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REVIEW

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Ventilator-associated pneumonia: present understanding and ongoing debates

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Abstract *Introduction:* Ventilator-associated pneumonia (VAP) is a common cause of nosocomial infection, and is related to significant utilization of health-care resources. In the past decade, new data have emerged about VAP epidemiology, diagnosis, treatment and prevention. *Results:* Classifying VAP strictly based on time since hospitalization (early- and late-onset VAP) can potentially result in undertreatment of drug-resistant organisms in ICUs with a high rate of drug resistance, and overtreatment for patients not infected with resistant pathogens. A combined strategy incorporating diagnostic scoring systems, such as the Clinical Pulmonary Infection Score (CPIS), and either a quantitative or qualitative microbiological specimen, plus serial measurement of biomarkers, leads to responsible antimicrobial stewardship. The newly proposed ventilator-associated events (VAE) surveillance definition, endorsed by the Centers for Disease Control and Prevention, has low sensitivity and specificity for diagnosing VAP and the ability to prevent VAE is uncertain, making it a questionable surrogate for the quality of ICU care. The use of adjunctive aerosolized antibiotic treatment can provide high pulmonary concentrations of the drug and may facilitate shorter durations of therapy for multi-drug-resistant pathogens. A group of preventive strategies grouped as a 'ventilator bundle' can decrease VAP rates, but not to zero, and several recent studies show that there are potential barriers to implementation of these prevention strategies. *Conclusion:* The morbidity and mortality related to VAP remain high and, in the absence of a gold standard test for diagnosis, suspected VAP patients should be started on antibiotics based on recommendations per the 2005 ATS guidelines and knowledge of local antibiotic susceptibility patterns. Using a combination of clinical severity scores, biomarkers, and cultures might help with reducing the duration of therapy and achieving antibiotic de-escalation.

Keywords Nosocomial pneumonia · Hospital-acquired pneumonia · Ventilator-associated pneumonia · Ventilator-associated complications · Prevention · Antimicrobial treatment

Introduction

Ventilator-associated pneumonia (VAP) is an important nosocomial infection that can complicate mechanical ventilation. The 2005 American Thoracic Society and Infectious Diseases Society of America (ATS/IDSA) guidelines provide a comprehensive approach to diagnosis and management of adults with nosocomial pneumonia [1], but in the past decade, new data have emerged about VAP epidemiology, diagnosis, treatment, and prevention.

The diagnosis of VAP is challenging and subject to considerable interobserver variability. The Centers for Disease Control and Prevention (CDC) definition of VAP uses a combination of clinical, radiographic, and microbiological criteria for diagnosis, but in the absence of a benchmark diagnostic test, the accurate diagnosis and treatment of VAP is limited. There has been a steady decline in reported VAP rates over the last several years in the USA, with the National Healthcare Safety Network (NHSN) reporting an incidence of VAP from 0.0 to 5.8 per 1,000 ventilator days [2]. It is unclear if this reduction in VAP incidence is the result of improved prevention measures or due to underestimation in a setting of public reporting to the Centers for Medicare and Medicaid Services (CMS) [3]. The CDC recently introduced a new concept—ventilator-associated events (VAE), a tiered approach as an objective surveillance measure to improve the accuracy of diagnosing ventilator-related complications [4]. However, the utility of VAE to identify all patients with pneumonia, the ability to prevent VAEs, and the role of VAEs in day to day clinical practice are uncertain.

The ATS/IDSA 2005 guidelines emphasize treatment based on the potential for developing infection with multidrug-resistant (MDR) pathogens. The microbiological agents and epidemiologic factors related to VAP have changed over the last decade and might influence treatment decisions and outcomes. The guidelines discussed invasive quantitative cultures as having some advantage over endotracheal aspirates for the diagnosis of VAP, but subsequent studies did not show any difference in mortality for either approach [5]. Recently, investigators have raised concerns about adherence to the guideline recommendation of using routine combination therapy for VAP [6, 7]. Prevention strategies based a group of interventions lumped into a 'daily bundle' have been shown to decrease the rate of VAP [8]. However, implementation has met with barriers in clinical practice, and the compliance rate with bundles is still modest.

There are several areas of uncertainty regarding VAP that require further clarification (as noted in Table 1). It is beyond the scope of this review to discuss all the topics, but we discuss the current understanding and controversies surrounding the major issues in VAP diagnosis, treatment, and prevention.

Changing epidemiology

VAP is generally divided into early onset or late onset (early, less than 5 days; late, more than 5 days after hospitalization), although some investigators have classified early-onset VAP as less than 7 days and late as more than 7 days since hospitalization [9, 10]. In previous guidelines, this classification has been related to bacteriology and empiric therapy choices, but recently, the bacteriologic differences between early- and late-onset VAP have been less clear, with some early-onset patients infected with drug-resistant pathogens, while certain patients in both groups can be infected with sensitive pathogens. Thus, antibiotic choice based on the time of pneumonia onset can lead to both over- and undertreatment with broad-spectrum agents.

Table 1 Areas of uncertainty and future investigations in VAP diagnosis, treatment, and prevention

Epidemiology
1. Changes in the microbiome related to the emergence of drug-resistant pathogens in VAP
2. Need for a central registry for extremely drug-resistant pathogens
3. Microbiology of VAP in special circumstances such as immune-compromised hosts, burn, trauma, and ARDS patients
Diagnosis
4. Role of invasive and semi-invasive cultures in the diagnosis of VAP
5. Role of biomarkers and clinical severity scores in diagnosis, duration of therapy, and de-escalation
6. New CDC surveillance definitions and their impact on and relevance in VAP diagnosis and prevention
Treatment
7. Benefit of guideline-concordant therapy versus guideline-discordant therapy
8. Does de-escalation decrease mortality in VAP?
9. Role of continuous and/or prolonged antibiotic infusion therapy in VAP
10. Role of therapeutic drug monitoring and impact on mortality
11. Role of localized adjunctive aerosol treatment for VAP
Prevention
12. How can VAE be prevented?
13. Role of VAP bundles on incidence and mortality of VAP
14. Does early tracheostomy prevent VAP?
15. Should preventive antibiotic strategies be routine in head-injury patients?
16. Benefit of modifications of endotracheal tube in VAP prevention

Table 2 Etiologic agents causing VAP

Core pathogens	MDR pathogens
S. pneumoniae	*P. aeruginosa*
H. influenzae	*Acinetobacter* sp.
Enterobacter spp.	*Stenotrophomonas maltophilia*
Escherichia coli	*Klebsiella pneumoniae* (ESBL+)
Klebsiella spp.	Methicillin-resistant *S. aureus* (MRSA)
Proteus spp.	
Serratia marcescens	
Methicillin-sensitive *S. aureus*	

Early- and late-onset VAP: is it important to make a distinction?

