Update on ventilator-associated pneumonia

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Purpose of review
To highlight the importance of escalating pathogen resistance in ventilator-associated pneumonia (VAP) along with diagnostic and treatment implications.

Recent findings
In a period of rising bacterial resistance, VAP remains an important infection occurring in critically ill patients. Risk factors for multidrug-resistant pathogens depend on both local epidemiology and host factors. New diagnostic techniques and antimicrobials can help with rapid bacterial identification and timely and appropriate treatment while avoiding emergence of bacterial resistance.

Summary
Clinicians should be aware of risk factors for multidrug-resistant pathogens causing VAP and also of particularities of diagnosis and treatment of this important clinical entity.

Keywords
antibiotics, rapid diagnostics, resistant pathogens, ventilator-associated pneumonia

INTRODUCTION

Ventilator-associated pneumonia (VAP) is a complication occurring in ventilator-dependent patients of all ages associated with hospital mortality rates as high as 40%, significantly greater hospital lengths of stay, and increased healthcare costs [1–5]. Despite research into the pathophysiology and microbiology of VAP, pneumonia complicating mechanical ventilation remains an important clinical problem because of the compromised critically ill hosts within whom it occurs and the resistant nature of the microorganisms it is caused by.

EPIDEMIOLOGY

Although VAP appears to be a global problem [6▪], the pathogens associated with VAP are variable, depending on host factors, exposure to the healthcare system and antibiotics, local epidemiology, and infection control practices [1,4,7]. However, it is important to recognize that one of the major clinical issues related to the management of VAP, and other nosocomial infections, is the increasing prevalence of multidrug-resistant (MDR) or extremely drug-resistant (XDR) pathogens [1,8–11]. Although rates of methicillin-resistant *Staphylococcus aureus* (MRSA) have finally dropped, resistance among gram-negative bacilli (GNB) causing VAP is showing concerning trends (Table 1). The recent recognition of *Enterobacteriaceae* containing the New Delhi metallo β-lactamase 1 (NDM1) gene, and the emergence of colistin resistance within carbapenem-resistant Enterobacteriaceae (CRE), raise the real possibility of endemic spread of common enteric bacteria possessing resistance to all currently available antibacterial agents [18,19▪,20▪].

The emergence of MDR/XDR pathogens as a cause of VAP has resulted in greater administration of inappropriate initial antimicrobial therapy (IIAT), defined as an antimicrobial regimen that lacks in-vitro activity against the isolated organism(s) responsible for the infection [21]. IIAT is associated with excess mortality in patients with VAP [12,22–24]. Escalating rates of antimicrobial resistance lead many clinicians to empirically treat critically ill patients with a combination of broad-spectrum antibiotics, which can perpetuate the cycle of increasing resistance. Moreover, the limited diversity of available antimicrobial agents has created a clinical situation in which patients are often repetitively exposed to the same class of antibiotics.

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KEY POINTS

- Escalating rates of resistance are noted among pathogens responsible for VAP.
- Rapid diagnostics on the horizon, including automated microscopy, proteomics, nucleic acid amplification, and volatile compounds methods, will allow fast identification of bacterial pathogens and will also appropriately narrow the spectrum of empirical antibiotics.
- VAP requires fast, aggressive, and adequately dosed antimicrobial treatment, considering the special pharmacodynamics and pharmacokinetics of the critically ill population.

Therefore, the broader concern for all clinicians caring for critically ill patients with presumed VAP is how best to treat these individuals and limit the emergence and spread of MDR/XDR bacteria. Knowledge of patient-specific risk factors for antibiotic resistance and the predominant pathogens associated with VAP at the local level should assist clinicians in avoiding the unnecessary administration of empirical broad-spectrum antibiotics.

