Preface

Controversies and Evolving Concepts in Hospital-Acquired Pneumonia

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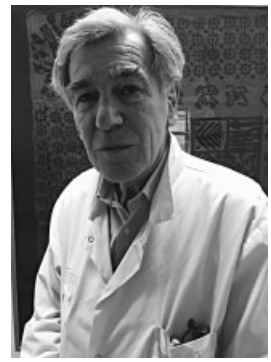

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Despite some advances in antimicrobial therapy, successful treatment of patients with hospital-acquired pneumonia (HAP) remains a difficult and complex undertaking. Persistently high mortalities for pneumonia in the intensive care unit (ICU) argue, however, for a continued reassessment of our current modalities of therapy and definition of better protocols. More active as well as less toxic antibacterial agents are still needed, especially for problematic pathogens that are now emerging in many countries worldwide, such as multidrug-resistant (MDR) nonfermenting gram-negative bacilli and extended spectrum beta-lactamase (ESBL)-producing *Enterobacteriaceae* (including carbapenemase-producing gram-negative bacilli), as well as a better use of already available antimicrobial agents. This issue of *Seminars in Respiratory and Critical Care Medicine* includes contributions from world-renowned experts in the field of HAP who have provided state-of-the-art information on important aspects of the clinical management of this dreadful disease.

In the first article, Nair and Niederman provide a detailed review of the many limitations and pitfalls inherent to any streamlined definition of the ventilator-associated event (VAE) for the surveillance of complications in mechanically ventilated patients, including ventilator-associated pneumonia (VAP). Outcome measures, such as VAE surveillance, can effectively circumvent the diagnostic limitations of VAP, but do not measure only infection, and do little to improve the quality of care since the validity and preventability of these events are still uncertain.

The next three articles deal with important topics that have plagued clinicians in the ICU for many years: Should we immediately start antibiotics in every patient with a clinical suspicion of HAP/VAP? What is the role of emerging diagnostic technologies? Should we treat ventilator-associated tracheobronchitis (VAT) with antibiotics? Although clearly deteriorating patients should undisputedly receive immediate new antimicrobial therapy covering the potentially responsible pathogens, Hassinger and Sawyer rightly point out that, in many cases, therapy could be directed at a confirmed infection following a positive culture result, avoiding medication-associated morbidity, including emerging-resistant microorganisms and *Clostridium difficile* infection. As indicated by Kollef and Burnham, new biomolecular techniques give us the possibility of rapidly detecting the causative pathogen and thus offer the potential for providing timely administration of appropriate antimicrobial therapy, as well as minimizing the use of broad-spectrum antibiotics when they are not justified. Antibiotic treatment for VAT, an intermediate infectious process limited to the upper airways that could precede VAP is still a matter for debate. When precisely defined by using quantitative culture results of endotracheal aspirates to quantify the bacterial load present in the airways, as proposed by Martin-Loeches, Coakley and Nseir, VAT is frequently associated with prolonged mechanical ventilation and subsequent VAP, probably justifying antimicrobial therapy in that circumstance.

Seven articles in this issue provide up-to-date and very useful information regarding how to improve the treatment of pneumonia caused by very difficult-to-treat bacteria in the ICU setting. With increasing rates of antimicrobial resistance and the marked physiological changes that can occur in ICU patients, which in turn affect antibiotic concentrations and therefore dosing requirements, the attainment of an optimal antibiotic therapeutic drug exposure becomes much more

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difficult. As indicated by Sulaiman et al, antibiotic therapeutic drug monitoring combined with knowledge of the isolate's minimum inhibitory concentration (MIC) would be required to ensure optimal therapy is provided. In the second article of this series, Timsit et al review the epidemiology and treatment of HAP caused by ESBL-producing *Enterobacteriaceae*, which have spread worldwide and are now involved in approximately 22 to 35% of VAP cases, as reported in large multicenter databases. Unfortunately, our armamentarium against these bacteria, although improving, is still limited, driving the extensive use of carbapenems. Infections caused by carbapenem-resistant *Enterobacteriaceae* (CRE) are an emergent problem due to the lack of therapeutic options available, leading to significant increases in morbidity and mortality. Bassetti et al, in a very thoughtful and up-to-date article, are proposing a possible strategy for the empiric and targeted treatment of HAP and VAP in which the involvement of CRE is suspected or confirmed, focusing on the role of both old and new available antimicrobial agents. The following two articles by Lynch et al are devoted to the management of MDR nonfermenters, including *Pseudomonas aeruginosa* and *Acinetobacter baumannii*. Over the past decades, antimicrobial resistance among these microorganisms has escalated globally, via dissemination of several international MDR "epidemic" clones. Many physicians advocate the use of combination therapy with agents that act by different mechanisms, but randomized therapeutic trials are sparse, and disparate results have been noted in both retrospective and prospective observational studies, as extensively reviewed in these two outstanding articles. Whether strategies targeting virulence factors expressed by *Staphylococcus aureus* or *P. aeruginosa* might be a valuable addition to conventional antimicrobial therapy is still an open question. However, as indicated by François et al, such a strategy could eliminate or reduce the risk of developing pneumonia before or during mechanical ventilation and improve patient outcomes through mechanisms that differ from those of antibiotics, with the major advantage of exerting less selective pressure for the development of antibiotic resistance. In the following article, Palmer and Rello summarize current evidence describing the use of inhaled antibiotics for the treatment of bacterial ventilator-associated infections. Although preliminary data obtained in observational studies and small randomized controlled trials suggest that aerosolized delivery of antimicrobials may effectively treat resistant pathogens with high MICs when delivered with appropriate devices, recent guidelines remain cautious about their use.

The two last articles of this issue present a very detailed and comprehensive discussion of two potentially useful, but controversial, prophylactic measures for HAP/VAP, namely, oropharyngeal decontamination with chlorhexidine and maintaining patients in a semirecumbent position for avoiding aspiration of gastric bacteria into the airways. For many years, practice guidelines have recommended routine oral care with chlorhexidine in all patients on mechanical ventilation. However, as discussed by Klompas in a very well argued article, such a preventive measure remains questionable, especially because it was never demonstrated that the use of chlorhexidine was associated with a significant reduction in the duration of mechanical ventilation or any other clinically relevant endpoint, including ICU length of stay or antibiotic exposure. Instead, there was a possible signal that oral chlorhexidine may increase mortality rates, maybe because of its toxicity for the lung. Extensive efforts have also been devoted in reducing, through body positioning, the risks for oropharyngeal colonization and aspiration of pathogens, with all guidelines recommending keeping ventilated patients in the semirecumbent position especially in the case of enteral nutrition. However, new data are available challenging the underlying rationale of the semirecumbent position, as thoroughly discussed by Li Bassi et al. Interestingly, these authors are now proposing to abandon this positioning for the lateral-Trendelenburg position to promote better outward clearance of respiratory secretions and circumvent any gravity-driven aspiration of fluids from the artificial airways into the lungs. Although attractive, clinical application of these new concepts may be challenging, and additional data are obviously needed before such positioning could be implemented.

We sincerely thank each of the authors who have contributed to this issue of *Seminars in Respiratory and Critical Care Medicine* dedicated to controversies and evolving concepts in HAP/VAP. We believe that the current state-of-the-art reviews presented here by an internationally recognized group of experts in the field will serve as a valuable resource for clinicians providing care for patients with severe bacterial pneumonia in the ICU.

Using Ventilator-Associated Pneumonia Rates as a Health Care Quality Indicator: A Contentious Concept

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Abstract

Pneumonia is a leading cause of hospital-acquired infections, although reported rates of ventilator-associated pneumonia (VAP) have been declining in recent years. A multifaceted infection prevention approach, using a "ventilator bundle," has been shown to reduce the frequency of VAP, while improving other patient outcomes. Because of difficulties in defining VAP, the Center for Medicare and Medicaid Service introduced a new streamlined ventilator-associated event (VAE) definition in 2013 for the surveillance of complications in mechanically ventilated patients. VAE measures are increasingly being measured by institutions in the United States in place of VAP rates and as a potential measure of the quality of intensive care unit (ICU) care. However, there is increased recognition that the streamlined definitions identify a different subset of patients than those identified by traditional VAP surveillance and that VAP prevention strategies may not impact all the causes of VAE. Also, VAP and VAE rates may not always reflect the quality of care in a given ICU, especially since patient factors, beyond the control of the hospital, may impact the rates of VAP and VAE. In this review, we discuss the issues related to VAP as a quality measure and the areas of uncertainty related to the new VAE definitions.

Keywords

- nosocomial pneumonia
- ventilator-associated pneumonia
- ventilator-associated events
- ventilator-associated complications
- prevention
- quality measure

Ventilator-associated pneumonia (VAP) is a serious nosocomial infection with substantial clinical and financial implications, incurring an additional hospital cost of $\geq$ 10,019 to 40,000 USD per admission.[1,2] The Center for Medicare and Medicaid Service's initiative for public reporting and performance evaluation, based on the frequency of hospital-acquired infections (HAIs), was originally conceived for reducing preventable complications in hospitalized patients and promoting a culture of safety. The Agency for Healthcare Research and Quality (AHRQ) has announced a 21% reduction in HAIs since 2010, including hospital-acquired pneumonia.[3] Similarly, the National Healthcare Safety Network (NHSN) estimates the incidence of VAP to range from 0.0 to 5.8/1,000 ventilator days.[2] These reported VAP incidence rates are considerably lower in recent years and are attributed to a multifaceted infection prevention program in the form of a "Bundle care approach" and its effective implementation.

Recently, the low incidence of VAP has been questioned. Metersky et al compared the rates of VAP reported by the Centers for Disease Control and Prevention (CDC) from 2006 to 2012, and the rates of VAP reported during the same time period by the Medicare Patient Safety Monitoring (MPSM) system.[4] They found that while the CDC surveillance system reported a decline in VAP rates from 3.2 to 0.9/1,000

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ventilator days, the MPSM data found a steady rate of 10 to 11% in patients 65 and older. These findings show a true discrepancy between rates reported in a quality monitoring program, compared with rates observed in a patient care program.

According to a recent study based on cost-effectiveness modeling in Medicare patients, the introduction of various prevention programs has led to an improvement in HAI rates with a gain of 6.55 quality adjusted life year for VAP patients, and reduction in intensive care unit (ICU) costs of 163,000 USD per index admission.[5] However, an accurate diagnosis of VAP is challenging, and both surveillance and clinical definitions lack specificity or reproducibility. Using VAP as a quality benchmark and considering VAP to be a medical error may result in disingenuous reporting by health care institutions. Throughout the United States, there is an increased reporting of hospitals with a "zero incidence" of VAP, even though the antibiotic prescription and clinical diagnosis remain prevalent.[6] This prompted the CDC to introduce a new "objective" surveillance paradigm in 2013 based on complications while on the ventilator.[7] However, ventilator-associated events (VAE) identifies patients at high risk of death but has a low sensitivity and specificity in diagnosing VAP.[8] In this review, we discuss the issues related with VAP as a quality measure and areas of uncertainty related to the new VAE definitions.

The Predicament

ICU patients, who develop VAP are twice as likely to die, compared with similar patients without VAP (odds ratio: 2.03; 95% confidence interval: 1.16–3.56).[9] The risk of developing VAP increases with duration of mechanical ventilation.[10] Whether or not a patient will develop VAP is determined by complex interactions between host defense mechanisms and virulence of the microorganisms. Early identification of VAP is advantageous, as it may allow timely initiation of appropriate antibiotics.[11] Clinicians at the bedside use a combination of clinical, radiographic, and microbiological criteria to diagnose pneumonia, which is different from the 2013 CDC surveillance definition of VAEs (see ►**Table 1**). In the absence of reliable confirmatory diagnostic testing, a definitive diagnosis of VAP remains elusive.

With the pressure of public reporting and the risk of being penalized if VAP rates are high, health care institutions may be reluctant to pursue aggressive testing for VAP.[12] Thus it begs the question, how much of VAP is truly preventable? Umscheid et al in a systematic review estimated the proportion of HAI that are reasonably preventable and reported that 55% of VAP cases are preventable with current evidence-based strategies, but the study only included two good quality VAP studies, and the assessment could be an overestimate.[13] In a retrospective analysis of the Michigan Keystone ICU database with 112 ICUs, more than half of the ICUs were able to sustain a median of 26. 2 "VAP-free months."[14] In that study, surgical/trauma ICUs had a higher risk of VAP, whereas the incidence was lower in hospitals with > 400 beds. In another study from Europe, including 78,222 patients and 525 ICUs, the investigators used a computation model-based simulation of individual patient profiles over time, and compared hospital VAP rates and performance, to VAP rates of patients in ICUs falling within the top decile (lowest frequency) of VAP events.[15] In this pragmatic model, 52% of VAP episodes were preventable.

A multifaceted infection prevention program in the form of a "bundled care approach" has been shown to reduce the incidence of VAP.[16,17] If VAP is preventable with effective implementation of preventative strategies, could "zero VAP" be consistently achieved as promulgated by the Institute for Healthcare Improvement? Bouadma et al compared the VAP rates at baseline and after the introduction of a 30-month infection prevention program and found a 43% reduction in VAP (22.6–13.1 total VAP episodes/1,000 ventilator days).[18] However in that study, even with high compliance with prevention strategies, there were a substantial number of patients with VAP, indicating that "zero VAP" is not easily achievable despite using the best prevention measures.

Lower VAP rates may not always reflect better care. Key quality indicators such as mortality reduction, the length of stay, and antibiotic use may not be affected by VAP prevention measures. The currently available data are subject to inaccurate collection from public reporting sources.[19] In a study comparing two hospitals, both under the same management and with similar staff structure, treating physicians and prevention protocols, VAP rates were different. One hospital had zero VAP, while the other had 2.4 VAPs/1,000 ventilator days. There were no significant differences in mortality between the two ICUs, in spite of different VAP rates. Also, the hospital with zero VAP had a shorter duration of ICU stay than the other hospital and often transferred their sickest patients to the other hospital. Thus, it is not surprising that the VAP rates in the two hospitals were different, but the quality of care did not seem better in the zero VAP hospital, and the mortality rates were not different.[20] In a prospective surveillance from 43 randomly selected U.S. hospitals, measuring the proportion of standardized cases classified as VAP, there was a wide discrepancy of how cases were classified, with a tendency for more rural hospitals to diagnose VAP more often than hospitals elsewhere.[21] The authors of this study concluded that VAP is poorly identified by surveillance definitions, and concluded that more objective measures are needed, but whether VAE meets this criterion is still controversial.

Development of VAP is related to several patient-related and extrinsic factors, and rates may vary from hospital to hospital, more as a reflection of patient case severity mix, than as a reflection of the quality of care. Under-reporting does not prevent widespread use of antibiotics and can contribute to increasing antimicrobial resistance. However, hospitals reporting an accurate, but the higher incidence in a pay for performance scenario, could end up with fewer resources to care for VAP patients and be at a disadvantage compared with institutions electing to underreport. Thus using VAP rate as a quality metric may not only be inaccurate but may also lead to undesirable clinical and economic consequences.