Traditionally, early-onset VAP was caused by drug-sensitive pathogens, such as *Streptococcus pneumoniae*, *Haemophilus influenzae*, and methicillin-sensitive *Staphylococcus aureus*, while late-onset VAP was caused by antibiotic-resistant pathogens, such as *Pseudomonas aeruginosa*, *Acinetobacter* spp., methicillin-resistant *S. aureus* (MRSA), and extended-spectrum beta-lactamase-producing Gram-negative bacilli. Recent studies have challenged these concepts (see Table 2).

In a large German database, the identity of the pathogens causing early- and late-onset VAP were similar, and the most frequent organisms were *S. aureus*, followed by *P. aeruginosa*, *K. pneumoniae*, and *E. coli* [11]. In another study, Restrepo and colleagues examined the cultures of 248 early-onset (less than 5 days) and 248 late-onset VAP (more than 5 days) patients and although patients with late-onset VAP had more significant antibiotic exposure in the prior month and higher Acute Physiology and Chronic Health Evaluation (APACHE) II scores on admission to ICU, both early- and late-onset VAP patients had similar rates of MDR pathogens (27.8 and 32.3 % respectively, $p = 0.33$) [12].

Ferrer and colleagues classified 276 patients with ICU-acquired pneumonia on the basis of time of onset and found that very few fell into group 1 (early onset without risk factors for MDR pathogens, $n = 38$, VAP in 18 patients), and that most were classified as group 2 (late onset or with risk factors for MDR pathogens, $n = 238$, VAP in 128 patients) [13]. Of the patients in group 1, 26 % had potentially drug-resistant pathogens isolated despite having no risk factors as per the 2005 guidelines. Investigators from the EU-VAP study group divided 485 patients with microbiology-confirmed nosocomial pneumonia into group 1, i.e., early onset with no MDR risk factors ($n = 152$), and group 2, i.e., early onset with MDR risk factors or late-onset pneumonia [14]. Of the patients in group 1, 50.7 % harbored resistant microorganisms including *P. aeruginosa*, *S. maltophilia*, MRSA, and *Acinetobacter baumannii*. Logistic regression analysis noted the presence of severe sepsis/septic shock (OR = 3.7) and pneumonia that developed in a center with greater than a 25 % prevalence of resistant pathogens (OR = 11.3) as independently associated with the presence of resistant pathogens in group 1 patients.

Thus classifying VAP patients based on time of onset might potentially result in undertreatment of those with early-onset infection and delayed institution of antibiotics and inadequate microbial coverage, both of which are related to adverse outcomes in patients with VAP [15–17]. On the other hand, empiric therapy can also result in overtreatment and thus therapy should be based on individual risks and the local prevalence of resistant pathogens.

Is there a difference between the etiologic agents causing VAP compared to those causing HAP?

The SENTRY antimicrobial surveillance program collected microbiological data from 1997 to 2008 in hospitalized patients with pneumonia from North America, Europe, and Latin America [18]. The top six pathogens isolated from patients with nosocomial pneumonia were *S. aureus* (28.0 %), *P. aeruginosa* (21.8 %), *Klebsiella* species (9.8 %), *E. coli* (6.9 %), *Acinetobacter* species (6.8 %), and *Enterobacter* species (6.3 %). There was no significant difference among the six common etiologic agents between patients with hospital-acquired pneumonia (HAP) and VAP. However, *P. aeruginosa* (26.6 %) and *Acinetobacter* species were more common in VAP than in HAP patients, and the incidence of *S. aureus* was lower among patients with VAP than among patients with HAP (19.5 vs. 26.6 %). Esperatti and colleagues prospectively compared 315 episodes of ICU-acquired pneumonia over a 3-year period in ventilated ($n = 164$) and non-ventilated patients ($n = 151$) [19]. There was no significant difference in the relative proportion of etiologic pathogens isolated in both the groups, except for *S. pneumoniae*, which was more common in non-ventilated ICU patients than VAP patients. In another prospective surveillance study comparing 327 episodes of VAP in 309 patients with 261 episodes of HAP in 247 patients, the patients with VAP had more episodes of Gram-negative bacilli, compared to patients with HAP (59 vs. 39.6 %, $p < 0.001$) and HAP patients had a higher incidence of *S. pneumoniae* and viruses [20].

Issues in the diagnosis of VAP

The CDC definition of VAP requires that patients be ventilated for more than 48 h and satisfy at least one radiographic, one systemic, and two pulmonary criteria [21] (see Table 3). Since many patients who are ventilated

Table 3 CDC definition for VAP

Radiographic criteria—two or more chest x-rays showing any of the following
1. New or progressive and persistent infiltrate
2. Consolidation
3. Cavitation
Systemic criteria—at least one of the following
1. Fever (>38 °C or >100.4 °F)
2. Leukopenia (4,000 WBC/mm^3) or leukocytosis (>12,000 WBC/mm^3)
3. For adults >70 years old, altered mental status with no other recognized cause
Pulmonary criteria—at least two of the following
1. New onset of purulent sputum, or change in character of sputum, increased respiratory secretions or increased suctioning requirements
2. Worsening gas exchange (e.g., desaturations, increased oxygen requirements, or increased ventilator demand)
3. New onset or worsening cough, or dyspnea, or tachypnea
4. Rales or bronchial breath sounds

Table 4 Clinical pulmonary infection score (CPIS)

Component	Value	Points
Temperature (°C)	≥36.5 and ≤38.4	0
	≥38.5 and ≤38.9	1
	≥39.0 or ≤36.0	2
Blood leukoctyes (WBC/mm^3)	≥4,000 and ≤11,000	0
	<400 or >11,000	1
Tracheal secretion	Few	0
	Moderate	1
	Large	2
	Purulent	+1
Oxygenation PaO_2/FiO_2	>240 or presence of ARDS	0
	≤240 and absence of ARDS	2
Chest radiograph	No infiltrate	0
	Patchy or diffuse infiltrate	1
	Localized infiltrate	2

may develop other diseases that can mimic pneumonia, some investigators have recommended obtaining quantitative lower respiratory tract samples by bronchoscopic protected brush, bronchoalveolar lavage (BAL), or endotracheal aspiration in conjunction with the initiation of antibiotic treatment when VAP is suspected [22]. The clinical pulmonary infection score (CPIS) was developed to objectively diagnose VAP and assigns points on the basis of clinical and radiographic data, but its role in diagnosing pneumonia remains controversial [23]. This score was subsequently modified by Singh and colleagues to include radiographic progression and a score of 6 at baseline and at 72 h is considered suggestive of pneumonia (see Table 4) [24]. The ATS/IDSA 2005 guidelines have incorporated both a clinical and bacteriologic strategy for VAP diagnosis in their final recommendation.