The cause of VAP is often divided according to time of onset and presence of risk factors for antibiotic resistance [25]. Certain risk factors, like the total duration of hospitalization prior to infection onset and recent antibiotic exposure, may be more important in determining the cause of VAP [9,26–29]. Moreover, it is now acknowledged that specific characteristics predispose patients with pneumonia to infection with more antibiotic-resistant bacteria. These risk factors include hospital admission from a long-term care facility, recent hospitalization, hemodialysis, immunosuppression, gastric acid suppression, nonambulatory status, and greater severity of illness [30–33]. Also, certain features present on admission, such as severe hypoxemia, bilateral infiltrates, and presence of pleural effusion, could point toward a resistant pathogen [34▪▪]. These risk factors in patients at risk for VAP should be considered in determining the likelihood of infection with antibiotic-resistant bacteria and choosing the empirical antimicrobial regimen [25,35].

Early-onset VAP (occurring within 4 to 5 days after onset of mechanical ventilation) was thought to usually be caused by more antibiotic-susceptible community-acquired pathogens (*Streptococcus pneumoniae*, *Haemophilus influenzae*) and anaerobic gram-positive microbial flora of the oral cavity. Conversely, late-onset VAP was traditionally attributed to infection with MDR bacteria [1,25]. However, recent reports suggest that this temporal classification does not always hold and that both early and late VAP experience similar rates (~30%) of MDR pathogens [26,27]. Local prevalence of MDR or XDR bacteria contributes significantly to each patient's risk of MDR pathogens and also modifies prediction rules, making constant epidemiological surveys very relevant.

DIAGNOSTICS

The diagnosis of VAP is problematic because noninfectious conditions can cause pulmonary

Table 1. Resistance trends in causative pathogens of VAP

Pathogen	Incidence and resistance trends
MRSA	Rate in VAP: 12–42%[a]
	Rate of methicillin resistance is decreasing: 1.4–82%[b]
Pseudomonas aeruginosa	Rate in VAP: 21–61% especially for the second episode of VAP[a]
	MDR/XDR rates as high as 38–46% with 8–20% susceptible only to colistin [12–14]
	Meropenem with >10% increase in resistance in North America with susceptibility across all classes of antimicrobials at 60–71% [10]
Enterobacteriaceae	Rate in VAP: 5–19.1% with rising rates of resistance to all classes of antimicrobials[a] [9,10,13]
	Rates of ESBL of 40% in Asia [9]
Acinetobacter spp.	Rate in VAP: 4.8–36.5% (highest in Latin America and Asia) [9,10,13]
	MDR rate as high as 80% and XDR 50% with 30% susceptible only to colistin [9,10,13]
	Meropenem and doripenem with >10% increase in resistance [10], colistin-resistant cases reported [15]

Abbreviations: ESBL, extended spectrum β-lactamases; MDR/XDR, multidrug resistant/extremely drug resistant; MRSA, methicillin-resistant *Staphylococcus aureus*; SA, *Staphylococcus aureus*; VAP, ventilator-associated pneumonia.
[a]Incidence of *Staphylococcus aureus* has been decreasing while rates for gram-negative bacilli (GNB), especially nonfermenting GNB, have been increasing [9,10,13,16].
[b]Rates of methicillin resistance in *Staphylococcus aureus* vary across continents and across hospitals within the same country: lowest in Europe and highest in Asia [9,13,17].

infiltrates and systemic findings such as leukocytosis, fever, and increased oxygen requirements [36]. Various diagnostic criteria with variable rigor have been developed to assist in the diagnosis of VAP. However, the most stringent criteria available were associated with the greatest observed mortality, and establishing the diagnosis of VAP took significantly longer when applying them compared with less stringent criteria, potentially resulting in delayed therapy [37▪▪]. Erring on the side of caution, most clinicians use the finding of a new or progressive radiographic infiltrate and at least one clinical feature (fever, leukocytosis, worsening oxygenation, or purulent tracheal secretions), which has high sensitivity but low specificity for VAP [25]. The difficulty in relying on clinical criteria for the diagnosis of VAP translates into the unnecessary administration of antibiotics to noninfected patients. This has the potential to promote further emergence of antibiotic resistance, especially when used for prolonged time periods, and to dilute out clinicians' ability to identify the impact of treating patients with IIAT [38,39].