Table 1 Definitions for VAP including CDC 2008, CPIS, CDC 2013 surveillance definition

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 y 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 the character of sputum, increased respiratory secretions or increased suctioning requirements 2. Worsening gas exchange (e.g., desaturation, increased oxygen requirements, or increased ventilator demand) 3. New onset or worsening cough, or dyspnea, or tachypnea 4. Rales or bronchial breath sounds		
Modified clinical pulmonary infection score (CPIS): VAP likely if score $\geq$ 6		
Temperature (°C)	$\geq$ 36.5 and $\leq$ 38.4	0
	$\geq$ 38.5 and $\leq$ 38.9	1
	$\geq$ 39.0 and $\leq$ 36.0	2
Blood leukocytes (/mm^3)	$\geq$ 4,000 and $\leq$ 11,000	0
	$<$ 400 and $>$ 11,000	1
Tracheal secretions	Few	0
	Moderate	1
	Large	2
	Purulent	+1
Oxygenation Pa_{O_2}/F_{IO_2}	$>$ 240 or presence of ARDS	0
	$\leq$ 240 and absence of ARDS	2
Chest radiograph	No infiltrate	0
	Patchy or diffuse infiltrate	1
	Localized infiltrate	2
CDC 2013 ventilator-associated events surveillance definition		
Ventilator-associated complication		
At least one of the following criteria: 1. Minimum daily F_{IO_2} values increase $\geq$ 0.20 (20 points) over baseline and remain at or above that increased level for $\geq$ 2 calendar days 2. Minimum daily PEEP values increase $\geq$ 3 cm H_2O over baseline and remain at or above that increased level for $\geq$ 2 calendar days		
Infection-related ventilator-associated complication		
Ventilator-associated complication + 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 2. Positive culture from respiratory tract		

Abbreviations: CDC, Centers for Disease Control and Prevention; PEEP, positive end-expiratory pressure; VAP, ventilator-associated pneumonia; WBC, white blood cell.

Areas of Uncertainty Related to the 2013 CDC Surveillance Definition

To address the uncertainties related to VAP diagnosis, in 2013, the CDC introduced a new VAE surveillance definition that could identify patients who develop complications during mechanical ventilation.[7] VAE uses a multistep approach to define several events, from ventilator-associated complications (VAC), to infectious ventilator-associated complication (IVAC), as well as probable or possible VAP. The VAC definition requires worsening oxygenation, measured by increasing daily minimum positive end-expiratory pressure (PEEP) by at least 3 cm H_2O or the fraction of inspired oxygen (F_IO2) by at least 0.20 (20 points) for $\geq$ 2 consecutive days, after having a period of stable, or improving oxygenation of at least 2 days.[22] Thus VAC can only develop after at least 4 days of ventilation and does not take into account clinical variables required for VAP diagnosis, including (by design) the development of a new radiographic infiltrate.

There are several putative advantages of using VAE surveillance. The definition is straightforward and "objective," hence making it easy to compare different institutions or a single institution over time. It can be measured via electronic surveillance with minimal manual collection and therefore is less time consuming than the traditional VAP surveillance methods. There is no need for chest radiograph interpretation, and the use of ventilator setting changes, as a surrogate for worsening oxygenation, is the pivotal factor, which facilitates rapid and easy measurement.[23] However, it is changed in the Pa_{O_2}/F_{IO_2} ratio which has been correlated with patient outcome in VAP and not simply changes in the ventilator settings. The choice to rely on changes in ventilator settings in making the VAE definition is one of the reasons that it is so easy to measure VAEs electronically from the medical record. However, this approach has led to using a surrogate that is not directly physiological, and one that is easily subject to manipulation. For example, if a hospital wanted to avoid having VAC, it would ventilate patients with an initially higher F_{IO_2} than necessary, and then have little need to increase the F_{IO_2} further when a patient develops pneumonia, thus avoiding one of the key criteria of the VAC definition.

VAE incidence rates range from 10 to 15 events/1,000 ventilator days.[24] In a study comparing 153 patients with VAC to 390 without VAC, Hayashi et al noted that VAC definitions identified "potential VAP" in 30.7% of cases, but it was not specific for VAP and included atelectasis in 16.3%, acute pulmonary edema in 11.8%, and acute respiratory distress syndrome (ARDS) in 6.5%.[25] VAC compared with non-VAC patients had a higher ICU length of stay (22 vs. 11 days), and duration of mechanical ventilation (20 vs. 5 days), but no difference in overall ICU mortality.[25] Boyer et al in a 12-month prospective study of 1,209 medical and surgical patients, noted common causes of VACs were IVACs (50.7%), ARDS (16.4%), pulmonary edema (14.9%), and atelectasis (9.0%).[26] In that study, VAC patients had a higher mortality compared with those without (65.7 vs. 14.4%, $p < 0.001$). However, the sensitivity of the VAC criteria for the detection of VAP was only 25.9% (95% confidence interval [CI], 16.7–34.5%).

Muscedere et al in a prospective study including 1,320 ventilated patients noted that VAC developed in 10.5% ($n = 139$), IVAC in 4.9% ($n = 65$), and VAP in 11.2% ($n = 148$).[27] A total of 39 patients had both VAC or IVAC and VAP. Patients who had VAC were more likely to develop VAP than those who did not have VAC (28.1 vs. 9.2%, $p < 0.001$). However, VAP and VAC often did not overlap, and of 148 patients with VAP, only 29 had VAC or IVAC. Patients with VAC or IVAC had significantly more ventilator days, hospital days, and antibiotic days and higher hospital mortality compared with patients who did not develop VAC or IVAC. Bouadma et al analyzed a large prospective cohort of 3,028 patients ventilated for more than 5 days and noted that 77% had at least one VAC, including 29% with IVAC. However, only 14.5% of VAC episodes and 27.6% of IVAC episodes were due to VAP, even though VAC and IVAC were correlated with both VAP and antibiotic use.[28]

Another study from two Dutch academic medical centers compared ongoing VAP surveillance to the VAE algorithm and found poor concordance between the two. Only 32% of patients with VAP identified using traditional methods were detected using the VAE algorithm.[29] In that study, hazards for mortality were higher for VAP identified by prospective surveillance, 7.2 (5.1–10.3), than for VAP identified by the VAE surveillance definition, 2.0 (1.1–3.6), demonstrating that each definition identified a different population of patients. Fan et al performed a systematic review and meta-analysis of 18 studies including 61,489 ventilated patients to determine the consistency between VAE surveillance and traditional VAP surveillance.[30] The pooled VAC prevalence was 13.8%, and traditional VAP was 11.9%, and VAE had poor sensitivity (42%) and specificity to detect VAP. Compared with VAP, the odds ratio for in-hospital mortality was 1.49 for VAC, and VAC length of stay was approximately 4 to 6 days shorter than that of VAP.

Wallace et al assessed VAP rates in 305 ventilated patients admitted to four different ICUs, using various currently available diagnostic scoring systems (including the Clinical Pulmonary Infection Score known as CPIS, 2008 CDC VAP definitions, and 2013 CDC VAE surveillance definitions) along with antibiotic use and clinical opinion of treating physicians.[31] They found significant inter- and intraunit heterogeneity in VAP rates between ICUs using the different diagnostic scoring systems, and poor correlation of VAP diagnosis using the different definitions with the clinical opinion of physicians, or antibiotic use ($k = 0.23$ and 0.17). In another study including two large ICUs with 1,209 patients, investigators compared semiautomatic VAE surveillance strategy with the prospectively performed clinical adjudication of the VAE criteria.[32] Both methods identified 56 patients to have VAE ($k = 0.81$, $p = 0.04$) with a significant negative agreement. However, 24 patients had VAE by only one method, and this was primarily related to uncertainties with the application of the definition in patients receiving unconventional modes of ventilation, such as airway pressure release ventilation, and in patients close to death. Lilly et al in a prospective cohort study on 8,402 ventilated patients reported that VAE surveillance detected less than one-third of VAP cases and that 93% of patients with

VAC did not have pneumonia.[33] Further, 93% of VAC could be eliminated by algorithmic manipulation of PEEP and F_{IO_2}.

Thus, multiple series showed that when VAE is present, the etiology is not just pneumonia, but other causes including pulmonary edema: 20 to 40%, lung atelectasis: 10 to 15%, and ARDS: 10 to 20%.[24] Also, patients can have VAP without having VAE. The VAE definition identifies sick patients at high risk for mortality, but VAC and IVAC may have different pathobiological causes than VAP, and VAC is not intended to be a specific infection-related diagnosis. VAC definitions are subject to gaming by manipulation of ventilator management protocols, making it hard to use VAC rates to objectively compare one hospital to another, for the purpose of comparing the quality of care. Also, the use of the VAC definition may prove inadequate when making decisions about the care of individual patients suspected to have pneumonia (see **Box 1** and ►**Table 2**). Although the VAE definitions track episodes of sustained respiratory deterioration in mechanically ventilated patients after a period of stability or improvement, the utility of these new definitions as a measure of the quality of care for ventilated patients should be reflected by both its reliability and its preventability, neither of which are proven.[8]

How Can We Prevent VAE?

Regardless of the performance indicator or definition used for surveillance, the ultimate test of its value depends on its capacity to be used serially to monitor an event that is known to reflect poor quality of care, and to then initiate an intervention plan to reduce the frequency of the event, and thereby improve patient outcomes. Use of ventilator bundles has been shown to improve outcomes in intubated patients and to reduce the overall incidence of pneumonia.[16] There are several key elements in this VAP prevention strategy including elevation of the head end of the bed, intestinal bleeding, and deep vein thrombosis prophylaxis, daily awakening trials and daily assessment for ventilator weaning (see ►**Table 3**). When these measures have been applied, they were shown to decrease the incidence of VAC and VAP, but not IVAC.[27]

In the study by Boyer et al, VAC occurred with a frequency of 5.5%, and two independent investigators adjudicated all VAC episodes to identify potentially preventable events.[26] A nonpreventable VAC was defined as an unavoidable injury caused by the patient's underlying disease process, associated with appropriate medical care. They considered preventable events to include inappropriate antibiotic therapy, procedure-related adverse events, aspiration of enteral feedings, ventilation with potentially injurious tidal volumes, pulmonary edema from excess intravenous fluid, excess sedation, or potentially avoidable infection, such as catheter-associated blood stream infection, wound infection, urinary catheter-associated infection, or probable VAP per CDC criteria. Only 37.3% of VACs ($n = 25$) were judged to be preventable, although the mortality rate of patients having a VAC was greater than in non-VAC patients (65.7 vs. 14.4%, $p < 0.001$).[26] Further, the sensitivity of VAC criteria to diagnose pneumonia was only 25%.

In a study of 2,660 patients, investigators evaluated the reduction in the risk of VAE with the use of a daily ventilator bundle.[34] They included 16,858 ventilator days with 77 VAEs and found only oral care was associated with a reduction in the risk of VAE (hazard ratio, 0.44; 95% CI, 0.26–0.77). In that study, IVAC was diagnosed later than the onset of clinical signs of pneumonia, emphasizing that this definition is not one that can be applied to the care of individual patients. In another study, Amaral and Holder explored the delay of antibiotics and adverse outcomes in patients with VAC.[35] Of the 45 episodes of VAC identified in the study, 27 were associated with delay in therapy, but this did not have an impact on ICU mortality, treatment failure, or superinfection, compared with immediate antimicrobial administration. This again reflects the poor correlation between VAC and VAP, and the limited ability to use the VAC definition in patient management.

Damas et al conducted a randomized control trial of 352 patients to evaluate the impact of subglottic secretion drainage (SSD) (170 with SSD and 182 without SSD) on VAP and VAE prevalence and antibiotic use.[36] Patients receiving SSD had fewer microbiologic VAPs (8.8 vs. 17.6%, $p = 0.018$) and less antibiotic days (absolute risk reduction of 6.9%) than those who did not get SSD. However, there was no change in the VAC rate (21.8 vs. 22.5%), and only 58.2% with VAP had VAC. Thus, in this study, a tool that could prevent VAP had no impact on VAC. In another study including 350 patients from Olmsted County, MN, investigators using data from electronic medical records to

Box 1 Issues with ventilator-associated event surveillance

- Does not necessarily identify pneumonia or even an infection
- Requires at least 4 days for developing after mechanical ventilation is started, and can miss patients with early-onset ventilator-associated pneumonia (VAP)
- Uncertain of its use in patients with unconventional modes of ventilation such as airway pressure release ventilation
- Difficult to ascertain in patients, who might die within a few days due to respiratory deterioration
- Does not take into account Pa_{O_2}/F_{IO_2} ratio, a physiological parameter correlated with VAP and VAP outcomes
- Too focused on automated data collection, using ventilator settings, which can be adjusted arbitrarily
- Easy to manipulate
- May not reduce the overuse of antibiotics or improve mortality if eliminated
- Replacing one problem definition (VAP) with another
- Methods for ventilator-associated event prevention are not defined and not known to correlate with quality of care

Table 2 Comparison between ventilator-associated events and VAP

	Ventilator-associated events	Clinical definition of VAP
Onset	At least 4 d of ventilation	Requires 2 or more days of ventilation
Oxygenation requirement	Requires stable baseline ventilator settings and threshold levels of oxygenation prior	Not applicable
Imaging	Not included	Required
Clinical findings	Not included	Required
Automation	Semiautomated	Manual and time-consuming
Susceptible to gaming	Yes	Yes
Sensitivity to diagnose infection	Moderate	Moderate
Reduced incidence if prevention strategies are implemented	Not clear	Yes

Abbreviation: VAP, ventilator-associated pneumonia.

evaluate the impact of a VAP bundle, looked at data from before and after its implementation (January 2003–December 2006—prebundle period [$n = 213$] and January 2007–December 2009—post bundle period [$n = 137$]).[37] They noted that the incidence of VAP using various definitions and the incidence of VAE remained unchanged post implementation of the VAP bundle despite good compliance. However, the mortality adjusted for severity of illness was less in the post bundle period (23 vs. 18, $p < 0.0001$), while the duration of mechanical ventilation (MV) and ICU and hospital length of stay did not change.

Klompas et al studied the preventability of VAE in 5,164 consecutive episodes of mechanical ventilation in a multicenter study in 12 ICUs. They examined the impact of using daily spontaneous awakening trial (SAT) and spontaneous breathing trials (SBT) and compared the findings to eight ICUs with surveillance alone.[38] The intervention reduced the duration of mechanical ventilation (mean by 2.4 days), ICU length of stay by 3 days, and hospital length of stay by 6 days after adjustment for age, sex, sequential organ failure assessment (SOFA), score, and comorbidity index. However, there was no change in VAE risk per ventilator day, but there was a significant decrease in VAE risk per episode of mechanical ventilation. There was a significant increase in SAT performed as a percent of days with SATs rising from 14 to 77% (cumulative change of +63%, $p < 0.0001$). On sensitivity analysis excluding a month with a high rate of VAE, the decrease in VAC was no longer significant.[38] The benefit of the intervention might have been related to a reduction in days of ventilation, but to perform SBT, there is often a reduction in PEEP and F_{IO_2}, which would make it more difficult to meet the ventilator setting rules (which require 4 days) for VAE. This alone could have reduced the VAE rate in the intervention group.

Table 3 Key VAP prevention strategies in ICU

"Ventilator bundles": individualize to each ICU
Oral care
Change ventilator circuits only when soiled
Noninvasive ventilation when possible
Reduce use of nasogastric tubes (place orally, and if possible postpyloric)
Infection control: hand washing, isolate patients with resistant organisms
Restricted blood transfusion policy
Consider subglottic secretion drainage endotracheal tubes
Daily interruption of sedation
Daily assessment for weaning

Abbreviations: ICU, intensive care unit; VAP, ventilator-associated pneumonia.