Quantitative sampling of the lower respiratory tract and the role of clinical diagnosis of VAP based on CPIS

Although quantitative cultures improve the specificity of VAP diagnosis, there is a chance of false negative cultures in patients with partially treated and early pneumonia and false positive results with chronic colonization during prolonged mechanical ventilation. Ventilator-associated tracheobronchitis (VAT) is a related condition, characterized by clinical signs (fever, leukocytosis, and purulent sputum), microbiologic findings (Gram stain with bacteria and leukocytes, with either a positive semiquantitative or a quantitative sputum culture), but the absence of a new infiltrate on chest radiograph [25]. Patients with VAT have been shown to have prolonged duration of mechanical ventilation, ICU stay, and increased mortality [26]. However, it has been controversial whether recognition and early therapy of VAT can prevent the development of VAP. Some investigators have found that VAT is independent from VAP, while others have found that VAT is a predecessor of VAP [27, 28].

Heyland and colleagues randomly assigned 740 ventilated patients with suspected VAP to undergo either BAL with quantitative culture or endotracheal aspiration with non-quantitative culture of the aspirate and found no significant difference in mortality, length of stay in the hospital or ICU, and the frequency of targeted therapy/de-escalation with both approaches [5]. In a meta-analysis of four randomized control trials, there was no significant difference in mortality between an invasive bronchoscopic approach versus a non-invasive approach, but the invasive approach helped with antibiotic utilization and focusing therapy [29]. A recent Cochrane review revealed no significant differences in terms of mortality, length of ICU stay, duration of mechanical ventilation, and rate of antibiotic change between qualitative culture of noninvasive samples and quantitative culture of invasive samples [30].

The CPIS score was originally shown to have a good correlation with the bacterial index of samples obtained via BAL [23], but it has a low sensitivity in patients with ARDS and in surgical patients; however, if measured serially, the CPIS score may help guide the duration of antibiotic treatment [31]. The CPIS score can be more valuable if used in conjunction with a good lower respiratory tract sample, which includes Gram staining [32]. In another study, 299 mechanically ventilated patients had twice weekly surveillance endotracheal aspirate cultures (EA) [33], and in the 41 patients diagnosed with VAP by BAL, the CPIS score was significantly elevated compared to 34 patients with negative BAL culture (6.6 vs. 5, $p = 0.001$). The initial empiric antibiotic therapies based on the EA cultures were adequate in 95 % of patients with VAP. Of the various measures included in CPIS, oxygenation measured by the ratio of partial pressure of oxygen compared to fractional inspired oxygen (PaO_2/FiO_2) has consistently proven to be a good indicator of outcome, particularly when followed serially [34].

Several biomarkers, including soluble triggering receptor expressed on myeloid cells-1 (sTREM-1), procalcitonin (PCT), copeptin, and C-reactive protein (CRP), have been studied in patients with VAP. In a prospective study, serial PCT measurements on days 1, 3, and 7 were significantly higher in microbiologically proven VAP patients who had an unfavorable outcome than those with a favorable outcome, while serial CPIS values were less discriminatory [35]. However, in that study, serial measurements of oxygenation did distinguish patients with an unfavorable outcome from those with a good outcome. Ramirez and colleagues found that a combination of CPIS of at least 6 points and serum PCT levels of at least 2.99 ng/mL had 100 % specificity and negative predictive value of 92 % (AUC = 0.961) for the diagnosis of VAP in a small study ($n = 44$) [36]. Although clinical features are not specific, serial measurements of oxygenation and biomarkers might be the most useful strategy for deciding when to use antibiotics and when to de-escalate once a particular pathogen is identified.

What is the role of new surveillance definitions for VAP and VAE?

The CDC definition of VAP is subject to interobserver variability and subjectivity, and thus Klompas and colleagues developed a simplified streamlined surveillance definition of VAP and compared it to the conventional CDC definition in 600 patients [37]. They excluded the criteria of delirium and rales, and defined worsening oxygenation as at least 2 days of stable or decreasing daily minimum PEEP, followed by an increase of at least 2.5 cmH_2O of PEEP for more than 2 days; or at least 2 days of stable or decreasing FiO_2, followed by an increase of at least 0.15 in FiO_2 sustained over 2 days. Compared to the conventional definition, the streamlined definition identified patients with VAP faster (3.5 vs. 39 min per patient) and more objectively, with no major difference in hospital mortality, ICU length of stay, and ventilator days between the two definitions. However, no chest radiograph was used in the streamlined definition, a feature that may be either a problem or an advantage.