American Thoracic Society guidelines reflect on the low accuracy of microbiology cultures as a diagnostic tool in VAP [25]. Contamination with upper respiratory tract pathogens or endotracheal tube colonizers is common. Traditional flow with gram staining, cultures, and antibiotic susceptibility testing requires at least 48–98 hours. Newer microbiology methods are gaining applicability in timely identification of respiratory pathogens. Nucleic acid amplification tests can target an unique pathogen (e.g., MRSA), or probably more useful in VAP will be the multiplex arrays that simultaneously identify multiple bacteria including resistance genes (e.g., mecA, blaKPC, blaIMI, etc.). With better understanding of the mechanisms involved in antimicrobial resistance (e.g., carbapenemases producers), more and more genes ought to be included in the multiplex arrays to allow complete testing. In addition, the mere presence of a resistance gene does not always correlate with antibiotic resistance [40▪]. The hope was that MRSA nasal swab PCRs would noninvasively predict MRSA pneumonia. In the best prospective study to date, positive predictive and negative predictive values (PPV, NPV) have been disappointing: 17.7% and 84.4% [41]. More recently, retrospective studies provided discordant results: across both community-acquired pneumonia and health care-associated pneumonia, PPV was 34.5% with NPV of 99.2% [42]. In a study of critically ill patients with probable selection bias (only patients with a clinical diagnosis of *S. aureus* pneumonia were included), PPV was 97.4% whereas the NPV dropped to 54.3% [43]. When performed on endotracheal aspirates in ventilated patients, Xpert MRSA (a real-time PCR MRSA platform) had a NPV of 98.9%, allowing rapid cessation of antimicrobials targeting MRSA [44]. So far, few multiplex platforms have been FDA cleared for bloodstream pathogens and respiratory viruses. Currently, some are expanding to include lower respiratory tract bacteria (BioFire, Salt Lake City, UT, USA; Curentis Unyvero, Holzgerlingen, Germany). PCR identification can also be used in exhaled breath condensate fluid, with one study showing a high correlation with bronchoalveolar lavage culture results [45▪▪]. For a nuclear amplification test to be widely accepted as a diagnostic tool in VAP, its performance needs to be validated across all respiratory samples including endotracheal aspirates, bronchoalveolar lavage (BAL), and protected brush specimens. In order to obtain a full susceptibility panel, routine antibiotic susceptibility testing normally accompanies the PCR/nucleic acid amplification testing, thus adding extra time needed to finalize the results. Following use in bloodstream infections, 'real-time PCR antibiogram' may be developed in the future for respiratory specimens to combine detection and susceptibility testing [46,47].

During the last decade, proteomics technologies have moved toward becoming the gold standard in bacterial identification. Excellent results with great reproducibility and fast turnaround time were obtained when using matrix-assisted laser desorption/ionization time of flight to identify protein mass patterns that lead to accurate bacterial detection [48,49]. This technology has been very well validated for rapid identification, but one major drawback remains the requirement for positive cultures.

Ideally, new methods would eliminate the need for both conventional cultures and antimicrobial susceptibility testing. A promising technology based on multiplexed automated digital microscopy traps individual bacterial clones and identifies them based on growth over time, single colony morphology, and fluorescent in situ hybridization [50,51,52▪]. After growth monitoring for 2 h, MDR pathogens obtained via mini BALs were identified with a sensitivity of 85–99% and specificity of 88–100% when compared with conventional cultures [53]. Automated systems using antimicrobial disks are being developed for respiratory specimens, with *S. aureus* successfully classified into vancomycin sensitive *S. aureus*, heterogeneous vancomycin intermediate *S. aureus* (hVISA), and vancomycin intermediate *S. aureus* (VISA) [54▪].