From the above, it is clear that reducing the length of mechanical ventilation will decrease potential complications on the ventilator, which might in turn decrease VAE rates, but would also decrease VAP. Several potential interventions similar to those used in the ventilator bundle, such as head end of bed elevation, early mobility, low tidal volume ventilation, conservative fluid management, and conservative transfusion thresholds have been suggested as strategies for preventing VAE.[24] Although, choosing the right denominator for surveillance is essential and prevention strategies could decrease duration of mechanical ventilation, it is premature to suggest the above measures would positively impact VAE rates. Also, it is still uncertain if a reduction in VAE or VAP rates reflects an improvement in the quality of care. Certainly, it is difficult to compare rates from one hospital to another, since different hospitals can care for patients with different comorbidities and severity of illness, and expected ventilator-related infection and complication rates would likely not be the same for all hospitals.

Future Approaches

Any performance measure requires standardization of included parameters and diagnostic testing, and all protocols should be followed consistently, and there should be an evaluation of improvement from a previous level. Manual surveillance is labor intensive and subject to misclassification. Kaiser et al incorporated a trigger activated pathway in 553 ventilated patients in combination with active screening

to identify VAP events.[39] The trigger was activated with invasive ventilation for 2 days plus specific antibiotic administration, and then the active screening part was begun, which included confirmation of lung infiltrates or consolidation by chest radiograph on at least 2 consecutive days. The sensitivity of trigger screening was 92.3%, and negative predictive value was 99.8%. Trigger-based screening reduced labor time from 2.2 to 0.3 hours/week, a workload reduction of 90%, but infections that were not treated with antibiotics would go undetected.[39] This approach, compared with VAE surveillance, could improve efficiency, the accuracy of identifying infection, objectivity, and reproducibility.

There are several protocols available to use in the care of critically ill patients. In a study of 59 ICUs in the United States, investigators compared patient outcomes in ICUs following a rigorous protocol-based care to those less highly protocolized ICUs.[40] They noted no differences in ICU and hospital mortality, the length of stay, use of mechanical ventilation, vasopressors, or continuous sedation among individuals in ICUs with a high versus a low number of protocols. Thus, having protocols in place may not equate to better care.

Multifaceted infection prevention programs have been shown to benefit ventilated patients. To improve safety outcomes, we have to differentiate preventable harm from events that are inevitable.[41] Many of the risk factors for VAP are nonmodifiable and may be present on admission, such as being on immune suppressive therapy, having a high number of comorbid illnesses, malnutrition, obesity, azotemia, age $>$ 60 years, smoking, trauma, burns, and prior antibiotic therapy. Since the patient case mix between hospitals is variable, the risk of drawing inaccurate comparisons is high.[42] In contrast, some risk factors for VAP are modifiable and can be used as quality indicators. Thus, monitoring processes of care, making sure that proven prevention methods were being used could be one quality measure that would not penalize hospitals with high severity of illness patients.

Valid performance indicators should have a numerator with clear definitions of the occurrence of preventable episodes and a denominator of those at risk for the event.[41] Our current surveillance measures do not measure some important outcomes in ventilated patients, such as duration of mechanical ventilation, antibiotic use or development of antimicrobial resistance. The focus should be to link care received by the patient to adverse outcomes. Thus, there may be a difference between a patient with an adverse outcome who received appropriate prevention efforts, from a patient with the same outcome who did not receive an accepted prevention tool. Patients who develop complications, without receiving appropriate prevention effort should be labeled as avoidable harm.[41] Prevention should be addressed by using standardized, evidence-based protocols, providing clinician compliance auditing and feedback, expert-led educational sessions and forums to improve clinician adherence and the quality of patient quality.

Conclusions

Outcome measures such as VAE surveillance can effectively circumvent the diagnostic limitations of VAP, but do not measure only the infection, and do little to improve the quality of care, since the validity and preventability of these events is still uncertain. One alternative to simply reporting VAP and VAC rates is to have a validated adjustment for case mix severity, and to focus on performing and measuring the relationship of these rates to the application of established and effective prevention strategies.

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Should We Immediately Start Antibiotics in Every Patient with a Clinical Suspicion of HAP/VAP?

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Abstract

Hospital-acquired pneumonia (HAP) and ventilator-associated pneumonia (VAP) remain two of the most commonly diagnosed nosocomial infections. Both are responsible for significant morbidity and mortality in hospitalized patients. The development of HAP and VAP is related to bacterial colonization of the oropharynx (and endotracheal tube in VAP) with subsequent microaspiration and development of clinical infection. Diagnosis is made based on the clinical presentation and can be confirmed by obtaining either noninvasive or invasive microbiology culture specimens. Decisions addressing initiation of antimicrobial therapy can be divided into clinical and bacteriological strategies. These strategies differ in the criteria used to determine the timing of empiric therapy, with the clinical strategy basing the decision on radiographic evidence of infection plus clinical signs and symptoms and the bacteriological strategy requiring growth of pathogens above a certain threshold from invasively obtained culture specimens. Despite the delineated pathways, these decisions remain multifactorial and should also include consideration of patient-related factors, such as immunocompetence, the risk of multidrug-resistant infection, and overall clinical condition. Patients with risk factors or signs of clinical decompensation should have empiric therapy initiated at a lower threshold. However, when possible, therapy should be directed at a confirmed infection following a positive culture result. Decisions regarding specific empiric regimens should be based on the local prevalence of infectious microorganisms along with their associated antimicrobial susceptibilities. Patients deemed at risk of infection with multidrug-resistant pathogens merit broader spectrum therapy, and immunosuppressed patients should have consideration of antifungal coverage.

Keywords

- hospital-acquired pneumonia
- ventilator-associated pneumonia
- quantitative culture
- empiric antimicrobial therapy
- multidrug resistance

Hospital-Acquired and Ventilator-Associated Pneumonia

Hospital-acquired pneumonia (HAP) is defined as pneumonia occurring as early as 48 hours after hospital admission that was not present at the time of admission.[1] Affected patients are managed on the acute care wards or in the intensive care unit (ICU) if merited by clinical condition. Ventilator-associated pneumonia (VAP) is a more specific subset of HAP, and it is defined as pneumonia occurring more than 48 to 72 hours after initiation of tracheal intubation.[2] Of note, while HAP includes the subset of patients with VAP, in

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the context of this review HAP will refer to only non-VAP. Despite significant efforts spent leading to advances in the understanding and prevention of HAP and VAP, these infections continue to cause significant morbidity and mortality in hospitalized patients.

Epidemiology

HAP and VAP account for 22% of all health care-associated infections according to a recent multistate point-prevalence survey, and it is estimated that HAP or VAP will complicate 5 to 10 per 1,000 hospital admissions.[1,3] These numbers do not appear to be declining, with a recent large randomly selected sample of hospitalized patients identifying a stable VAP rate of 10%.[4]

It is estimated that VAP affects 10 to 20% of all patients who require mechanical ventilatory support for more than 48 hours and accounts for 90% of all pneumonia occurring in the ICU.[1,5] As the majority of patients requiring ventilatory support remain intubated for a short period of time, a large proportion of VAP occurs during the first 4 days of mechanical ventilation.[6,7]

The all-cause mortality rate of VAP ranges from 20 to 50%, and a 2013 meta-analysis estimated the attributable mortality at 13%—primarily related to the prolonged exposure to risk associated with increased lengths of stay in the ICU.[8] Regarding length of stay, VAP has been estimated to increase days of mechanical ventilation from 7.6 to 11.5 and to extend hospital length of stay from 11.5 to 13.1 days.[9,10] With these increases in length of ICU and overall hospital stays, it is not surprising that VAP has financially strained the health care system with an estimated $40,000 in additional medical care costs per affected patient.[5,10–12]

Endotracheal intubation probably increases the risk of developing pneumonia by facilitating the growth of potential bacterial pathogens within the respiratory tract.[13] Patients are more likely to develop VAP if they are sicker, older, have undergone prior surgery, or are admitted with neurological and/or cardiovascular failure.[13,14]

While HAP is considered to be less severe, complications still occur in approximately 50% of patients. These complications range in severity and include pleural effusion, empyema, respiratory failure, sepsis, renal failure, and death. This holds true for both ICU and non-ICU patients, and the mortality of HAP in the ICU patient approaches that of VAP.[15]

Pathogenesis

The development of HAP and VAP is related to both the virulence and number of pathogenic organisms entering the lower respiratory tract as well as the interaction with the immunological response of the host. Involved microorganisms are primarily bacterial pathogens, with fungal and viral causative agents uncommon in immunocompetent hosts.[16] The primary mechanism of pathogen entry is via microaspiration of organisms colonizing the oropharynx or less commonly those found within gastric contents.

Colonization with microorganisms from the health care environment occurs within as little as 48 hours after hospitalization, and this results in a different composition of causative etiologies for nosocomial and community infections.[17,18] In the case of VAP, the insertion of an endotracheal tube provides a nidus for colonization of the lower respiratory tract. Also, the presence of the foreign body leads to decreased host defenses against infection, namely, through reduction of tracheobronchial mucous flow. This increase in retained secretions potentiates the microaspiration of bacteria-harboring secretions collecting at the endotracheal tube cuff, ultimately leading to the development of VAP.[19] Hospitalized patients are also prone to alterations of gastric pH due to critical illness and medication effects, leading to loss of gastric near-sterility.[20]

Microbiology

Aerobic gram-negative bacteria are some of the commonly implicated pathogens in HAP and VAP, including *Pseudomonas aeruginosa*, *Escherichia coli*, *Klebsiella pneumoniae*, and species of *Acinetobacter*.[21] Polymicrobial infections vary in incidence but are most common in patients with acute respiratory distress syndrome (ARDS).[22] For the most part, similar organisms are typically implicated in both HAP and VAP, though there is a lack of convincing evidence. Several studies have shown VAP to involve *P. aeruginosa*, *Acinetobacter*, and *Stenotrophomonas maltophilia* more commonly.[16,23] Frequency of infection with *Staphylococcus aureus* is comparable between HAP and VAP, though affected patients are more likely to have diabetes mellitus, head trauma, or admission to the ICU.[24] Certainly host factors and the local hospital flora also influence pathogen frequency, as well.

In addition to these commonly encountered infecting microorganisms, the incidence of multidrug-resistant (MDR) bacterial causes of HAP and VAP is on the rise. Recognition of the increasing rate is clinically significant, as cases of HAP and VAP due to MDR pathogens are associated with elevated crude and attributable mortality.[12,25] Methicillin-resistant *S. aureus* (MRSA) and MDR *P. aeruginosa* are the most frequently encountered MDR pathogens. *Klebsiella*, *Enterobacter*, and *Serratia* species are also on the rise, though the presence and frequency of specific microorganisms vary based on patient location, even down to hospital unit.[26] This necessitates an awareness of local susceptibility patterns when choosing empiric antimicrobial therapy.

Numerous risk factors for MDR pathogens have been identified. Factors associated with an increased risk of MDR VAP have been more extensively researched and include: use of intravenous antibiotics in the past 90 days, septic shock at time of VAP, ARDS preceding VAP, acute renal replacement therapy before VAP, and hospitalization for $\geq$ 5 days before VAP.[26–29] Only prior exposure to intravenous antibiotics has been consistently identified as a risk factor for MDR HAP.[26]

Regarding specific MDR pathogens, both infections involving MRSA and *P. aeruginosa* are most closely associated with

exposure to intravenous antibiotics within the past 90 days.[30–32] Many centers now perform routine screening for MRSA nasopharyngeal colonization, and there is limited evidence that patients with positive screening tests are more likely to have HAP or VAP caused by MRSA.[33] A negative screen decreases the likelihood that the pneumonia is due to MRSA; however, a negative screening test should not be considered definitive evidence, particularly in centers with a high baseline prevalence of MRSA.[34,35] Patients with cystic fibrosis and bronchiectasis are predisposed to pulmonary infections caused by *P. aeruginosa* due to frequent colonization, and this may increase the risk of MDR VAP caused by these microorganisms in this population.[36]

Clinical Features and Diagnosis

The diagnosis of HAP or VAP is suspected with the appearance of a new or progressing pulmonary infiltrate on chest radiograph (►**Fig. 1**) and the presence of clinical signs and symptoms including tachypnea, fever, purulent sputum, and

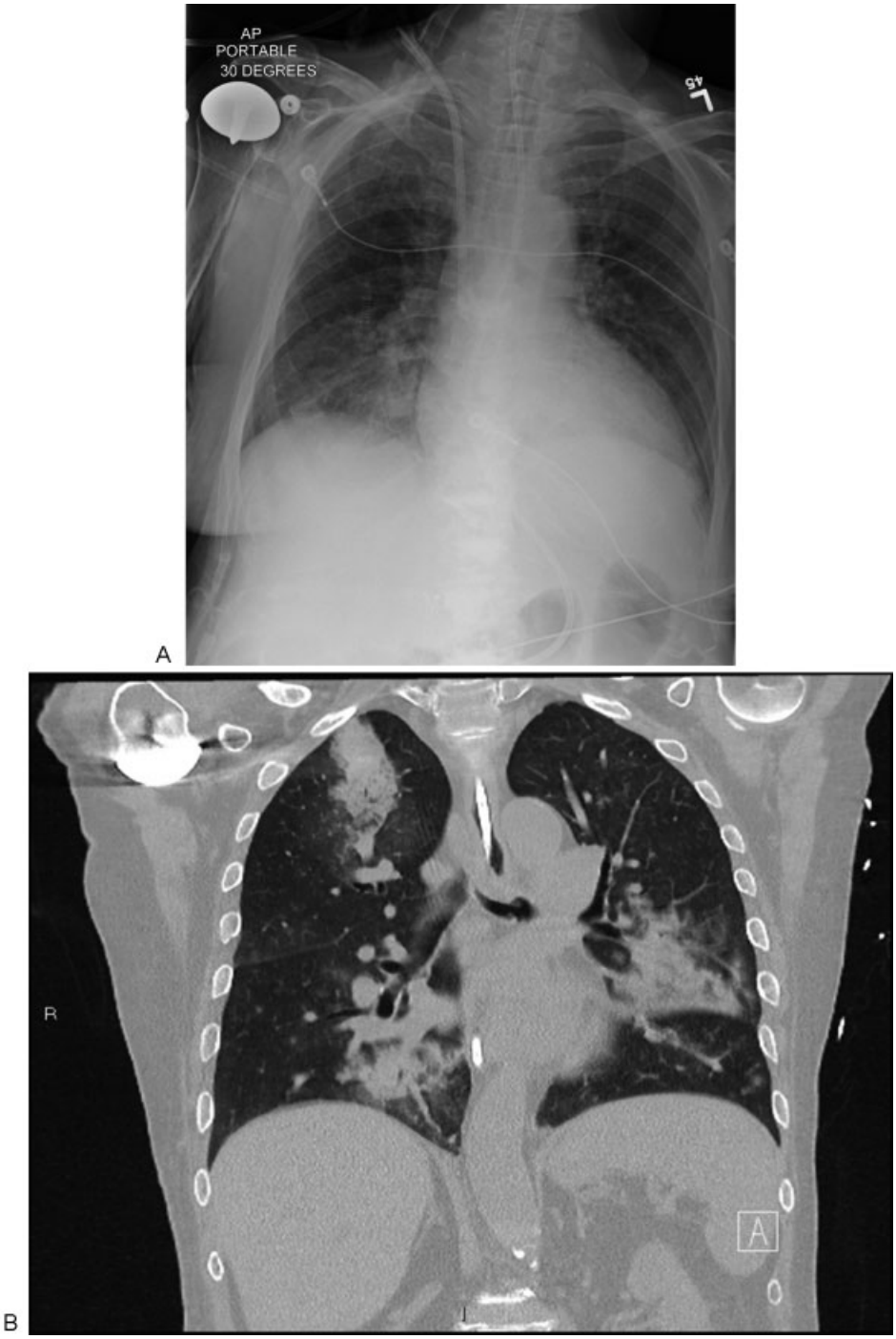

Fig. 1 (**A**) CXR with right basilar heterogeneous opacities, favored to represent asymmetric pulmonary edema and atelectasis on official read. (**B**) Coronal slice of chest CT from the same patient on the same day revealing multifocal pneumonia with consolidation in the right upper and lower lobes and inferior portion of the left upper lobe. CT, computed tomography; CXR, chest X-ray.