Table 5 New CDC definition for ventilator-associated events

Ventilator-associated complication	*At least one* of the following indicators of *worsening oxygenation* 1. Minimum daily FiO_2 values increase ≥0.20 (20 points) over baseline and remain at or above that increased level for ≥2 calendar days 2. Minimum daily PEEP values increase ≥3 cmH_2O over baseline and remain at or above that increased level for ≥2 calendar days
Infection-related ventilator-associated complication	Patient has VAC and also fits *both* of the two following criteria 1. Temperature greater than 38 °C or WBC greater than 12,000 or less than 4,000/mm^3 2. A new antimicrobial agent is started and is continued for 4 or more calendar days
Possible VAP	On or after calendar day 3 of mechanical ventilation and within 2 calendar days before or after the onset of worsening oxygenation, *one* of the following criteria is met 1. Purulent respiratory secretions (defined as secretions from the lungs, bronchi, or trachea that contain >25 neutrophils and <10 squamous epithelial cells per low power field [lpf, ×100]; If the laboratory reports semiquantitative results, those results must be equivalent to the above quantitative thresholds) 2. Positive culture (qualitative, semiquantitative, or quantitative) of sputum, endotracheal aspirate, bronchoalveolar lavage, lung tissue, or protected specimen brushing
Probable VAP	On or after calendar day 3 of mechanical ventilation and within 2 calendar days before or after the onset of worsening oxygenation, *one* of the following criteria is met 1. Purulent respiratory secretions (from one or more specimen collections—and defined as for possible VAP) and one of the following: positive culture of endotracheal aspirate, ≥10^5 CFU/ml or equivalent semiquantitative result, or positive culture of bronchoalveolar lavage, ≥10^4 CFU/ml or equivalent semiquantitative result, or positive culture of lung tissue, ≥10^4 CFU/ml or equivalent semiquantitative result, or positive culture of protected specimen brush, ≥10^3 CFU/ml or equivalent semiquantitative result 2. One of the following (without requirement for purulent respiratory secretions): positive pleural fluid culture (where specimen was obtained during thoracentesis or initial placement of chest tube and *not* from an indwelling chest tube), or positive lung histopathology, or positive diagnostic test for *Legionella* spp., or positive diagnostic test on respiratory secretions for influenza virus, respiratory syncytial virus, adenovirus, parainfluenza virus

To improve objectivity and reproducibility, a CDC working group recently proposed an alternative definition for VAE, which include ventilator-associated complications (VAC), infectious ventilator-associated complications (IVAC), and probable versus possible VAP (see Table 5) [38, 39]. The definitions focus on worsening oxygenation (defined by ventilator settings and not by physiologic measurements) and systemic signs of infection and exclude the use of chest radiography. Problems with this definition include the need for an initial 2 days of stability, thus excluding some early VAP, and dependence on changes in the FiO_2 rather than on a more physiological PaO_2/FiO_2 ratio. Hayashi and colleagues retrospectively analyzed the data from 543 patients receiving mechanical ventilation, comparing 153 patients with VAC to 390 without, and observed that those with VAC had a higher ICU length of stay (22 vs. 11 days), duration of mechanical ventilation (20 vs. 5 days), and use of antibiotics but no difference in overall ICU mortality [40]. VAC definitions were not specific for VAP and included atelectasis in 16.3 %, acute pulmonary edema in 11.8 %, and acute respiratory distress syndrome in 6.5 %. Thus the VAC definition identified sick patients, but not all VAC patients had pneumonia.

Muscedere and associates studied the clinical impact and preventability of VAC and IVAC, and the relationship to VAP, using prospectively collected data [41]. Of the 1,320 patients included, VAC developed in 10.5 % and patients who had VAC were more likely to develop VAP than those who did not (28.1 vs. 9.2 %, $p < 0.001$). However, only 39 of 139 with VAC had VAP, and most patients with VAP did not have VAC or IVAC. When prevention efforts were undertaken, they were able to reduce the incidence of VAC and VAP, but not IVAC. In another recent study of 2,080 patients from the Netherlands, electronic surveillance for VAE found the incidence of VAC, IVAC, and VAE-VAP to be 10.0, 4.2, and 3.2 per 1,000 ventilation days, respectively [42]. The incidence of VAE was higher in patients receiving at least 7 days of mechanical ventilation compared to those receiving less than 7 days. Only 32 % of patients with VAP identified by prospective surveillance were detected using the VAE algorithm.

Data from the above studies indicate that VAC and IVAC are not always VAP, and that prevention efforts for VAP do not always affect VAC and IVAC rates, raising doubt about the utility of these new definitions as a measure of the quality of care for ventilated patients.

Treatment of VAP

Therapy choices for VAP are based on the presence of risk factors for infection with MDR pathogens and may be initially broad-spectrum, necessitating de-escalation of therapy once clinical and microbiologic data become available. This approach balances the need for early appropriate therapy with avoidance of promoting antimicrobial resistance and drug toxicity, by not continuing multidrug therapy longer than is needed (see Fig. 1) [43].

Is there a difference in VAP outcomes between guideline-concordant and guideline-discordant therapy?

Ferrer and colleagues performed a validation study of the 2005 ATS guidelines in 276 patients with ICU-acquired pneumonia. Empiric treatment was considered adequate when the isolated pathogens were susceptible to one of the antimicrobials administrated, except for *P. aeruginosa*, where a combination of two active antibiotics was needed. Guideline adherence resulted more often in adequate therapy, compared to non-adherence (83 vs. 64 %, $p = 0.013$) [13]. In another multicenter trial with 740 mechanically ventilated patients, combination therapy with meropenem and ciprofloxacin increased the likelihood of appropriate empiric therapy in VAP for those with MDR pathogens (84.2 vs. 18.8 %, $p < 0.001$), but had no impact on mortality; however, in this population, MDR pathogens were uncommon [44]. In a study with initial empiric antibiotic therapy based on the German PEG guidelines, clinical improvement occurred in 82 % of the guideline-adherent group compared to 47 % in the non-adherent group ($p = 0.001$), with better survival in the guideline-adherent group (86 vs. 74 %, $p = 0.021$) [45].

Piskin and colleagues reported that previous antibiotic usage within 3 months (OR = 3.16) and admission to a surgical unit (OR = 2.9) were independent risk factors for inadequate initial VAP therapy [46]. In a study of 110 patients with ICU-acquired P. *aeruginosa* pneumonia, including 71 VAP patients, inadequate initial antibiotic therapy was related to higher mortality and more days on ventilation, and dual therapy was associated with less inadequate treatment [47]. In another multicenter study, using a propensity-matched cohort design, Kumar and colleagues evaluated 1,223 matched pairs of patients with septic shock, who received either adequate combination therapy or adequate monotherapy [16]. They found that early combination therapy with antibiotics having different mechanisms of action resulted in lower mortality (29 vs. 36.3 %; hazard ratio 0.77; 95 % confidence interval 0.67–0.88; $p = 0.0002$) than monotherapy, even though both groups of patients were receiving appropriate therapy. Also patients receiving combination therapy had increased ventilator and inotrope-free days (10 vs. 17; $p = 0.008$ and 23 vs. 25; $p = 0.007$) compared to patients receiving monotherapy.