A few steps behind, but very appealing because of the noninvasive sampling and possibility of continuous monitoring, come the exhaled breath test

analyses looking at bacterial volatile organic compounds (VOC). Very specific peaks in the volatile metabolites captured by mass spectrometry can single out certain bacteria like *S. aureus* and *Pseudomonas aeruginosa* [55]. VOC patterns or fingerprints produced by various bacterial strains can be identified by electronic noses or optical spectra systems [56–58]. Based on the assumption that colonizing bacteria experience different metabolism, VOC fingerprints were able to classify noninfected, colonized, and infected ventilated patients when monitored with an electronic nose thrice weekly [59▪]. A similar study showed that breath analysis profiles correlated with bacterial load in the respiratory tract of intubated patients [60]. As VOCs are also produced by humans, exhaled breath profiling could theoretically be used in differentiating VAP from other causes of respiratory failure in ventilated patients [61].

TREATMENT FACETS

Recent years have brought significant strides in clinical bacteriology, but the quest for a perfect test for VAP continues. The cumbersome task of choosing the right empirical antibiotics remains. In addition, the timing of antibiotic delivery, ideally within the first hour, is an essential element in determining the outcome of critically ill patients with infection [62,63▪]. Iregui *et al.* [22] found that 30.8% of the 107 patients with VAP in their study received antibiotic treatment that was delayed for 24 h or more, with the most common reason being a delay in writing the antibiotic orders ($n = 25$; 75.8%). The administration of delayed appropriate therapy was identified as a risk factor independently associated with hospital mortality [adjusted odds ratio (OR), 7.68; 95% confidence interval, 4.50–13.09; $P < 0.001$]. Similarly, a study of 2154 septic shock patients (37.2% secondary to pneumonia) found that each hour of delay over the first 6 h was associated with an average decrease in survival of 7.6% per hour [64]. Faster administration of appropriate antibiotics can probably be obtained using protocolized management of septic shock [65]. As discussed above, prediction tools for the presence of antibiotic resistance and rapid diagnostics may provide timely guidance in antibiotic choices. However, ICUs should also insure that they have processes in place to obtain and deliver antibiotic therapy expeditiously. In addition, adequate drug concentrations at the site of infection are needed to optimize clinical outcomes. Murine models of *Pseudomonas* pneumonia evidence the importance of antibiotic-mediated initial bacterial kill, which allows granulocytes to efficiently accomplish bacterial clearance [66]. GNB responsible for infections in the critically ill populations exhibit higher minimum inhibitory concentration (MIC; as much as eight times higher for meropenem in a study across eight German ICUs) compared with GNB causing infections in ward patients [67]. So, knowing the MIC becomes necessary in calculating target levels for maximal antibiotic effect.

Many factors influence the pharmacokinetics and dynamics of antimicrobials in the critically ill. Hypoalbuminemia, large volume crystalloid administration, large effusions, catecholamines, augmented renal clearance, renal replacement therapies, and organ dysfunction can all significantly alter infection site concentrations of administered antibiotics [68,69]. Studies determining accurate dosing in healthy volunteers tend to underestimate appropriate antimicrobial dosing in critically ill patients [70].

β-Lactam and carbapenem antibiotics are time-dependent antimicrobials whose activity is primarily related to the duration of time the free drug concentration exceeds the pathogen MIC (T_{FREE}/MIC). A T_{FREE}/MIC of 100% of the dosage interval should be a theoretical target for β-lactams. For carbapenems, which have a longer postantibiotic effect, a bactericidal effect is observed for a T_{FREE}/MIC of 40%. In a multicenter trial, the investigators aimed to determine whether β-lactam antibiotic dosing in critically ill patients achieves concentrations associated with maximal activity and whether antibiotic concentrations affect patient outcome [71▪▪]. Sixteen percent of the patients treated for infection did not achieve $T_{FREE}/MIC > 1$ at 50% of the dosing interval. Positive clinical outcome was associated with T_{FREE}/MIC ratio > 1 at both 50% and 100% of the dosing intervals (OR, 1.02 and 1.56, respectively; $P < 0.03$). Furthermore, additional improvement in efficacy has been observed when concentrations four-fold to five-fold greater than the MIC are achieved for prolonged time periods during each dosing interval [72,73]. Therapeutic drug monitoring may become particularly useful in attaining antimicrobial target levels in high-inoculum infections like pneumonia [74–77].