leukocytosis. Current recommendations from the American Thoracic Society and the Infectious Disease Society of America suggest the use of noninvasive sampling with the endotracheal aspiration to obtain semiquantitative or quantitative cultures to diagnose VAP. Invasive bronchoscopic techniques including bronchoalveolar lavage (BAL) and protected specimen brush (PSB) are also commonly used to elucidate the causative pathogen(s).[26] A high index of suspicion is necessary for patients with unexplained hemodynamic instability, significant deterioration of respiratory performance (decreased tidal volume, increased minute ventilation, decreased oxygenation), or ARDS, and early sampling should be performed in these patients.[37,38]

This strategy is challenging in patients with HAP not requiring supportive mechanical ventilation, as bronchoscopy is rarely used in this scenario. This results in less reliable bacteriological information, and thus the diagnosis of HAP is primarily made based on clinical presentation.[39]

Initiation of Antimicrobial Therapy

It is imperative to initiate antimicrobial therapy in a timely fashion to treat HAP and VAP, as a delay in appropriate treatment is associated with increased mortality.[40] However, the risks associated with overuse of antimicrobial medications must also be included in the decision paradigm. For instance, early treatment is involved in the increase of MDR VAP caused by MRSA and *P. aeruginosa*, highlighting the importance of responsible antibiotic stewardship.[41]

The decision to start antimicrobial therapy in a patient suspected of having HAP or VAP can be divided into two relatively distinct strategies. The clinical strategy bases a suspected diagnosis on the presence of a new lung infiltrate in combination with clinical evidence of infection. Initiation of treatment for the presence of at least two clinical features (fever, leukocytosis, purulent secretions) is the most accurate combination of criteria for starting empiric therapy.[42] Starting therapy in patients with only one clinical feature decreases the specificity of this clinical strategy, resulting in significantly more antibiotic treatment. If all three criteria are required for diagnosis, the strategy loses sensitivity, and too many patients with a true diagnosis of HAP or VAP will be left untreated.[1] This method becomes more complicated in patients treated in the ICU, as the chest radiographs in these patients are likely more challenging to interpret based on other comorbid conditions (volume overload, ARDS, etc.).[43] Endotracheal aspirates or sputum samples can be used to determine the etiological cause of infection via semiquantitative analysis or Gram stain results. Semiquantitative methods grow more microorganisms than invasive quantitative techniques, but it is rare for the causative agent not to be included in the result.[44] A negative result has a high negative predictive value for diagnosis.[45]

The Clinical Pulmonary Infection Score (CPIS) was developed to assist with the clinical diagnosis of VAP. The score is calculated on the basis of points assigned to categories including fever, leukocytosis, and the ratio of the partial pressure of arterial oxygen to the fraction of inspired oxygen (Pao_2/Fio_2), among others. Some studies have shown that a CPIS greater than 6 correlates with VAP; however, the preponderance of the research has suggested that the CPIS has both limited sensitivity and specificity in accurately diagnosing VAP, particularly when compared with quantitative culture results.[46] The interobserver variability is substantial, which also limits the utility of this tool to assist with the clinical diagnostic strategy.[24,47] The use of other biomarkers (including procalcitonin, soluble triggering receptor expressed on myeloid cells, and C-reactive protein) in conjunction with the clinical strategy is also not recommended.[26]

The clinical approach does not require advanced microbiological techniques, and thus has the potential to be applied in more facilities. All patients clinically suspected of having HAP or VAP are treated, which minimizes the number of infections that go untreated.[48] The clear downside of this strategy is its oversensitivity, as this leads to more antibiotic therapy prescribed than when the diagnosis is based on findings of the microbiological assessment. For example, noninfectious etiologies including pulmonary thromboembolism, drug reactions, or ARDS may result in a false-positive diagnosis in the clinical approach.[1]

The bacteriological strategy bases the initiation of antimicrobials on a diagnosis of HAP or VAP made by quantitative cultures of lower respiratory tract secretions obtained via BAL or PSB. This approach requires pathogen growth above a certain threshold to diagnose HAP or VAP. Growth that remains under the defined threshold is considered colonization or contamination, and the threshold necessary to diagnose infection varies with the technique used.[49]

The bacteriological strategy attempts to avoid the overuse of antibiotics through the use of specimen collection to distinguish infection from colonization.[1] Using these methods, fewer patients will receive antimicrobial therapy than when using the clinical strategy. The worry is that by heightening the threshold necessary to initiate treatment, more patients with a true infection go untreated. This is primarily due to a false-negative culture result secondary to recent initiation or change in antibiotic therapy before obtaining the specimen.[50] Likely this becomes more of an issue in patients already being treated with antimicrobial therapy for a separate infection. In this particular situation, a 10-fold lowering of the necessary growth threshold can be considered; however, even with this adaptation, some patients with pneumonia will have growth below the threshold, particularly during the early stages of infection.[51]

The main concern regarding the use of the bacteriological strategy is that patient outcomes may suffer secondary to the withholding of antimicrobial therapy until a diagnosis of HAP or VAP is confirmed by culture growth. A recent observational study investigated the difference in in-hospital mortality for ICU patients with infections treated with an aggressive (clinical) strategy versus a conservative (bacteriological) strategy. While this study included a variety of ICU-acquired infections, pneumonia comprised the largest subgroup. Results revealed that while patients managed with a clinical strategy had a more rapid initiation of antimicrobial

medications, they also had a decreased chance of receiving initially appropriate therapy, a lengthened duration of treatment, and a significantly higher rate of in-hospital mortality.[52] These findings suggest that the bacteriological strategy is a reasonable treatment paradigm for HAP and VAP, serving to balance the care of the individual patient with the potential damage caused by the selection of resistant pathogens.

The recently released 2016 clinical practice guidelines from the Infectious Diseases Society of American and the American Thoracic Society also address this debate. Although all recommendations are classified as weak and based on low-quality evidence. The guidelines favor a somewhat hybrid approach to the diagnosis of HAP and VAP as well as to the initiation of antimicrobial therapy. The societies recommend basing the diagnosis of HAP and VAP on noninvasively obtained semiquantitative cultures before the initiation of antimicrobial therapy. However, for patients who do have invasive sampling with quantitative cultures, treatment should be withheld if growth remains below the diagnostic threshold (PSB with $< 10^3$ colony-forming units [CFU]/mL, BAL with $< 10^4$ CFU/mL). In both cases, this strategy values the choice of accurate initial antimicrobial therapy with allowance for de-escalation of treatment based on culture results, rather than a focus on purely empiric treatment.[26]

The ultimate goal of both strategies is to promptly initiation empiric antimicrobial therapy in all patients with HAP and VAP, as delayed initiation of treatment has been shown to correlate with increased mortality.[40] If the institution has the specialized laboratories necessary to process quantitative specimens obtained from BAL or endotracheal aspirates, many clinicians favor the bacteriological strategy due to its ability to diagnose infection concomitantly with its etiology. Using this strategy to diagnose an infection and start antimicrobial therapy helps combat the overuse of these medications and the subsequent uptake in MDR microorganisms, particularly when clinical doubt exists regarding the diagnosis.[53]

Despite these benefits, there are multiple deviations from this strategy which must be considered. First, the obligate wait time for culture results complicates the exclusive use of culture results to diagnose an infection before the initiation of empiric therapy.[48] This becomes a significant issue when caring for critically ill patients with the hemodynamic compromise of unknown etiology that includes HAP or VAP in the differential diagnosis. Some studies have advocated for the use of Gram stain results as a surrogate while awaiting formal quantitative results, arguing that this approach decreases the use of antibiotics with no adverse effect on mortality.[54] Still, not all clinicians are comfortable with withholding antimicrobial therapy until culture results become available, and this is not recommended for clinically unstable patients. In these situations, the pretest probability of the HAP or VAP diagnosis must be weighed in conjunction with the severity of the patient's illness.[49] Ultimately, empiric antimicrobial therapy should be started immediately in a patient with signs of clinical infection in the setting of clinical instability (septic shock) regardless of status of quantitative culture results.[1]

Immunocompromised patients—including organ transplant recipients and individuals with malignancies or on chronic corticosteroids—should also have an early and aggressive consideration of empiric antimicrobial therapy, as respiratory infections in this population often present atypically and with rapid progression. Some fungal and viral pathogens can be diagnosed via rapid antigen tests on urine; however, the majority are diagnoses are based on the culture of BAL specimens.[55] As delays in diagnosis of specific pathogens remain likely, empiric coverage of commonly encountered fungal pathogens should be considered without delay. Viral causes are important to recognize, but the treatment remains primarily supportive.[1,55]

The use of invasive testing and quantitative culture results will sometimes not be possible. From a systems standpoint, some centers—predominantly smaller, local hospitals—will not have the resources to perform the clinical procedure to collect the specimens, the laboratory capabilities to process quantitative results or both.[26] Also, for patients with HAP not requiring mechanical ventilation for respiratory support, invasively obtaining specimens for quantitative cultures may be neither feasible nor advisable due to the risks of bronchoscopy—including the risk of respiratory decompensation during the procedure.[56] In these patients, initiation of empiric antimicrobial therapy based on the clinical strategy is advisable.

Selection of Empiric Antimicrobial Therapy

Similar to the decision to start empiric antimicrobial therapy, the selection of specific agents is also multifactorial. Patient-related risk factors for MDR infections, local patterns of antimicrobial resistance, and the overall prevalence of specific pathogens must be considered.[1,57] The timing of presentation can also affect the choice of therapy. Ultimately, the goal of treatment is to balance the need for early and appropriate antimicrobial therapy with the minimization of medication-associated morbidity, including pathogen resistance and *Clostridium difficile* infection.[26]

The classification of VAP as early- or late-onset is based on the historical observation that the majority of cases occur within the first 4 days of hospitalization, with the timeline beginning at time of admission rather than time of intubation. This factors into empiric therapy decisions, as airway colonization patterns change from a community-acquired to nosocomial pattern within 3 to 4 days of hospitalization.[58] The nosocomial pattern of colonization is associated with the development of late-onset HAP and VAP, with an increased risk of MDR causative pathogens in patients who develop infection after 5 days of hospitalization versus those cases with an earlier onset.[26] Early-onset HAP patients with a recent history of antibiotics or hospitalization within the past 90 days are also at an increased risk of MDR infection, and these patients should be considered in the same category as patients with late-onset HAP and VAP.[23]

Empiric treatment for suspected HAP and VAP should be based on the local prevalence of infectious microorganisms along with their associated antimicrobial susceptibilities. As prevalence and resistance patterns vary widely between geographical regions, separate hospital-specific antibiograms should be created for HAP and VAP, or at least for overall ICU infections.[57,58] This is likely not feasible for all centers, and in that case clinicians can rely on national surveys.[26] Ultimately, the use of a broad-spectrum initial regimen that is specific to the center can significantly reduce the rate of inappropriate empiric therapy with an inferred improvement in mortality.[48,59]

In the United States and worldwide, VAP is most commonly caused by *S. aureus*, *P. aeruginosa*, *Acinetobacter* species, and enteric gram-negative bacilli.[21] Many of these common organisms have unfortunately developed resistance, with almost 50% of *S. aureus* isolates resistant to methicillin (MRSA) and significant numbers of *P. aeruginosa* isolates resistant to either cefepime or piperacillin-tazobactam.[60] Empiric antimicrobial therapy for suspected VAP should thus include coverage of these organisms. When deciding whether or not to include coverage of resistant strains, patient-related risk factors should be considered along with the regional prevalence of MDR pathogens. Therapy for patients with specific risk factors for MRSA should include an anti-MRSA agent, such as vancomycin or linezolid.[32] Double-coverage of *P. aeruginosa* should be considered for patients in centers with elevated rates of resistance to a monotherapy agent or for ICUs lacking resistance data.[1,26]

The recommended empiric coverage of HAP is fairly similar to VAP—particularly for late-onset HAP, which carries the same increased risk of MDR pathogens.[23] Coverage of *S. aureus* and gram-negative bacilli (including *P. aeruginosa*) is advised for all HAP patients. In addition, those patients deemed at increased risk for MDR infection or at high risk for mortality—defined as ventilator support and septic shock—warrant additional coverage of MRSA.[26]

Special Considerations: Immunosuppressed Patients

Viral Pathogens

Viral causes of HAP and VAP are uncommon in immunocompetent patients. The most common viral causes include influenza, parainfluenza, adenovirus, and respiratory syncytial virus, with influenza A representing the most commonly involved viral pathogen.[1] Both influenza A and B can cause pneumonia as a primary infection, secondary bacterial infection, or both. The diagnosis is typically made by rapid antigen testing and serological assays or viral culture.[61,62]

The clinical course and severity of viral HAP and VAP is similar to bacterial and fungal pneumonia, and patients with concomitant bacterial and viral infection experience a greater severity of illness than a bacterial or viral infection alone. There is a role for antiviral therapy, particularly for influenza; however, the treatment of purely viral HAP or VAP remains primarily supportive.[63]

Fungal Pathogens

Fungal causes of HAP and VAP, namely, species of *Candida* and *Aspergillus*, are also uncommon in immunocompetent hosts.[64] These infections occur in organ transplant patients or in immunocompromised and neutropenic patients. The addition of empiric antifungal coverage—usually with fluconazole—should be seriously considered in these patient populations.[65] Of note, it is common for *Candida* species to be present in respiratory culture results of immunocompetent patients, but this is usually representative of colonization and not infection.[66]

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Ventilator-Associated Pneumonia: The Role of Emerging Diagnostic Technologies

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Abstract

Antibiotic resistance has emerged as a key determinant of outcome in patients with serious infections along with the virulence of the underlying pathogen. Within the intensive care unit (ICU) setting, ventilator-associated pneumonia (VAP) is a common nosocomial infection that is frequently caused by multidrug-resistant bacteria. Antimicrobial resistance is a growing challenge in the care of critically ill patients. Escalating rates of antibiotic resistance add substantially to the morbidity, mortality, and cost related to infection in the ICU. Both gram-positive organisms, such as methicillin-resistant *Staphylococcus aureus* and vancomycin-intermediate *S. aureus*, and gram-negative bacteria, including *Pseudomonas aeruginosa*, *Acinetobacter* species, carbapenem-resistant *Enterobacteriaceae*, such as the *Klebsiella pneumoniae* carbapenemase–producing bacteria, and extended spectrum β-lactamase organisms, have contributed to the escalating rates of resistance seen in VAP and other nosocomial infections. The rising rates of antimicrobial resistance have led to the routine empiric administration of broad-spectrum antibiotics even when bacterial infection is not documented. Moreover, there are several new broader-spectrum antibiotics that have recently become available and others scheduled for approval in the near future. The challenge to ICU clinicians is how to most effectively utilize these agents to maximize patient benefits while minimizing further emergence of resistance. Use of rapid diagnostics may hold the key for achieving this important balance. There is an urgent need for integrating the administration of new and existing antibiotics with the emerging rapid diagnostic technologies in a way that is both cost-effective and sustainable for the long run.

