 0.0001$). Mortality and ICU LOS did not differ despite a shorter duration ($P = 0.0001$) and lower cost ($P = 0.003$) of antimicrobial therapy in the experimental arm.

Patients treated for VAP who do not improve clinically after appropriate antimicrobial therapy pose a dilemma. Inadequate therapy, misdiagnosis, or a pneumonia-related complication (*e.g.*, empyema or lung abscess) must all be considered. A diagnostic evaluation should be repeated, including resampling of the lower respiratory tract for quantitative cultures (using a lower diagnostic threshold when interpreting quantitative microbiology given recent antibiotic exposure) and consideration of broadened coverage until new data become available.

Current literature suggests a discrepancy between the standard of care discussed herein and contemporary clinical practice. Rello et al.[156] reported that, in a cohort of 113 patients with VAP, nearly 25 per cent received inadequate initial therapy. In a second cohort study of 398 ICU patients with suspected VAP from 20 ICUs throughout the U.S., Kollef et al.[25] documented more than 100 different antibiotic regimens prescribed as initial therapy of VAP. Furthermore, the mean duration of therapy was 11.8 ± 5.9 days, and in 61.6 per cent of cases, there was not escalation de-escalation. The use of standardized treatment protocols can substantially improve the likelihood that adequate therapy is delivered for an appropriate duration. Ibrahim et al.[135] compared outcomes before and after implementation of a VAP treatment protocol that involved standardized, broad-spectrum initial coverage, with termination after 7 days absent persistent signs of active infection. The proportions of patients who received inadequate initial therapy and therapy of inappropriate duration were significantly lower in the protocol arm. Several additional studies have confirmed the effectiveness of protocol-driven therapy.[157, 158]

Conclusions

VAP remains a common and problematic disease. Fortunately, health care practitioners may intervene successfully at several points in the natural history of VAP. Curtailing the incidence of VAP begins with

implementation of evidence-based preventive measures. When the diagnosis of VAP is suspected clinically, it must be confirmed microbiologically through the culture of lower respiratory tract samples, which is accomplished most effectively via quantitative cultures obtained using bronchoscopy. Broad-spectrum antimicrobial therapy must be initiated promptly, although preferably not before sputum specimen collection. Adequate initial therapy based on individual patient risk factors and institutional antibiograms is imperative to maximize survival. However, de-escalation and short-course therapy, when appropriate, are equally important in deterring the emergence of MDR pathogens. Finally, it is through continued research that evidence-based recommendations will emerge to elucidate current areas of controversy and inspire novel therapies in the management of VAP.

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