Clinicians practicing in the ICU setting should attempt to optimize antimicrobial exposure by insuring that maximal dosing occurs. Once a concentration higher than the bacterial MIC is achieved with a maximal loading dose, further improvements in exposure can possibly be obtained with the use of prolonged/continuous infusions. Most trials looking at prolonged infusions have been retrospective, with various designs and conflicting results regarding meaningful clinical outcomes [78–82]. A recent,

small sample multicenter trial randomized patients with severe sepsis to continuous infusion versus intermittent boluses of β-lactams [83]. Pneumonia was responsible for approximately 40% of the infections, but only a very small number of microbes were presumed MDR pathogens [one *Acinetobacter*,

Table 2. Resistance mechanisms and treatment options in causative pathogens of VAP

Pathogen	Major mechanisms of resistance	Antibiotics affected	Treatment options
MRSA	1. hVISA, MIC creep and VRSA (vanA gene alters the target site, changing d-ala to d-lac)	1. Vancomycin	Linezolid[a]
	2. Point mutations in the gene encoding the ribosomal binding site – very rare	2. Linezolid	Telavancin[b]
			Ceftaroline[c]
			Ceftobiprole[d]
			Tigecycline[e]
Enterobacteriaceae	1. ESBL	1. PCNs (including antipseudomonal PCNs) + oxymino-β-lactams (ceftazidime, ceftriaxone, cefepime) +aztreonam	Carbapenems[f]
	2. Carbapenemases	2. Substrates of ESBL + carbapenems + cephamycins (cefoxitin, cefotetan)	Tigecycline[e]
	3. ampC enzymes	3. Substrates of ESBL + cephamycins	Colistin
Pseudomonas aeruginosa	1. oxa-type ESBL	1. PCNs (including antipseudomonal PCNs) + oxymino-β-lactams (ceftazidime, ceftriaxone, cefepime) +aztreonam	Carbapenems[f]
	2. Carbapenemases [metallo-β-lactamases (Zn^{2+})]	2. Substrates of ESBL + carbapenems +cephamycins	Colistin
	3. Loss of porins	3. AG and carbapenems (25% of Pseudomonas isolates lose porins while on therapy with imipenem)	
	4. MDR efflux pumps	4. β-lactams, fluoroquinolones, aminoglycosides	
Acinetobacter spp[g]	1. Carbapenemases [metallo-β-lactamases (Zn^{2+})] and oxa-derived	1. Substrates of ESBL + carbapenems + cephamycins	Carbapenems[f]
	2. ampC enzymes	2. Substrates of ESBL plus cephamycins	Tigecycline[e]
	3. loss of porins		Colistin[h]
	4. MDR efflux pumps		

Abbreviations: AG, aminoglycosides; ESBL, extended spectrum β-lactamases; GNB, gram-negative bacilli; hVISA, heterogeneous vancomycin intermediate *Staphyloccoccus aureus*; MDR, multidrug resistant; MIC, minimum inhibitory concentration; MRSA, methicillin-resistant *Staphylococcus aureus*; PCN, penicillin; VAP, ventilator-associated pneumonia; VRSA, vancomcyin-resistant *Staphylococcus aureus*.

[a]Linezolid is a superior alternative to vancomycin, especially in isolates with MIC >1 mg/ml [84–86] with also a favorable cost effectiveness [87,88▪,89].

[b]Telavancin maintains activity against hVISA isolates. Studies found it to be noninferior to vancomycin in treatment of hospital-acquired pneumonia except for patients with preexisting renal dysfunction [90–92].

[c]Only small case series and retrospective pneumonia studies (unclear how many VAP episodes) [93,94].

[d]Approved for community-acquired pneumonia and health care-acquired pneumonia, excluding VAP since it was inferior to ceftazidime and linezolid in a randomized trial. The lower cure rates observed in VAP patients were attributed at least in part to underdosing of ceftobiprole [95].