Keywords
- rapid diagnostics
- antibiotic resistance
- microbiology
- outcomes

Ventilator-associated pneumonia (VAP) is one of the most common infections occurring in mechanically ventilated patients and is frequently caused by antibiotic-resistant bacteria.[1] Mortality, hospital lengths of stay, and health care costs are typically greater among patients with respiratory failure complicated by VAP compared with patients who do not develop VAP.[2] Moreover, we know that the administration of inappropriate initial antibiotic therapy (IIAT) for VAP, usually attributed to multidrug-resistant (MDR) bacteria, is associated with greater hospital mortality and longer hospital lengths of stay.[3,4] These outcome influencing characteristics of VAP make it an important infection for intensivists to manage in an optimal manner. The ideal management of VAP requires intensive care units (ICUs) and hospitals to have consensus-derived strategies in place for the prevention, diagnosis, and treatment of this important nosocomial infection, which unfortunately are often lacking. Moreover, the overall perceived clinical importance of VAP has diminished in the United States due to the imprecise under-coding of this nosocomial infection using

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the Centers for Disease Control and Prevention surveillance definitions.[5] This has resulted in the promotion of ventilator-associated events (VAEs) as a preferred surveillance tool for assessing the quality of ICU care in the United States and reducing VAP to a nonreportable condition.[6] This may encourage suboptimal practices for VAP treatment that could be detrimental for patient outcomes and promote further antibiotic resistance.

The clinical importance of VAP is demonstrated by recent surveillance studies showing that it is a common nosocomial infection across all continents.[7–9] Moreover, the emerging problem of antibiotic resistance has added a new premium to the importance of accurately diagnosing and more importantly treating VAP with appropriate initial antibiotic therapy.[10,11] It is also imperative to recognize that one of the major clinical issues related to the management of VAP, as well as other nosocomial infections, is the increasing prevalence of MDR or extremely drug-resistant (XDR) pathogens.[12–15] There appears to be a direct relationship between overall antibiotic consumption for VAP and the emergence of newly resistance bacterial strains.[16,17] The latest and most fearsome example of this trend, due in large part to escalating use of colistin, has been the emergence of plasmid-mediated colistin resistance.[18] The development of colistin resistance in carbapenem-resistant *Enterobacteriaceae*, including New Delhi metallo-β-lactamase-1 (NDM-1) strains, brings a renewed sense of urgency to minimize any further resistance emergence and to prevent spread of these XDR bacteria.[19] As a result of this trend of increasing antibiotic resistance and boarder spectrum empiric antibiotic treatment of suspected VAP, more precise and rapid microbiologic diagnostic approaches for the antibiotic management of suspected VAP are urgently needed.

Diagnostic Criteria for VAP

The diagnosis of VAP is problematic because noninfectious conditions can cause pulmonary infiltrates and systemic findings such as leukocytosis, fever, and increased oxygen requirements.[20] Various diagnostic criteria with variable rigor have been developed to assist in the diagnosis of VAP. However, the most stringent criteria available have been 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.[21] Erring on the side of caution, most clinicians employ 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.[22] The difficulty in relying on clinical criteria for the diagnosis of VAP is the potential for over diagnosis, resulting in the unnecessary administration of antibiotics to noninfected patients. This has the potential to promote further emergence of antibiotic resistance, especially when employed for prolonged time periods, and to dilute out the ability of clinicians to identify the beneficial impact of treating patients with appropriate initial antibiotic therapy.[23,24]

Owing to the lack of a proven diagnostic method, two different strategies have been used and compared using clinical or bacteriologic criteria, each associated with advantages and disadvantages.[22] The clinical strategy employs the abovementioned clinical and radiographic criteria in diagnosing VAP. A combination of two out of three clinical criteria and a radiographic infiltrate yielded a sensitivity of 69% and a specificity of 75% for the diagnosis of VAP in 25 mechanically ventilated patients using histology and quantitative lung tissue culture on autopsy as the reference.[25] Increasing the number of clinical criteria resulted in greater specificity but at the cost of lesser overall sensitivity.[25] In a postmortem analysis of 39 mechanically ventilated patients, clinical criteria did not provide reliable predictive accuracy for histologic pneumonia.[26] A semiquantitative endotracheal aspirate culture can be used to identify a causative pathogen of VAP and, if positive, has been shown to correlate with quantitative cultures of the lower respiratory tract obtained via protected specimen brush (PSB).[27] Additionally, a negative endotracheal aspirate culture has good negative predictive value in excluding the presence of VAP if antibiotics have not recently been started or changed.[28] However, semiquantitative cultures are generally not as reliable as quantitative cultures of the lower respiratory tract due to an inability to differentiate between colonization and infection.[29] The use of clinical criteria and a reliance on semiquantitative cultures can result in clinical false-positive results for the diagnosis of VAP resulting in unnecessary antibiotic use.

The bacteriologic strategy uses quantitative cultures obtained from the lower respiratory tract via endotracheal aspirate, PSB, or bronchoalveolar lavage (BAL) to confirm or exclude the diagnosis of nosocomial pneumonia based on thresholds of bacterial growth of $\geq 10^5$ colony forming units (CFU)/mL for an endotracheal aspirate, $\geq 10^4$ CFU/mL for a BAL specimen, and $\geq 10^3$ CFU/mL for a PSB sample. Results of these procedures guide decisions such as when to initiate or stop antibiotics and which drug should be used against the offending agent. There are no definitive data to support the use of one sampling technique over another; however, the cellular analysis of BAL fluid may provide an advantage, as a sample containing less than 50% neutrophils was associated with excellent negative predictive value in one study.[26] Also, given the multifocal nature of VAP, even mini-BAL samples obtained blindly without the use of bronchoscopy can be effective.[30–32] However, other studies caution on the use of unilateral cultures even when directed to the side of the dominant radiographic abnormality.[33] The bacteriologic strategy has resulted in less overall prescription and more narrowed antibiotic use, an important point given the surge of antibiotic resistance in the ICU setting.[34–36] A major disadvantage of the bacteriologic approach is the concern for false negatives which could result in cases of nosocomial pneumonia going untreated, especially in the setting of recently introduced antibiotics.[37]

Multiple studies have compared the clinical and bacteriologic strategies. Only one prospective, randomized trial demonstrated a mortality benefit when using the bacteriologic strategy at 14 days.[34] Others have failed to reproduce these findings, including a large study conducted by the Canadian

Critical Care Trials Group and a comprehensive meta-analysis.[38,39] In addition, the bacteriologic strategy does not seem to reduce the duration of mechanical ventilation or ICU length of stay.[39] The decision to employ either the clinical or bacteriologic strategy rests with the clinician on a case-by-case basis. If bronchoscopic sampling can be performed safely and the appropriate personnel is available, it is reasonable to utilize this approach as antibiotic decisions may change based on culture results allowing for more effective antimicrobial deescalation. If the clinical strategy is used, the clinician should reevaluate the patient often for guidance on antibiotic usage. Regardless of the diagnostic strategy, an unstable patient with a high pretest probability of nosocomial pneumonia should be initiated on empiric antibiotics, as a delay in antibiotic administration leads to higher mortality.[40–42]

The lack of consistency in establishing a precise diagnosis of VAP has led some national guidelines to reflect on the relatively low accuracy of microbiology cultures as a diagnostic tool in VAP.[22] Moreover, contamination with upper respiratory tract pathogens or endotracheal tube colonizers is common and traditional microbiology laboratory flow with Gram staining, cultures, and antibiotic susceptibility testing requires at least 48 to 96 hours for information to be processed for clinical decision making. These current limitations in establishing a rapid and precise microbiologically confirmed diagnosis of VAP serve as the impetus for developing new rapid diagnostic approaches for this important infection.

New Diagnostic Technologies

Multiplex Real-Time Polymerase Chain Reaction

A broad range of viral and bacterial pathogens can cause acute respiratory tract infections including VAP often with similar clinical and radiographic presentations (►**Fig. 1**). Rapid detection of the causative pathogen offers the potential for providing timely administration of appropriate antimicrobial therapy as well as minimizing the use of broad-spectrum antibiotics when they are not justified based on microbiologic evaluation. Multiplex real-time polymerase chain reaction (PCR) offers rapid detection of a broad array of respiratory pathogens to optimize antimicrobial treatment. The FilmArray Respiratory Panel (RP; bioMérieux BioFire, Salt Lake City, UT) assay (►**Fig. 2**) is the first FDA-cleared assay for the qualitative detection of nucleic acid targets from both viruses and bacteria in nasopharyngeal swab specimens.[43] The FilmArray RP can detect 17 viral targets and three bacterial species (*Bordetella pertussis*, *Chlamydophila pneumoniae*, and *Mycoplasma pneumoniae*) more typically associated with community-acquired pneumonia with a turnaround time of approximately 1 hour and has been applied to direct respiratory specimens, including BAL specimens from mechanically ventilated patients (►**Table 1**).[44–46] More recently, the FilmArray RP has been employed to demonstrate that more than 24% of nonventilated hospital-acquired pneumonia (HAP) episodes were associated with respiratory virus infection alone or concomitant viral and bacterial infection.[47] This type of information could have important implications in terms of modifying or deescalating antibiotic therapy.[44]

A new Luminex NxTAG Respiratory Pathogen Panel (NxTAG-RPP, Austin, TX) has been introduced as a high-throughput system that can detect nucleic acid from 21 respiratory viruses, including all pathogens detected by the FilmArray RP except *B. pertussis* plus *Legionella pneumophila* and human bocavirus.[48] A comparison of these two technologies demonstrated complete concordance in 98.8% (318/322) of positive results (kappa = 0.92). The high sample throughput with reasonable turnaround time of these

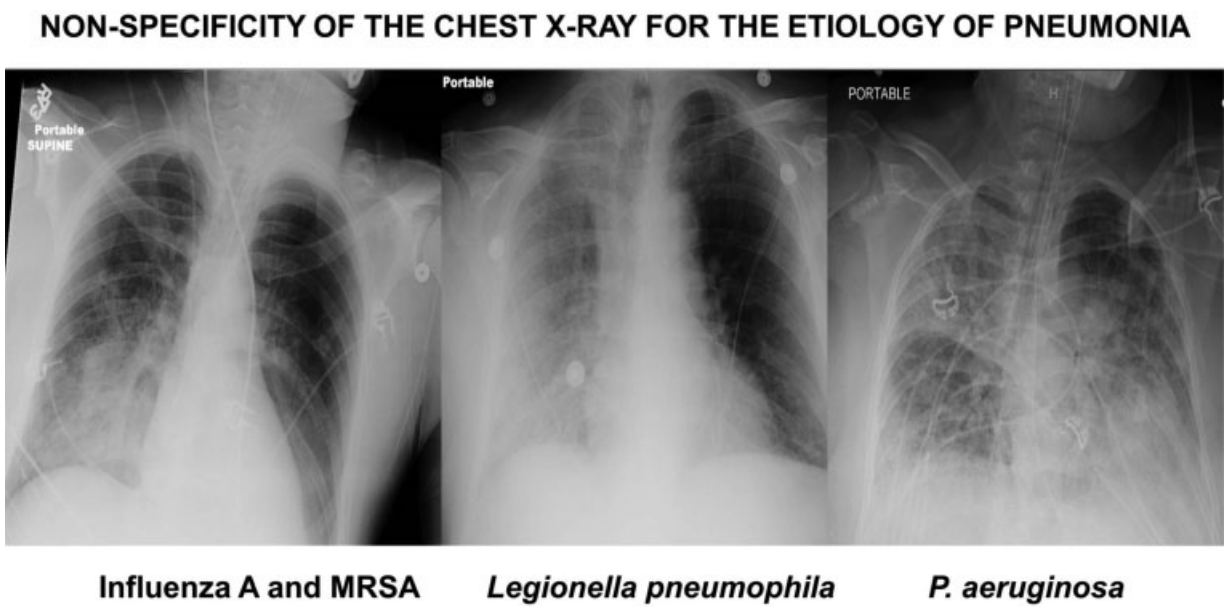

Fig. 1 Three chest X-rays of patients with microbiologically confirmed pneumonia showing similar types of infiltrates for different pathogens. These X-rays illustrate the general nonspecificity of the radiographic findings for establishing a precise microbiologic diagnosis of pneumonia. MRSA, methicillin-resistant *Staphylococcus aureus*.

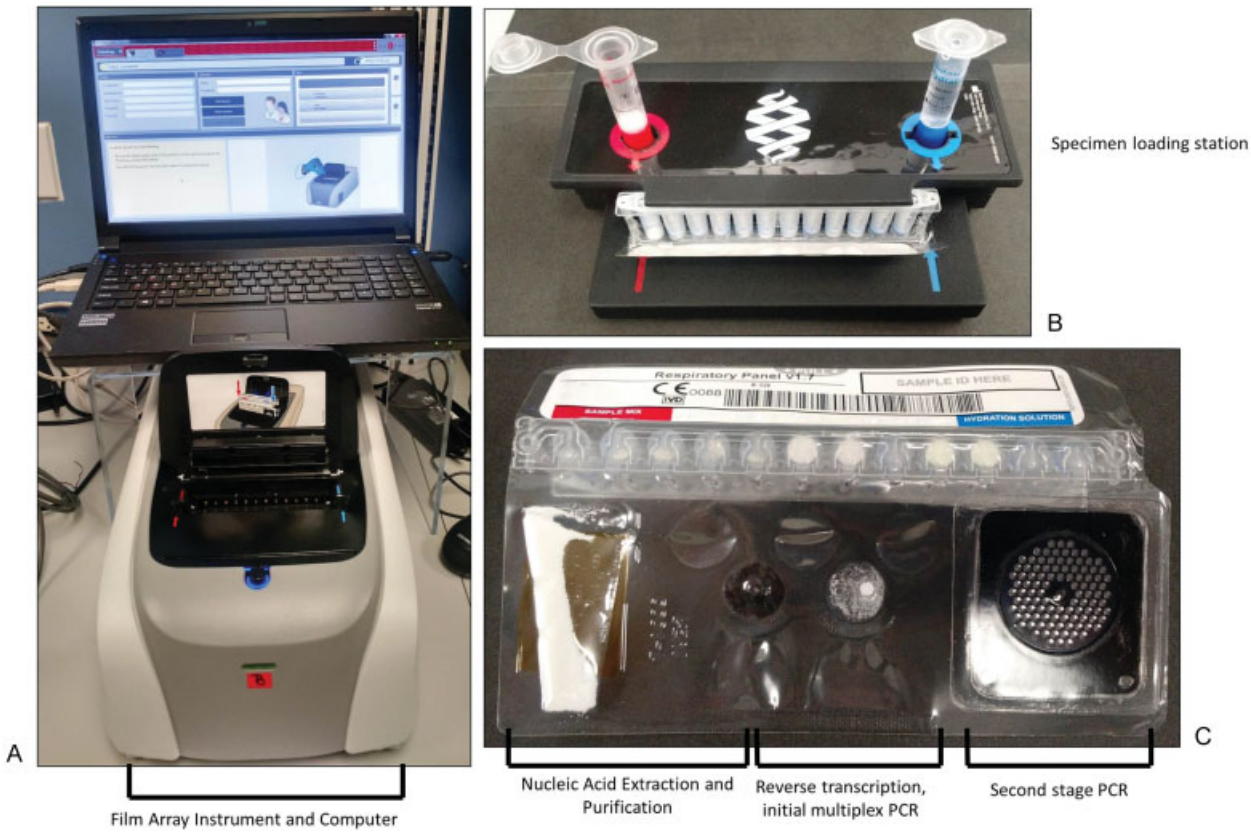

Fig. 2 The BioFire FilmArray System. (**A**) The BioFire instrument and computer. Each instrument can run one FilmArray pouch at a time. (**B**) The specimen loading station. The FilmArray pouch is fixed in the station, and rehydrating buffer and specimen are added. (**C**) The FilmArray pouch. The specimen is moved through a series of reagents, including nucleic acid extraction and purification steps, a reverse transcriptase and initial PCR step, and a second-stage PCR. PCR product detection is performed in the "honeycomb" of the second-stage PCR.