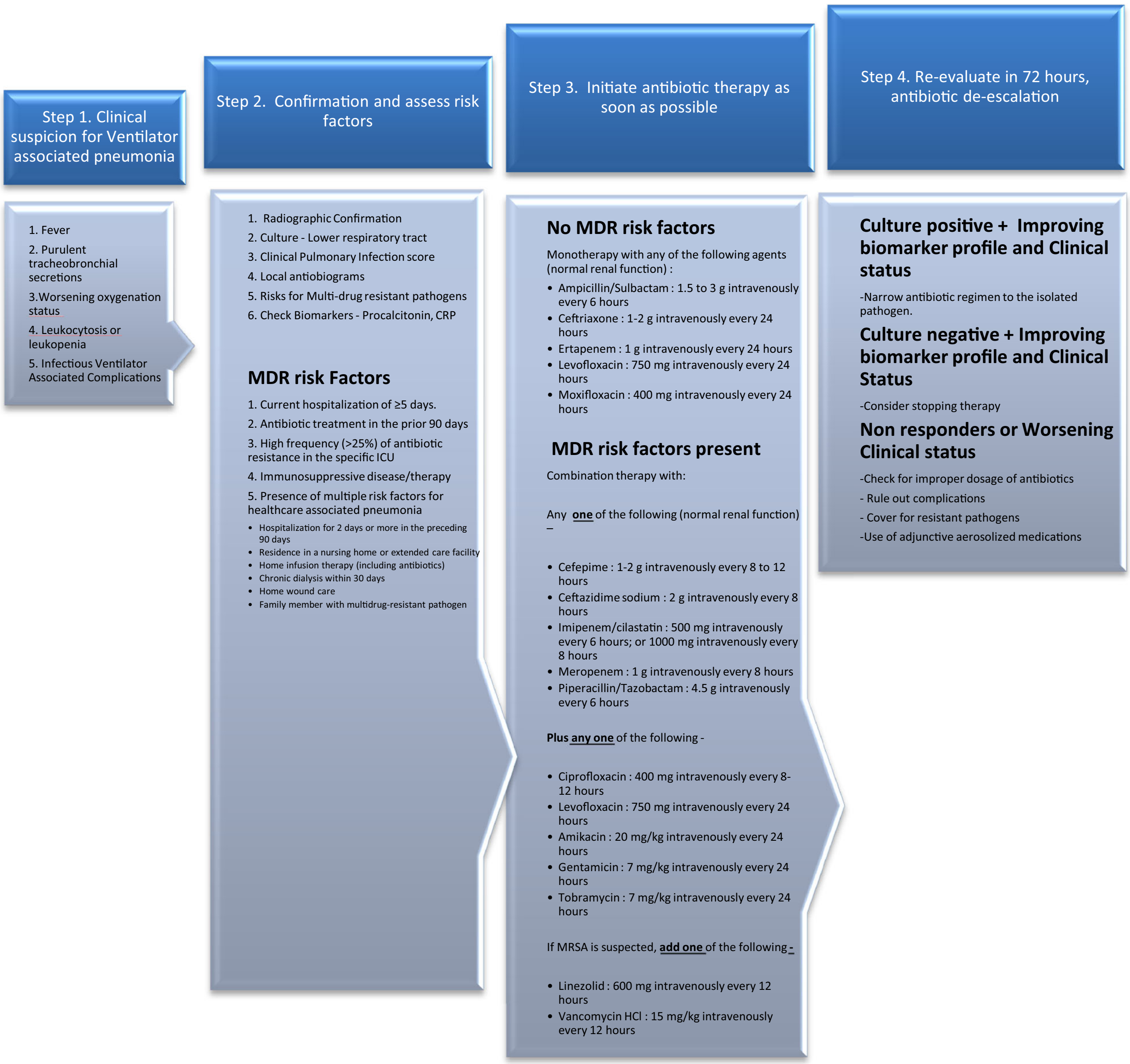

Fig. 1 Suggested algorithmic approach with diagnosis and management of ventilator-associated pneumonia

In contrast to the data favoring the use of guideline-concordant, combination therapy, Kett and associates reported increased mortality when patients received therapy according to guidelines [7]. In a multicenter study of 303 patients with nosocomial pneumonia (132 VAP and 171 HAP + HCAP), patients who were not compliant with the ATS guidelines ($n = 174$), because of the non-use of dual coverage for Gram-negative pathogens or MRSA coverage, had a lower 28-day mortality (20 vs. 34 %), compared to guideline-complaint patients ($n = 129$). However, in this retrospective study, the reasons for patients receiving non-compliant regimens were not explained, and patients in the compliant arm were sicker (with higher APACHE II scores, and more often had sepsis), with less de-escalation of antibiotics, than the non-compliant group.

The focus on guideline adherence should not only be on starting a specific combination regimen but also ensuring that treatment is given as soon as possible, in proper dosages, on the basis of an updated local antibiogram, preferably with a different agent than used recently [48].

How does de-escalation of antibiotics affect VAP outcomes?

The IDSA antimicrobial stewardship guidelines emphasize antibiotic de-escalation as a method to optimize clinical outcomes, while avoiding antibiotic overuse, giving high evidence grading to this approach [49]. Other recommended stewardship approaches include prospective audit and physician feedback on antibiotic usage patterns, dose optimization, and the use of antibiotic treatment guidelines based on knowledge of local microbiologic patterns. While the benefits of de-escalation are becoming clear, there is much opportunity to increase its implementation, with the rates of de-escalation in VAP patients varying from 22 to 74 %. The highest rates occur when there is a protocol for antibiotic modification, rather than usual care, if initial therapy is appropriate, if cultures are positive rather than negative, and if the frequency of MDR pathogens is low [50].

Some studies have shown improved clinical outcomes for VAP when de-escalation is done. In one study of 137 patients with ICU-acquired pneumonia, de-escalation was done in 32 %, and these patients had a lower pneumonia-related mortality than those without de-escalation [51]. However, de-escalation may not have been the reason for a better outcome, but simply a marker of a responding patient, since those with de-escalation had a lower APACHE II and CPIS score at day 5 than those who did not. In a recent study of 714 patients with septic shock, the 35 % who had de-escalation had a lower mortality than those who did not, and this benefit persisted even if only those receiving appropriate therapy were examined [52]. In another observational study, including 89 suspected VAP patients with negative BAL results, investigators compared the effects of early discontinuation (antibiotics stopped within 1 day of final negative quantitative BAL culture results) to late discontinuation of antibiotics, and found no mortality benefit to prolonged therapy, with less frequent superinfections among those with early discontinuation [53].