[e]Used as salvage therapy because of the increased mortality found in meta-analyses and randomized control trials of tigecycline (dosed at 75 mg every 12 h) mainly in GNB nosocomial pneumonia [96–99]. Higher doses had same efficacy as imipenem [100]. Lower MICs have been proposed for *Staphylococcus aureus* species [101]. Developing resistance among GNB while on treatment has been reported [102], although most Enterobacteriaceae remain susceptible [103,104].

[f]Based on retrospective data in bacteremia [105]. Failures of cefepime and piperacillin–tazobactam noted even with susceptible isolates, probably because of high inoculum effect. A study including patients with microbiologically confirmed VAP at risk for MDR pathogens who were randomized to 7 days of doripenem and 10 days of imipenem–cilastatin [106] was halted at the interim analysis because of higher 28-day mortality in the doripenem arm (excess mortality in patients with *Pseudomonas aeruginosa* who received shorter courses of treatment). Animal models and very limited human data suggest that dual carbapenem therapy may be an alternative in infections caused by *Klebsiella pneumoniae* Carbapenemase (KPC) organisms [107,108].

[g]Usually multiple mechanisms of resistance coexist.

[h]Retrospective studies showed utility of colistin (iv or aerosolized as adjunctive) in the treatment of VAP caused by MDR pathogens [109,110▪▪,111]. A randomized control trial comparing meropenem and colistin as empirical therapy in VAP is ongoing [112].

one extended spectrum β-lactamase (ESBL) *Escherichia coli*, and two *Pseudomonas* isolates]. The intervention group achieved higher plasma antibiotic concentrations and cure rates. Although the trial was not powered to capture a difference in other outcomes, survival also showed a favorable trend.

Treatment options for the most frequent causative pathogens of VAP are detailed in Table 2, focusing on antimicrobial options for MDR microbes. Among infections in critically ill patients, VAP occupies a distinct place, with multiple studies showing different evolution and outcomes despite a prompt appropriate antibiotic regimen. Trials using potent antibiotics such as tigecycline, doripenem, and ceftobiprole failed in VAP after successful outcomes in other infectious diseases, suggesting the need for higher dosing and/or longer duration in VAP.

The data supporting the use of shorter courses of antibiotic therapy of 7–8 days are robust for VAP, accounting for clinical severity and evolution, and most importantly the underlying microbiology [113–116]. The exceptions to shorter courses of antibiotic therapy in VAP are difficult-to-treat pathogens such as *P. aeruginosa* and other nonfermenters that experience higher recurrence rates with shorter treatment regimens [113]. Moreover, at least one randomized trial has found a greater mortality among patients with *P. aeruginosa* VAP receiving only 7 days of treatment with doripenem [106]. In patients with clinically suspected VAP and negative bronchoscopy cultures, antibiotics can probably be stopped earlier. In a retrospective study, early discontinuation of antibiotics (at day 4, 1 day after negative quantitative bronchoscopy cultures) did not increase mortality when compared with late discontinuation (at day 9) [117].

When feasible, shorter duration of antibiotic therapy may help to curb the rising prevalence of MDR pathogens in VAP. Another useful strategy may be antibiotic heterogeneity, an idea backed up by mathematical models and a recent study, which showed that mixing the available antibiotics may prevent emergence of resistant pathogens [11].

CONCLUSION

In summary, clinicians should be aware that prevalence of MDR pathogens is rising in VAP, but each patient's risk depends primarily on local epidemiology and host factors. Better rapid diagnostics on the horizon will transform empirical antimicrobial therapy into targeted therapy. VAP requires prompt and accurately dosed antibiotic treatment. When appropriate, shorter duration, rapid de-escalation and antibiotic diversity may decrease emergence of resistant pathogens.

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Conflicts of interest

M.K. is also a consultant for Merck, Cubist and Accelerate Diagnostics. The remaining author has no conflicts of interest.

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