assays makes them suitable multiplex platforms for routine screening of respiratory specimens in hospital-based laboratories. Moreover, the use of multiplex real-time PCR has been associated with reduced antibiotic utilization in patients evaluated for respiratory tract infections demonstrating their potential value as antibiotic stewardship adjuncts.[49,50] Another potential use of multiplex real-time PCR would be the addition of emerging respiratory viral pathogens to the panel, facilitating surveillance to identify patients with new, and often virulent, respiratory virus syndromes such as Middle East respiratory syndrome coronavirus infection.[51]

A preclinical evaluation was recently conducted to evaluate the performance of the Cepheid Xpert MRSA/SA SSTI real-time PCR assay (Cepheid, Sunnyvale, CA) on 135 lower respiratory tract secretions for detection of methicillin-resistant *Staphylococcus aureus* (MRSA) and *S. aureus*.[52] Compared with the gold standard quantitative culture, the sensitivity, specificity, and positive and negative predictive values were 99.0, 72.2, 90.7, and 96.3%, respectively. The same assay has been employed to exclude the presence of MRSA and *S. aureus* in VAP demonstrating negative predictive values of 99.7% (98.1–99.9%) and 99.8% (98.7–99.9%) for methicillin-susceptible *S. aureus* (MSSA) and MRSA, respectively.[53]

Other Nucleic Acid Detection Techniques

New point-of-care PCR systems for rapid identification of pathogens and antibiotic resistance markers are available and show promise for the management of infections like VAP. Kunze et al evaluated point-of-care multiplex PCR (Unyvero, Curetis AG, Holzgerlingen, Germany) for patients with HAP.[54] Mean turnaround test result times were 6.5 hours (4.7–18.3 hours) for multiplex PCR and 71 hours (37.2–217.8 hours) for conventional microbiology. However, they found concordant results in only 45% and nonconcordant results in 45% of all patients. Only 55% of the results were concordant in patients with a clinical pulmonary infection score higher than 5, suggesting a high likelihood for the presence of HAP. These authors concluded that Unyvero allowed point-of-care microbial testing with short turnaround times, but the system performance was poor and what was needed was an improved system with more reliable performance and an extended microbial panel.

Vincent et al employed culture-independent polymerase chain reaction/electrospray ionization-mass spectrometry (PCR/ESI-MS) to test 616 bloodstream infection samples, 185 pneumonia samples, and 110 sterile fluid and tissue specimens from 529 patients.[55] From the 616 bloodstream samples, PCR/ESI-MS identified a pathogen in 228 cases (37%) and conventional culture methods in just 68 (11%). Conventional

Table 1 Pathogens identified with the FilmArray panels

FilmArray respiratory panel	FilmArray blood culture ID panel
Adenovirus	*Staphylococcus* species
Coronavirus 229E	*Staphylococcus aureus*
Coronavirus HKU1	*Streptococcus* species
Coronavirus OC43	*Streptococcus agalactiae*
Coronavirus NL63	*Streptococcus pyogenes*
Human Metapneumovirus	*Streptococcus pneumoniae*
Human Rhinovirus/ Enterovirus	*Enterococcus* species
Influenza A	*Listeria monocytogenes*
Influenza A/H1	*Klebsiella oxytoca*
Influenza A/H1–2009	*Klebsiella pneumoniae*
Influenza A/H3	*Serratia* species
Influenza B	*Proteus* species
Parainfluenza 1	*Acinetobacter baumannii*
Parainfluenza 2	*Haemophilus influenzae*
Parainfluenza 3	*Neisseria meningitidis*
Parainfluenza 4	*Pseudomonas aeruginosa*
RSV	*Enterobacteriaceae*
Bordetella pertussis	*Escherichia coli*
Chlamydophila pneumoniae	*Enterobacter cloacae* complex
Mycoplasma pneumoniae	*Candida albicans*
	Candida glabrata
	Candida krusei
	Candida parapsilosis
	Candida tropicalis
	mecA
	vanA/B
	bla_{KPC}

cultures were positive and PCR-ESI-MS was negative in 13 cases, and both were negative in 384 cases, giving PCR/ESI-MS a sensitivity of 81%, specificity of 69%, and negative predictive value of 97% at 6 hours from sample acquisition. Similar observations were made for pneumonia and sterile fluid and tissue specimens. An independent clinical analysis of results suggested that PCR/ESI-MS technology could potentially have resulted in altered treatment in up to 57% of patients. The findings of this study were promising in suggesting that clinical decision making could potentially be influenced in a positive manner with PCR/ESI-MS by allowing more rapid and accurate modifications in antibiotic therapy.

Banerjee et al performed a randomized trial in a total of 617 patients with positive blood culture bottles (BCBs) who underwent stratified randomization into three arms: standard BCB processing (control, $n = 207$), rapid multiplex PCR reported with templated comments (rmPCR, $n = 198$), or rmPCR reported with templated comments and real-time audit and feedback of antimicrobial orders by an antimicrobial stewardship team (rmPCR/AS, $n = 212$).[56] The primary outcome was antimicrobial therapy duration. The rmPCR panel used in both intervention arms was the FilmArray Blood Culture ID Panel (BioFire Diagnostics/bioMérieux BioFire), which was performed as soon as a BCB signaled positive, 24 hours a day, 7 days a week. This assay detects the pathogens and resistance genes shown in ►**Table 1**. Compared with the control group, both intervention groups had decreased broad-spectrum piperacillin-tazobactam use and increased narrow-spectrum β-lactam antibiotic use, and fewer instances of antibiotic therapy for contaminants. Time from Gram stain to appropriate antimicrobial deescalation or escalation was shortest in the rmPCR/AS group. The aim would be to replicate these types of findings in patients with pneumonia using lower respiratory specimens.

The Verigene Nanosphere system is a multiplex nucleic acid detection assay that is being used in clinical laboratories for pathogen identification and resistance gene detection in positive blood culture broth and for respiratory pathogen detection (►**Table 2**, ►**Fig. 3**).[57–59] Similar to the BioFire blood culture assay, use of the Verigene assay for bacteremic patients has been associated with reduced length of stay, reduced mortality, and improvement in time to optimization of antimicrobial therapy.[57,59,60] Panels directed toward lower respiratory tract pathogens are in development.

Matrix-Assisted Laser Desorption Ionization Time-of-Flight Mass Spectrometry

Traditionally, the identification of microbes recovered in culture has relied on microbial growth and metabolism in the presences of various biochemical substrates. In contrast, matrix-assisted laser desorption ionization time-of-flight mass spectrometry (MALDI-TOF MS) uses proteomic profiling to assign an identification; this can be applied to a variety of microbes, including bacteria, yeast, mold, and mycobacteria.[61–66] It is primarily ribosomal proteins that are detected using this method. The MALDI BioTyper system (Bruker Daltonics, Billerica, MA) and the VITEK MS (bioMerieux, Durham, NC) are the commercially available MALDI-TOF MS instrumentation/database platforms for microorganism identification. While MALDI-TOF MS has been used most frequently for expediting the identification of microbes recovered on solid culture media, it has also been used to identify some microbes from clinical specimens, including positive blood culture broth and urine.[67–69] In addition, proof-of-principle studies have demonstrated the power of this method to simultaneously identify important resistance determinants during routine organism identification, such as a vancomycin-intermediate *S. aureus* and certain KPC-containing plasmids.[70,71] As this technology becomes more widespread, it is likely that the rapid and accurate identification of pathogens will facilitate optimization of antimicrobial therapy in patients with all types of infection, including respiratory infection.

Fluorescence In-Situ Hybridization

The fluorescence in-situ hybridization (FISH) technique is based on fluorescently labeled oligonucleotide probes that

Table 2 Pathogens detected with the Verigene panels

Verigene respiratory pathogen panel	Gram-positive blood culture test	Gram-negative blood culture test
Adenovirus	*Staphylococcus aureus*	*Escherichia coli*
Human Metapneumovirus	*Staphylococcus epidermidis*	*Klebsiella pneumoniae*
Influenza A	*Staphylococcus lugdunensis*	*Klebsiella oxytoca*
Influenza A (subtype H1)	*Streptococcus anginosus* Group	*Pseudomonas aeruginosa*
Influenza A (subtype H3)	*Streptococcus agalactiae*	*Acinetobacter* spp.
Influenza B	*Streptococcus pneumoniae*	*Citrobacter* spp.
Parainfluenza 1	*Streptococcus pyogenes*	*Enterobacter* spp.
Parainfluenza 2	*Enterococcus faecalis*	*Proteus* spp.
Parainfluenza 3	*Enterococcus faecium*	CTX-M
Parainfluenza 4	*Staphylococcus* spp.	IMP
Rhinovirus	*Streptococcus* spp.	KPC
RSV A	*Listeria* spp.	NDM
RSV B	*mecA*	OXA
Bordetella pertussis	*vanA*	VIM
Bordetella parapertussis/B. bronchiseptica	*vanB*	
Bordetella holmesii		

Fig. 3 The Nanosphere Verigene System, consisting of instrumentation (**A, B**) and the test cartridge (**C**). Sample and reagents are added to the processing unit. After analysis is completed, the cartridge is moved briefly to the reading unit for interpretation.

complementarily bind to specific target ribosomal RNA sequences of bacteria, yeasts, or other microorganisms. Target sequences are naturally present in bacteria at a concentration high enough to enable visual detection of the specific fluorescent signal.[72] FISH can be used to detect pathogens that are difficult or time consuming to identify with traditional culture methods, especially when more than one species is present in the sample, as in the case of polymicrobial infections including VAP. RespiFISH HAP Gram (−) Panel (miacom diagnostics GmbH, Duesseldorf, Germany) is a classic FISH technology employing fluorescently labeled DNA molecular beacons as probes to develop a simple procedure known as the beacon-based FISH technology.[73] This panel is able to detect most gram-negative bacterial pathogens and has been shown to be accurate in detecting the causative pathogens in patients with pneumonia, including VAP.[74]

Automated Microscopy

Douglas et al employed a real-time multiplexed FISH-based microscopy ID/AST system (Accelerate Diagnostics, Tucson, AZ), capable of evaluating antibiotic sensitivity and resistance against live pathogenic organisms from blood cultures or respiratory samples using automated phenotypic growth pattern analysis (►**Fig. 4**), to study surveillance for potential preempted treatment of VAP.[75] Seventy-seven mini-BAL specimens were obtained in 33 patients. One patient (3%) was clinically diagnosed with VAP. Of 73 paired samples, conventional culture methods identified seven, containing pneumonia panel bacteria ($>10^4$ colony-forming units/mL) from five patients (four *S. aureus* [three MRSA], two *Stenotrophomonas maltophilia*, one *Klebsiella pneumoniae*) and resulted in antimicrobial changes/additions to two of five of those patients. Microscopy identified seven of seven microbiologically positive organisms and 64 of 66 negative samples compared with culture. Antimicrobial changes/additions would have occurred in three of seven microscopy-positive patients had those results been clinically available in 5 hours, including one patient diagnosed later with VAP despite negative mini-BAL cultures. Overall, automated microscopy was 100% sensitive and 97% specific for high-risk pneumonia organisms compared with clinical cultures suggesting that rapid microscopy-based surveillance may be

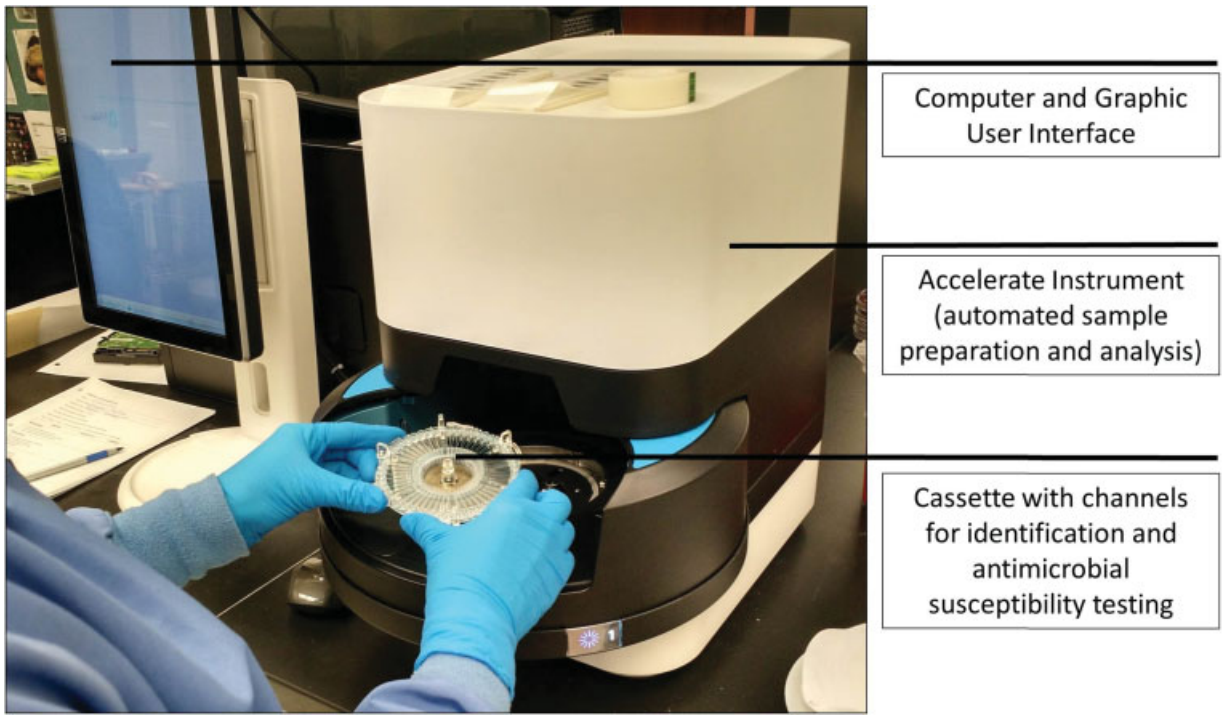

Fig. 4 The Accelerate System. A cassette, regent pack, and clinical sample are loaded into the analyzer. Following automated sample preparation, organism identification and antimicrobial susceptibility testing are performed. The results are available via the graphic user interface.

informative for treatment and antimicrobial stewardship in patients at risk for VAP. In addition, this system has been demonstrated to rapidly detect carbapenem resistance in *K. pneumoniae*, and, if present, predict if the resistance can be attributed to KPC carbapenemase.[76]

Analysis of Exhaled Breath Condensate Fluid and Volatile Organic Compounds

May et al employed a novel strategy for the rapid diagnosis of VAP utilizing exhaled breath condensate fluid (EBCF) obtained from heat moisture exchangers to provide a substrate for testing with PCR to identify bacterial DNA.[77] These investigators showed in critically ill surgical patients excellent concordance between pathogen identification using PCR of EBCF and pathogens isolated from BAL fluid using conventional microbiology techniques. Additionally, they found that increasing DNA load among serial EBCF samples preceded the clinical suspicion of VAP. The potential advantages of this type of diagnostic approach include noninvasive sampling of EBCF, ease of acquiring serial samples to potentially allow preemptive or targeted preventative treatment of early VAP or tracheobronchitis, and pathogen-specific characterization. The latter could help direct antibiotic therapy limiting the unnecessary use of broad-spectrum antibiotics for pathogens that are not identified, thus promoting antibiotic stewardship principles. The main disadvantage of this type of PCR-directed diagnostic approach is that it does not provide true antimicrobial susceptibility testing of the causative pathogens.