Role of surveillance culture for de-escalation

One method to choose accurate, focused therapy for VAP is to base therapy choices on surveillance cultures of tracheal aspirates, collected before the onset of pneumonia. Luna and associates prospectively studied an antibiotic strategy based on routine endotracheal aspirate (ETA) culture in 283 ventilated patients, compared to empiric therapy based on the 2005 ATS/IDSA guidelines [54]. Sensitivity for ETA to predict a BAL-obtained pathogen was 62.4 % and was better if done within 3 days of VAP onset. Antibiotic choice based on the ATS/IDSA guidelines led to appropriate therapy in 97.9 %, compared to only 77.4 % based on ETA cultures, but there were fewer antibiotic days using the ETA-based culture. In another study, Brusselaers and colleagues performed a meta-analysis of 14 studies with 791 VAP episodes to analyze the predictive accuracy of twice weekly lower respiratory tract surveillance cultures on subsequent VAP microbiology [55]. The pooled sensitivity and specificity were 0.75 (95 % CI = 0.65–0.83) and 0.92 (95 % CI = 0.85–0.96) respectively for surveillance cultures, and the accuracy improved with twice weekly cultures and if only the latest cultures are used for prediction. But, most importantly, the surveillance cultures had a high negative likelihood value in culture-positive VAP patients especially with MDR pathogens and thus, potentially, routine surveillance cultures can reduce the antibiotic usage. However, the included studies in this meta-analysis are heterogeneous (included studies ranged from 1995 to 2012) and potentially subject to ascertainment bias. Thus, surveillance-based cultures may be helpful in guiding de-escalation and in reducing antibiotic use.

Biomarkers for de-escalation

Serial measurements of serum PCT have been shown to be able to reduce the duration of antibiotic therapy for ICU infection, without an adverse affect on outcome. Bouadma and colleagues performed a prospective, multicenter, open label trial in ICU infection, and found that with PCT guidance, patients with ICU infection (including 75 patients with VAP) had similar mortality as a control group (with duration of therapy based on guidelines), but with fewer days on antibiotics (absolute difference of 2.7 days) [56]. In another trial of 101 VAP patients randomized to antibiotic discontinuation according to guidelines (control group) versus serum PCT measurements, patients in the PCT group more "antibiotic free-days alive" at 28 days after VAP onset (13 vs. 9.5 days) compared to controls, and there was a 27 % reduction in overall antibiotic duration, with no difference in mortality, length of ICU stay, or days on mechanical ventilation [57].

Duration of treatment: short versus long

Chastre and colleagues established the safety and efficacy of 8 days' duration of therapy for VAP, provided that patients received initially appropriate therapy and were not infected with non-fermenting Gram-negatives [58]. A subsequent study corroborated this finding and confirmed that using 15 versus 8 days of therapy led to no difference in mortality, ICU length of stay, and mechanical ventilation days [59]. However, the rate of secondary infection was higher in the shorter duration group (35.3 vs. 19.3 %, $p = 0.01$). In a recent multicenter, randomized, double-blind study of VAP, a 7-day course of high dose (1 g) of doripenem, given by a 4-h infusion, was compared to a

10-day course of a 1-g dose of imipenem, each given every 8 h [60]. The study was prematurely stopped because of documented inferiority of the 7-day regimen, particularly for VAP patients infected by *P. aeruginosa*. All-cause 28-day mortality was also higher in the doripenem arm compared to imipenem, although not significantly (21.5 vs. 14.8 %), but mortality was statistically higher for patients with *P. aeruginosa* who were treated with a 7-day course of doripenem. A recent meta-analysis of four randomized controlled trials comparing short (7–8 days) with longer (10–15 days) duration regimens in VAP showed no difference in mortality, and increased antibiotic-free days in the shorter course group [61]. There was a trend towards more relapses with non-fermenting Gram-negative bacilli in the shorter duration antibiotic cohort.

Other issues in VAP treatment

Although a comprehensive discussion is beyond the scope of this review, there are other areas of VAP pathogenicity and treatment that warrant attention (see Table 6).

Linezolid versus glycopeptides in the treatment of MRSA VAP

Choosing between the agents with activity against MRSA—linezolid, vancomycin, telavancin, or teicoplanin—has been controversial. Linezolid achieves higher lung epithelial lining fluid concentrations than glycopeptides and could therefore have an advantage for MRSA lung infections. However, two older meta-analyses demonstrated comparable clinical and microbiologic success with using linezolid and glycopeptides and a significantly increased risk of thrombocytopenia and gastrointestinal events with linezolid [62, 63]. Since those analyses, a multicenter prospective randomized trial of linezolid versus vancomycin for patients with documented MRSA pneumonia was completed, and linezolid led to a significantly higher rate of clinical response than optimally dosed vancomycin [64]. Although there was no difference in mortality between the two groups, this could potentially be explained by the fact that patients who failed vancomycin were able to be salvaged with linezolid, and any survival in this setting was attributed to vancomycin. Kalil and associates repeated their meta-analysis, using nine randomized controlled trials, including patients from the last study, and concluded that there was no significant difference in mortality and microbiological response comparing linezolid and vancomycin [65]. However, there were concerns regarding the quality of trials included in the analysis, with a trend in favor of linezolid in the better designed trials. In a response to this meta-analysis, Wunderink et al. found a significantly better clinical response with linezolid, if only patients with documented MRSA pneumonia were included [66]. Another recent meta-analysis that also included the new randomized controlled trial of linezolid versus vancomycin did find a higher microbiologic eradication rate for linezolid, and more nephrotoxicity when glycopeptides (vancomycin or teicoplanin) were used [67]. Recent data from the IMPACT-HAP study also demonstrated that patients with MRSA VAP treated with linezolid were more likely to experience clinical resolution of pneumonia than vancomycin-treated patients ($p = 0.018$) [68].