Volatile organic compound (VOC) detection is another promising diagnostic technology with probably the greatest applicability in VAP. Both humans and bacteria produce VOCs (volatile carbon molecules) as part of their metabolism. The VOCs vary depending on disease states, growth environment, and the presence of other bacteria. This technology is particularly appealing to lung diseases, as it can be monitored noninvasively analyzing exhaled breath (similar to EBCF). Changes in VOC patterns can trigger an early workup and also can be monitored to assess response to treatment. Mass spectrometry can swiftly identify and quantify VOCs. New technologies like electronic noses and optical spectra systems can describe the VOC patterns or fingerprints of bacteria.[78,79] In a study that included 38 ventilated patients, electronic nose–derived VOC fingerprints showed good correlation with clinical pneumonia scores.[80] A recent study monitored 45 ventilated patients thrice weekly using electronic nose technology.[81] The obtained VOC fingerprints were able to differentiate between infected, colonized, and noninfected patients. The potential for VOC detection in diagnosing lung infections using either few specific biomarkers or the whole VOC fingerprint is currently being actively pursued.[82,83]

Potential Limitations and Implications of Novel Diagnostics for VAP

As suggested earlier,[56] experiences with rapid diagnostics for the evaluations of blood culture specimens suggest that rapid diagnostics may play an important role in enhancing antimicrobial prescribing practices in hospitalized patients. The benefits to this can be numerous, including optimizing

clinical outcomes, reducing toxicity, and facilitating clinical trials for new anti-infective agents by stratifying patients eligible for the trial at the earliest possible opportunity. However, it is also important to understand the limitations of these new technologies including that they cannot differentiate colonization from infection, which could be highly problematic in mechanically ventilated patients, nor give us the true susceptibility patterns of the responsible pathogens. The latter is true with the exception of a few specific mechanisms of resistance provided by the previously described molecular techniques and automated microscopy which has the potential to provide real susceptibility data.

Further illustrating the potential role of rapid diagnostics in improving antimicrobial therapy and outcome when embedded in a well-organized antimicrobial stewardship program is the study by Huang et al from the University of Michigan.[84] These investigators performed a quasi-experimental study to analyze the impact of MALDI-TOF MS in conjunction with an antimicrobial stewardship team intervention in patients with bloodstream infections.[84] The antimicrobial stewardship team provided antibiotic recommendations after receiving real-time notification following blood culture Gram stain, organism identification, and antimicrobial susceptibilities using conventional microbiology methods in the before-period and MALDI-TOF MS in the after-period. Use of MALDI-TOF MS significantly decreased time to organism identification, and improved time to effective antibiotic therapy as well as optimal directed antibiotic therapy. Mortality, length of ICU stay, and recurrent bacteremia were also lower during the intervention period. Similarly, the PCR-based GeneXpert MRSA/SA diagnostic platform (Cepheid, Sunnyvale, CA) was studied at the Veterans Affairs Medical Center in Houston demonstrating that for MSSA bacteremia, the mean time to initiation of appropriate therapy was reduced from 49.8 to 5.2 hours and the duration of unnecessary MRSA drug therapy was reduced by 61 hours per patient.[85] It is hoped that the application of rapid diagnostic methods to respiratory specimens could have a similar impact on patients with pneumonia including VAP.

It is clear that we are entering a new era in the management and treatment of serious infections such as VAP. Spellberg et al made a recent plea to change our current patterns of managing patients with proven and presumed infections to reverse the spiraling trend of antibiotic resistance that has occurred over the last century.[86] Within the next 3 to 5 years, new antibiotics directed against MDR Gram-negative bacteria, in addition to the recently approved ceftolozane–tazobactam and ceftazidime-avibactam, will likely become available, including carbavance, plazomicin, eravacycline, relebactam, brilacidin, BAL30072, aztreonam-avibactam, carbapenems with ME 1071, and S-649266—a novel siderophore cephalosporin. These agents can provide enhanced activity against β-lactamase producers, carbapenem-resistant bacteria, and in some cases even metallo-β-lactamase–producing bacteria.

The challenge to ICU clinicians is how to most effectively utilize these agents once they become available to maximize patient benefits while minimizing the emergence of resistance (►**Table 3**). This is an especially important challenge in resource-limited countries that have often been at the forefront of the emergence of novel antimicrobial resistance mechanisms due to local patterns of antibiotic use. The use of rapid diagnostics may hold the key for achieving this important balance. There is an urgent need for clinical studies aimed at understanding how to best integrate the use of these new antibiotics with the emerging rapid diagnostic technologies in a way that is cost-effective and sustainable for the long run.[87] In addition, the microbiology laboratory must work closely with their clinical partners to deploy these new diagnostic tools in a manner that will afford the maximum benefit of these new technologies, including incorporation of the antimicrobial stewardship team and interpretative report comments, when applicable. Clinical outcome studies demonstrating the benefit of these new technologies on patient outcomes are needed. VAP may be an ideal infection to demonstrate the impact of rapid diagnostics as a means of enhancing antimicrobial treatment and stewardship.[88]

Table 3 Characteristics of diagnostic methods for ventilator-associated pneumonia

Diagnostic method	Conventional culture time (h)	Pathogen/Biochemical identification time (h)	True antibiotic susceptibility available	Antibiotic susceptibility time (h)	Total diagnostic time (h)
Conventional culture method	24–36	n/a	Yes	12–24	36–72
BioFire/Luminex	n/a	2–4[a]	No	n/a	2–4
PNA-FISH	n/a	2–4[a]	No	n/a	2–4
AXDX ID/AST	n/a	2–4[a]	Yes	3–6	6–10
VOC fingerprints	n/a	2–4[a]	No	n/a	2–4

Abbreviations: FISH, fluorescence in situ hybridization; ID/AST, identification/antibiotic susceptibility testing via automated microscopy; n/a, not applicable; VOC, volatile organic compounds.
[a]Assumes direct specimen inoculation from respiratory samples including endotracheal aspirates and bronchoalveolar lavage samples.

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Should We Treat Ventilator-Associated Tracheobronchitis with Antibiotics?

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Abstract

Patients admitted to intensive care units (ICUs) often require lung organ support. The use of mechanical ventilation, while lifesaving can be associated with subsequent complications. The most common complication in patients under mechanical ventilation is the development of ventilator-associated lower respiratory tract infections (VA-LRTIs). Before the development of VA-LRTI, there is a continuum process that ranges from airway colonization to ventilator-associated pneumonia (VAP). There is an intermediate process called ventilator-associated tracheobronchitis (VAT). Contemporary treatment of VA-LRTI emphasizes the importance of prompt broad-spectrum antimicrobial therapy. Previous studies reported prolonged duration of mechanical ventilation and ICU stay in patients with VAT. This negative impact on outcome is related to increased inflammation of the lower respiratory tract, sputum production, and higher rates of VAP. Extubation failure and difficult weaning have been reported to be associated with increased sputum volume in mechanically ventilated patients. Antibiotic treatment for VAT patients is still a matter for debate. Observational studies suggested a beneficial effect of antimicrobial treatment in VAT patients, including a reduced duration of mechanical ventilation and lower rates of subsequent VAP. Previous studies demonstrated beneficial effects of systemic and aerosolized antibiotics in preventing VAP in critically ill patients. However, antibiotic treatment is a recognized risk factor for the emergence of multidrug-resistant bacteria. Infections related to these bacteria are associated with increased morbidity, mortality, and cost. Therefore, a large well-designed study is warranted to determine whether patients with VAT should receive antimicrobials. Furthermore, a short course of antimicrobials could be sufficient in these patients.

Keywords
- intensive care
- ventilator-associated tracheobronchitis
- pneumonia
- antimicrobial

Patients admitted to intensive care units (ICUs) often require lung organ support. The use of mechanical ventilation, while lifesaving can be associated with subsequent complications. The most common complication in patients under mechanical ventilation is the development of ventilator-associated lower respiratory tract infections (VA-LRTIs).[1] Before the development of VA-LRTI, there is a continuum process that ranges from airway colonization to ventilator-associated pneumonia (VAP). There is an intermediate process called ventilator-associated tracheobronchitis (VAT). While VAP is an accepted entity that has a very clear algorithm for diagnosis and treatment, VAT is commonly a neglected entity

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by many researchers and treatment options have not been adequately addressed to date. In this review, we analyze the impact and pathophysiology of VAT, and we discuss the best strategic and therapeutic approach based on scientific evidence.

When a patient is critically ill, mechanical ventilation is often provided and is a common artificial organ support provided in ICUs. VAP is associated with significant patient morbidity and mortality globally.[2] It is estimated in the United States that VAP consumes $1.2 billion annually of critical care resources.[3] Previous epidemiological studies have shown that an intermediate process, VAT, exerts a similar burden on critical care resources.[4]

Mechanical ventilation is a cornerstone of supportive therapy in ICUs worldwide. Studies have shown that in the United States, utilization of mechanical ventilation for nonsurgical indications has increased from 178.9/100,000 adults in 1993 to 310.9/100,000 in 2009.[5] Ventilator-associated complications (VACs) are those complications that develop during a period of mechanical ventilation. The most frequent VACs are ventilator-associated infections (VAIs), namely, VAPs and VATs.[1] The problem that VACs and VAIs present for health care systems is of such magnitude that in the United States, the Critical Care Societies Collaborative agreed with the Department of Health and Human Services to address the challenging problem of VAIs.[6] Significant published work exists on the diagnosis, treatment, and impact of VAP on the outcome of critically ill patients, with a recent CDC algorithm that outlines an optimal approach to care.[7] However, similar levels of research work and clinical guidelines are lacking in VAT. This article seeks to address this critical knowledge deficit and to explore the treatment options for VAT.

Contemporary treatment of VA-LRTI emphasizes the importance of prompt broad-spectrum antimicrobial therapy. There is an implicit risk within this strategy that the liberal use of combinations of antimicrobial therapy will encourage the emergence of resistant organisms and generate untreatable infections. Given the more recent significant falloff in the discovery of next-generation novel antibacterial agents by the pharmaceutical industry, the emergence of antibiotic-resistant pathogens has led global leaders to warn of a future where common bacterial infections become untreatable and oftentimes fatal. The development of antibiotic resistance represents a global public health challenge that is causing widespread concern as expressed by Dame Sally Davies, England's Chief Medical Officer, who opined in 2013 that untreatable infection caused by antibiotic-resistant bacteria poses a catastrophic threat to humans and she has urged for immediate global action.

The absence of clinically useful biomarkers that identify mechanically patients with greater propensity to develop respiratory infection, and that predict the severity of such infections on an individual basis, is a significant unmet need. In the absence of these biomarkers therapy becomes empiric, there is no attempt to individualize therapy, patients are treated by protocol, and there is unrestricted overuse of antimicrobials with inevitable emergence of resistant pathogens. However, the absence of these biomarkers is underpinned by our fundamental ignorance of patient immune and inflammation response in this area of medicine.

A Neglected Disease in the Scientific Community that Needs a Paradigm Shift

Until recently, epidemiological data on patients with VAT have been lacking. A recent article published compared VAP and VAT in a large study with more than 3,000 patients admitted to 114 ICUs.[6] This study reported that VAT accounts for 1:6 of ICU infections, with similar requirement for ventilation and ICU resources as VAP patients, but without an increase in attributable mortality. Thus, VAT is an important clinical entity that has been underappreciated. Based on different definitions, incidence of patients with VAT varies widely.

In the United States, VAC surveillance is publicly reported for each institution and is linked with remuneration on the basis of pay for performance. This is a rather blunt approach with significant limitations. The clinical diagnosis of VAP, based on the aspiration of purulent tracheobronchial secretions and signs of systemic inflammation, is often inaccurate as purulent tracheobronchial secretions are invariably present in patients receiving prolonged mechanical ventilation even in the absence of either VAT or VAP. In addition, the systemic signs of inflammation, such as fever, tachycardia, and leukocytosis, are nonspecific. Clinical diagnosis is further undermined as the criteria for VAP include both subjective and objective components.

Prior reports, including a recent multicenter study, have shown that VAP can develop in patients with VAT when antimicrobial therapy is inappropriate.[8,9] However, it is also plausible that VAT might represent an intermediate process between lower respiratory tract colonization and VAP or even a less severe spectrum of VAP. Translational data have profiled gene expression in critically ill patients prior to the onset of respiratory infection, and identified a significant depression of the complement system pathway in patients who subsequently developed VAP when compared with those who developed VAT.[10] Thus, the continuum from colonization to VAT and then to VAP in ventilated patients may be linked with altered host immunity. Furthermore, divergent clinical disease pathways leading to either VAT or VAP may in reality be a surrogate of underlying immunity based on a compartmentalized versus noncompartmentalized hypothesis (►**Fig. 1**).

There is an urgent need for new concepts in the area of VAIs. Ideally, one would prefer to prevent rather than treat respiratory infection in ventilated patients. Currently, there is a wide range of measures in clinical use that generally involve some physical patient manipulation aimed at reducing the incidence of respiratory infection in mechanically ventilated patients. However, despite numerous and sometimes imaginative efforts to validate the benefit of these measures, most clinicians now accept that currently available measures have failed to eradicate VA-LRTI.

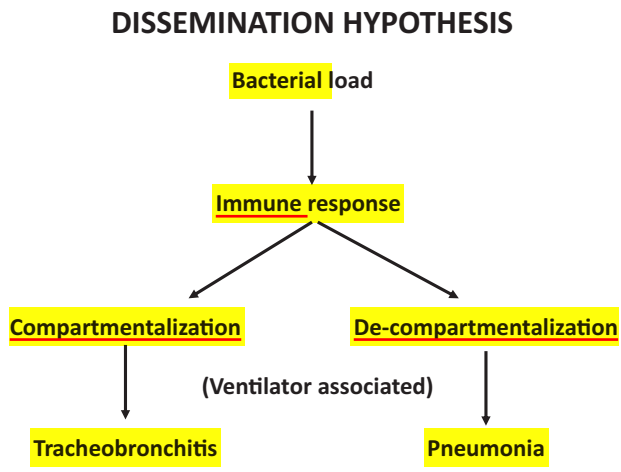

Fig. 1 Dissemination hypothesis accounting for bacterial load in respiratory airways.