Role of tigecycline in treatment of VAP patients with *A. baumannii*

In a large double-blind, randomized, multicenter trial comparing imipenem/cilastatin to tigecycline in 945 HAP patients, those patients with VAP who were treated with tigecycline had a significantly lower cure rate and more deaths compared to patients with imipenem [69]. Therefore, several investigators have warned against using tigecycline monotherapy in VAP patients. Guner and associates reported the efficacy of tigecycline in 33 patients (19 with VAP) with carbapenem-resistant *Acinetobacter* spp., usually when used as part of a combination regimen [70]. In an exploratory study that tried to improve the efficacy of tigecycline against *Acinetobacter* spp. by increasing the dosing, tigecycline was comparable to imipenem in VAP patients, when used with a 200-mg loading dose, followed by 100 mg every 12 h (which is twice the dose that was used in the negative study above) [71]. Montravers and associates in a prospective study of 156 ICU patients treated with tigecycline (mostly intra-abdominal infections and 24 %

Table 6 Other issues with VAP treatment

1. Linezolid versus glycopeptides in treatment of MRSA VAP
2. Role of tigecycline in treatment of *Acinetobacter* sp.
3. Use of adjunctive aerosolized antibiotics in VAP treatment
4. Role of non-bacterial pathogens in VAP—viruses and fungi
5. VAP in trauma patients
6. Role of low pathogenicity organisms such as *Staphylococcus epidermidis* and anaerobic bacteria in VAP
7. Continuous or prolonged infusion of antibiotics versus standard intermittent dosing
8. Role of therapeutic drug monitoring to decrease mortality

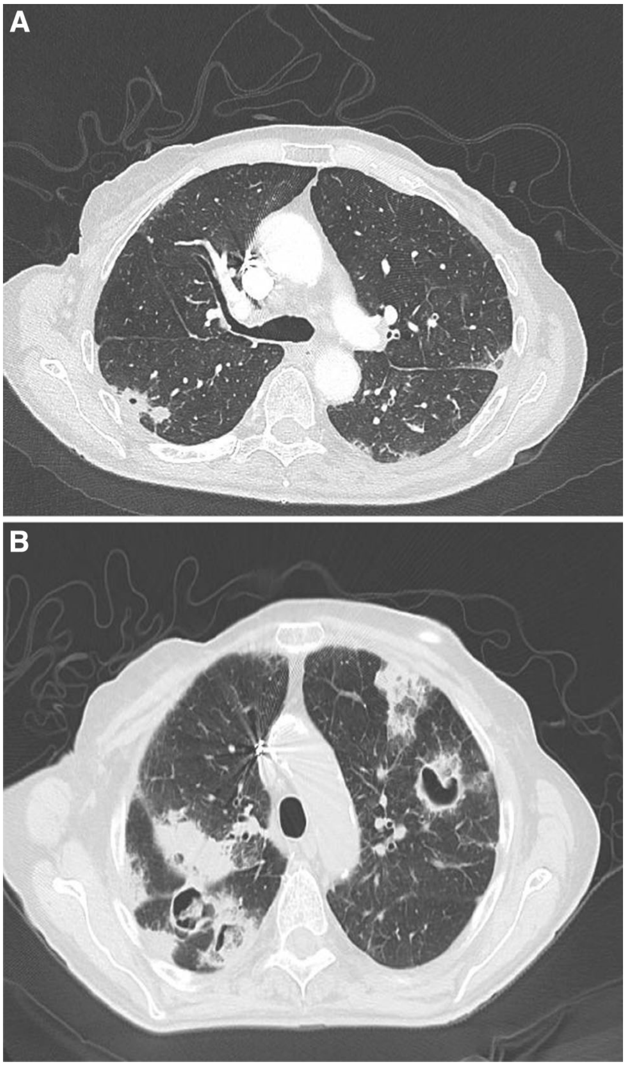

Fig. 2 **a**, **b** CT scan of the chest of a 68-year-old woman with history of breast cancer on chemotherapy, diagnosed with Gram-negative ventilator-associated pneumonia (bronchoscopy with biopsy and BAL—positive for *Klebsiella* in culture and in the tissues, along with *E. coli*). She was initially treated with tigecycline in view of beta-lactam allergy but had clinical and radiographic deterioration (**b**). Antibiotics were changed to intravenous aztreonam and inhaled tobramycin with clinical and radiographic improvement

lung infections) noted that the success rate was higher with longer duration of treatment (more than 9 days). They used tigecycline as part of a combination regimen in 67 % of patients, but with no impact of combination therapy on mortality [72].

Use of adjunctive inhaled antibiotics for the therapy of MDR pathogens

The use of adjunctive aerosolized antibiotics such as aminoglycosides, colistin, or ceftriazone can achieve high concentrations in the lung that could overcome in vitro levels of resistance, and also avoid the poor lung penetration of certain systemic antibiotics. This may be helpful in VAP patients who are not responding despite adequate systemic therapy or in patients infected with highly resistant organisms (Fig. 2). In a prospective randomized controlled trial, use of adjunctive aerosolized amikacin, compared to placebo, and combined with systemic antibiotics, the aerosol therapy led to a shorter duration of systemic therapy. The study was done using an investigational drug-delivery system in patients with Gram-negative VAP and at risk for MDR pathogens [73]. In another randomized study, patients received aerosolized ceftazidime and amikacin as the only agent for treatment of P. *aeruginosa* VAP, compared to systemic therapy and after 8 days of treatment, both the systemic therapy group and the inhalation therapy group had similar efficacy, treatment failure, and super-infection rates [74].

Continuous/prolonged infusion of antibiotics in VAP

Pharmacokinetics and pharmacodynamics are altered in patients with severe sepsis and dose adjustment may be necessary. Bactericidal activity related with aminoglycosides and quinolones is concentration-dependent, while with the beta-lactams, killing is dependent on how long the antibiotic concentration exceeds the minimum inhibitory concentration (MIC) of the target pathogen, and killing can be optimized by prolonged or continuous infusion methods. Nicasio and associates used an optimized dosing clinical pathway (incorporating prolonged infusions of cefepime and meropenem) and observed a reduction of infection-related mortality in 94 patients with VAP [75]. Dulhunty and colleagues in a double-blind randomized controlled trial compared continuous versus intermittent bolus dosing of piperacillin–tazobactam, meropenem, and ticarcillin–clavulanate in 30 patients with severe sepsis and found higher concentration above MIC and higher clinical cure rate, but no difference in ICU or hospital length of stay or mortality in the intervention arm than in the 30 control subjects [76].

VAP in trauma patients

Trauma patients have a higher incidence of VAP that is associated with prolonged mechanical ventilation and late tracheostomy. In a prospective, multicenter, observational study of 630 trauma patients, predictors of VAP were male sex and pulmonary contusion, while using a ‘VAP prevention bundle’ did not reduce the VAP incidence. Mortality in this study was related to age and higher APACHE II scores and injury severity scores [77]. Chaari and associates in a prospective study showed that late tracheotomy and stomal infection were independent factors predicting VAP onset, and patients with VAP had prolonged mechanical ventilation and ICU stay, but not an increased overall mortality [78]. Parks et al. in a study of 1,028 VAP episodes in trauma patients noted that using CPIS scores would have resulted in unnecessary antibiotic continuation in 59 %. CPIS has low sensitivity and specificity in determining VAP resolution in trauma patients [79]. Trauma patients with Glasgow coma score less than 9 are at risk for staphylococcal infection. In a study comparing intermittent versus continuous infusion of vancomycin in trauma patients with suspected VAP, more patients in the continuous group achieved therapeutic concentrations (7.4 vs. 57.1 %, $p < 0.0001$) with a similar incidence of adverse renal injury [80].

Prevention

VAP prevention measures are increasingly being adopted as a quality of care indicator in ICUs around the world. Endotracheal tube biofilm formation and microaspiration of oropharyngeal secretions, contaminated by endogenous flora, remain as important mechanisms for the development of VAP and are the target of several intervention strategies. In many ICUs, prevention strategies have been implemented in the form of "ventilator bundles", which have been able to reduce VAP rates, but controversy remains about whether it is possible to reduce rates to achieve "zero VAP". Ventilator bundles commonly include daily interruption of sedation, daily weaning trials, head of the bed elevation, and oral care. In addition, selected ICUs have added newer endotracheal tubes (silver coated, or with modified cuffs to avoid aspiration), subglottic secretion drainage via continuous or intermittent suction, new devices to remove biofilm from the inside of the endotracheal tube, saline instillation prior to suction, and early tracheostomy [81].

What is the role of VAP prevention bundles and behavior modification strategies in VAP incidence?

A group of ventilator care strategies, when performed as part of a daily care bundle, have been shown to decrease the VAP rates [82]. In a study from Scotland analyzing the effects of a VAP prevention bundle, there was a significant reduction in the reported VAP rates, post intervention, compared to the pre-intervention time period (12 vs. 32/1,000 ventilator days, $p < 0.001$), but no difference in mechanical ventilation days or ICU length of stay [8]. Despite several behavior modification strategies, including the use of nurse and medical champions, teaching materials, education sessions, bedside cues, and feedback about compliance, the overall bundle compliance rate was 70 % in this study. In another multicenter study, involving 1,320 patients, investigators used a 2-year multifaceted intervention via educational sessions, supplemented with reminders and local opinion leaders, to improve concordance with VAP prevention and treatment guidelines [83]. Over time, there was more improvement in prevention strategies than in therapy approaches, and overall, a significant increase in guideline concordance [aggregate concordance (mean [SD]), 50.7 % (6.1), 54.4 % (7.1), 56.2 % (5.9), 58.7 % (6.7) $p = 0.007$, in three consecutive 6-month periods]. They also observed a reduction in VAP rates (events/330 patients): 47 (14.2 %), 34 (10.3 %), 38(11.5 %), 29 (8.8 %) ($p = 0.03$) over the study period, but ICU mortality and length of ICU remained unchanged. Thus the data from these two studies showed a decrease in VAP rates after introduction of preventive interventions, but also highlight several potential barriers to guideline implementation and variable practices that exist within the community.

Is there a role of early tracheostomy to avoid VAP development?

Studies of early tracheostomy and its influence in reducing the incidence of VAP have not been conclusive, with some studies showing benefit, while others with no clear advantage. A meta-analysis by Griffiths and colleagues compared early tracheostomy with either late tracheostomy or prolonged endotracheal intubation. Early tracheostomy (within 7 days of invasive mechanical ventilation) did not significantly reduce the risk of VAP or mortality but reduced the number of days on the ventilator and ICU stay [84]. Blot and associates randomized critically ill patients expected to require more than 7 days of mechanical ventilation to either (open or percutaneous) early tracheostomy within 4 days or prolonged intubation [85]. The study was prematurely stopped after enrolling 125 patients as no difference was found between the two groups in mortality, VAP incidence, duration of mechanical ventilation, ICU stay, sedation use, or laryngeal or tracheal complications. In another trial, investigators compared the effectiveness of early tracheotomy (after 6–8 days of endotracheal intubation) to late tracheotomy (after 13–15 days) in reducing the incidence of pneumonia [86]. Even though 209 patients were randomized to the early group and 210 patients to the late group, 31 % of the early group and 43 % of the late group did not receive tracheostomy. Although there was a trend towards decreased VAP incidence with the early tracheotomy group, there was no significant difference between the groups in VAP rates (14 vs. 21 %, $p = 0.07$) or mortality. As with earlier trials, there were significantly more ventilator-free days and ICU-free days at 28 days in the early tracheotomy group. Another recent multicenter, open, randomized trial by Young and associates did not show any difference in 30-day mortality, length of ICU stay, or tracheostomy-related complications in the early (within 4 days) compared to late tracheostomy group (after 10 days) [87]. Thus on the basis of these studies there is not enough compelling evidence that routine early tracheotomy can prevent the development of pneumonia, but patients who underwent early tracheostomy had significantly more ventilator-free days.

Conclusion

VAP microbial etiology has changed over the last several decades and the relative prevalence of individual pathogens varies based on geographic location and patient risk factors. The morbidity and mortality related to VAP remain high and, in the absence of a gold standard test for diagnosis, suspected VAP patients should be started on antibiotics recommended as per the 2005 ATS guidelines and a knowledge of local antibiotic susceptibility patterns. Using a combination of clinical severity scores, biomarkers, and cultures might help with reducing the duration of therapy and achieving antibiotic de-escalation. The new CDC surveillance definition of VAE is not helpful in identifying all patients with VAP. There is still uncertainty regarding VAP diagnosis and management, and controversies are highlighted in this review. Having a centralized national registry for VAP patients might be beneficial in answering several of the controversial questions, but governmental penalties and institutional policies might be challenging as we seek to achieve this goal.

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