In nosocomial infections in critically ill patients, there are several important factors (►**Fig. 2**) that play major roles in determining severity of infection. Obviously, the ICU-specific biodiversity represents an important and largely immutable risk factor. When deciding on appropriate antibiotics, it would be important to take into account the risk factors for the occurrence of antimicrobial-resistant infections (severity and ecology) specific to that hospital. In separate studies, while there is no doubt that the appropriateness of antibiotic therapy represented an important risk factor for better outcome,[9] the severity of VA-LRTI also appears to depend on host-specific factors and also upon the progression of the underlying disease.[2]

Both early recognition of infection and prompt initiation of appropriate antimicrobial therapy are key to improving outcomes with VAT/VAP.[11,12] A recently published multicenter prospective observational study could identify a panel of biomarkers, spanning the inflammatory cascade, apoptosis, and early phases of immune response using a multiplex technology in mechanically ventilated patients.[13] This study devised a predictive model for the diagnosis of VAP. Although this study focused on VAP, there is a lack of information on biomarkers in VAT.

Future Directions for Understanding the Disease

A capacity to predict the onset and severity of VA-LRTI will dramatically change antimicrobial prescribing and management in these critically ill patients. It would allow clinicians to logically individualize antimicrobial therapy based on a validated biomarker set rather than the current subject approach, which is less than optimal. Antimicrobial therapy will be individualized by either expanding therapy from a single to a multidrug regimen, or by using a shorter or a more prolonged duration of therapy. This logical and objective regimen for antimicrobial prescribing may curtail the overall antimicrobial usage and may delay or prevent emergence of antimicrobial-resistant pathogens. A patient would be less likely to develop overwhelming infection and more likely to

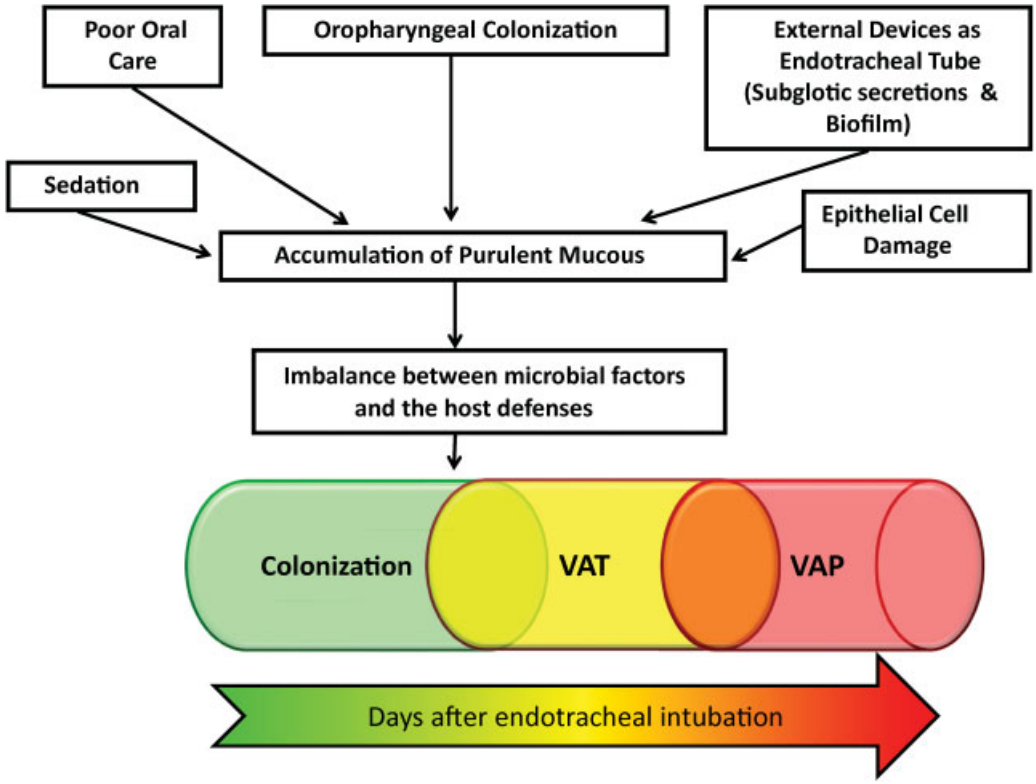

Fig. 2 Risk factors associated with development of VA-LRTI. VA-LRTI, ventilator-associated respiratory tract infections; VAT, ventilator-associated tracheobronchitis; VAP, ventilator-associated pneumonia.

survive VA-LRTI when they receive early optimal bespoke antimicrobial therapy. The duration and intensity of therapy would be tailored to their individual response, based on the changing patterns of gene expression in a panel of immune/inflammatory biomarkers. Antimicrobial stewardship is obviously of vital importance in the longer term. However, there would be a more immediate and direct benefit for individual patients with this novel approach. In short, it is vital that alternative and more logical strategies for treating VA-LRTI need to be developed.

Immunity-Based Approach for Lower Respiratory Tract Infections

Available data suggest that there is a continuum among colonization of lower respiratory tract, VAT, and VAP.[3,14] However, in some patients, VAP might occur without previous VAT, suggesting two different pathogenic pathways. We also agree that there is probably an overlap between these two infections, but no available examination could differentiate them. Computed tomography scan and lung ultrasound are more efficient in diagnosing lung infiltrate than chest X-ray.[15] However, to diagnose a new infiltrate, a baseline examination is required. Fiberoptic bronchoscopy and bronchoalveolar lavage (BAL) will most likely not be used to differentiate VAT from VAP, as previous studies reported frequent high burden of bacteria on BAL in chronically ventilated patients without local or systemic signs of infection.

In a pilot study, intubated patients with VAP showed a relative depression of the genes involved in the complement system, cyclic adenosine monophosphate, and calcium signaling pathways which all play a key role in the immune response to bacteria.[10] The relative depression of these routes may lead to an impaired immunocompetent status, and contribute to explain why patients with VAP exhibit more inflammation and worse outcomes than those with VAT.[6] Therefore, therapy of VAP should be more aggressive than VAT. These findings suggest that VAP does not have an abrupt onset and risk of VAP might be anticipated by identification of the signature that precedes pneumonia, facilitating preemptive therapy. Moreover, further translational research done in VA-LRTI will offer a dramatic change in the paradigm to understanding the pathogenesis of respiratory infections, with implications for prevention or earlier diagnosis. Indeed, early monitoring of immunosuppression in the postintubation period will ultimately determine if prevention of VAP is a realistic goal.

Impact of Ventilator-Associated Tracheobronchitis on Outcome

Previous studies reported prolonged duration of mechanical ventilation and ICU stay in patients with VAT.[1,3,4,6] This negative impact on outcome is related to increased inflammation of the lower respiratory tract, sputum production, and higher rates of VAP.[7,16,17] Extubation failure and difficult weaning have been reported to be associated with increased sputum volume in mechanically ventilated patients.[16,17]

In a large cohort of intubated and mechanically ventilated patients, VAT was significantly associated with longer duration of mechanical ventilation and ICU stay in medical and surgical patients.[3] However, no significant difference was found in ICU mortality rate between patients with VAT and those who did not develop VAT or VAP. Two matched case–control studies were conducted in patients with chronic obstructive pulmonary disease (COPD) and patients without chronic respiratory disease to adjust for confounding factors.[18,19] Matching criteria included (1) duration of mechanical ventilation prior to VAT occurrence; (2) primary diagnosis for admission; (3) indication for mechanical ventilation; (4) simplified acute physiology score II on admission $\pm$ 5 points; (5) age $\pm$ 5 years; and (6) date of admission when more than one potential control was well matched to a case. In these studies, VAT was significantly associated with longer duration of mechanical ventilation and ICU stay. However, no significant difference was found in ICU mortality between patients with VAT and those without VAT.

Another observational study compared outcomes between patients with VAT and those with VAP in a cohort of 1,241 COPD patients requiring intubation and mechanical ventilation for $>$ 48 hours.[1] Although no significant difference was found in the duration of mechanical ventilation (26 ± 17 vs. 24 ± 15 days, $p = 0.3$) and ICU stay (28 ± 20 vs. 26 ± 17 days, $p = 0.06$), ICU mortality rate was significantly lower in VAT patients compared with VAP patients (45 vs. 64%, $p < 0.001$). However, a recent study performed on 111 patients (28 patients with VAT and 83 patients with VAP) found no significant difference in hospital mortality between patients with VAT and those with VAP (19 vs. 21%, respectively, $p = 0.7$).[20]

Recently, Karvouniaris et al performed an observational single-center study on 236 patients.[4] The occurrence of VAT was a significant risk factor for increased duration of ICU stay (odds ratio, OR [95% confidence interval, CI]: 3.04 [1.35–6.85]; $p = 0.01$). In the above-discussed TAVeM international study, mean time to ICU discharge in survivors was significantly longer in the VAP and VAT groups compared with no lower respiratory infection group (hazard ratio of 1.65; 95% CI: 1.38–1.97).[6] However, patients with VAP presented a significantly ($p < 0.001$) higher mortality rate (40%) than those with VAT (29.2%) or those with no lower respiratory tract infection (30.2%).

Impact of Antimicrobial Treatment on Outcome in Patients with VAT

Antibiotic treatment for VAT patients is still a matter of debate.[21,22] A recent international survey was conducted in 288 ICUs from 16 different countries to determine the current practices in VAT patients.[23] Approximately half of the respondents stated that patients should receive antibiotics for the treatment of VAT.

Observational studies suggested a beneficial effect of antimicrobial treatment in VAT patients, including a reduced

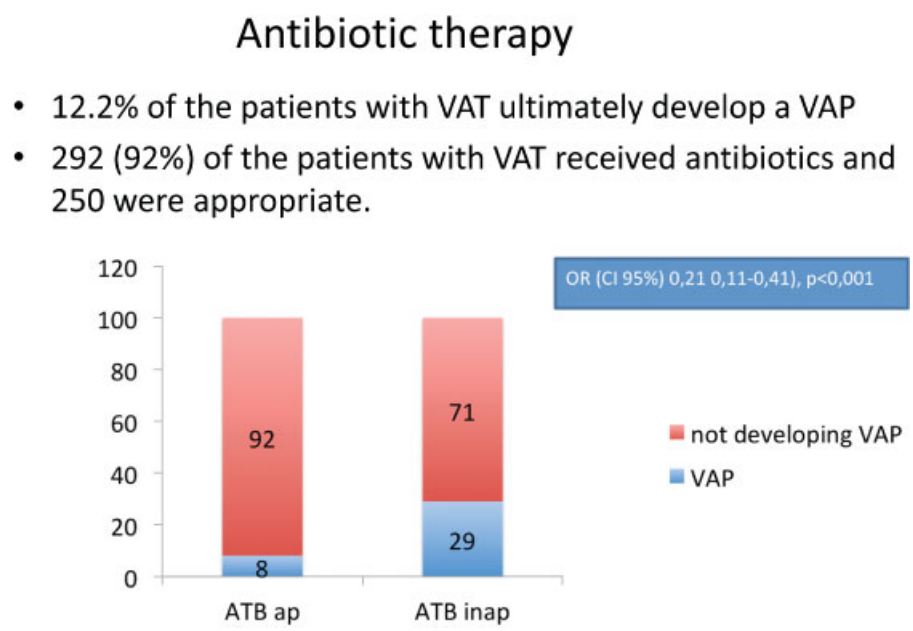

Fig. 3 Progression from VAT to VAP. CI, confidence interval; OR, odds ratio; VAP, ventilator-associated pneumonia; VAT, ventilator-associated tracheobronchitis. Adapted from Martin-Loeches et al.[6]

duration of mechanical ventilation and lower rates of subsequent VAP.[3,6,9] A European multicenter observational study aimed to determine the factors associated with transition from VAT to VAP in a cohort of 120 patients with VAT.[9] Appropriate antimicrobial treatment was identified as an independent predictor of lower rates of VAP subsequent to VAT (OR [95% CI]: 0.12 [0.02–0.59]). Furthermore, the TAVeM study found the use of appropriate therapy in VAT to be associated with a significantly lower progression to VAP, compared with inappropriate treatment (28.6 vs. 7.6%; $p < 0.001$; crude OR: 0.21; 95% CI: 0.11–0.41).[6] However, this study was observational, and the impact of appropriate antibiotic treatment was a secondary outcome (►**Fig. 3**).

Two small randomized studies evaluated the impact of antimicrobial treatment on the outcome of VAT patients.[24,25] Palmer et al performed a randomized blinded placebo-controlled trial to determine the impact of aerosolized antibiotics on outcomes in patients with VAT. Forty-three patients were randomized to receive aerosolized antibiotics or placebo for 14 days. Choice of aerosolized antibiotic was based on Gram stain. Vancomycin or gentamicin was used in patients with gram-positive and gram-negative microorganisms, respectively. Both antibiotics were used if gram-positive and gram-negative microorganisms were present. Most of the 43 included patients also had VAP at randomization and were treated with systemic antibiotics. The authors found aerosolized antibiotics to be associated with significantly lower rates of subsequent VAP, reduced usage of systemic antibiotics, and increased weaning (►**Table 1**). The limitations of this study included coexistence of VAP and systemic antibiotics in most patients, lack of specificity in VAT definition, and small number of included patients.

The impact of systemic antimicrobial treatment on outcomes in VAT patients was evaluated in a multicenter randomized unblinded controlled study.[25] In all patients, quantitative tracheal aspirate was performed at ICU

Table 1 Randomized studies assessing the impact of antimicrobial treatment on outcome in patients with VAT

	Aerosolized antibiotics[24]			Intravenous antibiotics[25]		
	Yes $n = 19$	No $n = 24$	*p*-Value	Yes $n = 22$	No $n = 36$	*p*-Value
Days free of MV, median (IR)	10 (26)	0 (27)	0.069	12 (8–24)	2 (0–6)	< 0.001
Subsequent VAP, %	35.7	78.6	0.007	13	47	0.011
ICU mortality, %	21.1	16.7	0.990	18	47	0.047
MDR bacteria emergence, %	0	16.6	0.005	36	40	0.784

Abbreviations: ICU, intensive care unit; IR, interquartile range; MDR, multidrug-resistant; MV, mechanical ventilation; VAP, ventilator-associated pneumonia; VAT, ventilator-associated tracheobronchitis.

admission and weekly thereafter. Systemic antibiotics were given for 8 days based on results of previous endotracheal aspirate. The study was stopped early because planned interim analysis found significant difference in mortality rate between the two groups. Fifty-eight patients were included (22 patients in antibiotic group and 36 patients in control group). No significant difference was found between the two groups in patient characteristics at ICU admission and at randomization. Although duration of mechanical ventilation and ICU stay were similar in the two groups, number of days free of mechanical ventilation was significantly higher in the antibiotic group compared with the control group. In addition, subsequent VAP and ICU mortality rates were significantly lower in antibiotic group compared with control group. The lower ICU mortality in antibiotic group is probably related to difference in patient characteristics between the two groups. Limitations of this study included absence of blinding, lack of standardized antibiotic treatment, and small number of included patients.

A meta-analysis, including the above-discussed randomized trials and other observational studies, found that administration of systemic antimicrobials (with or without inhaled ones), as opposed to placebo or no treatment, in patients with VAT was not associated with lower mortality (OR: 0.56; 95% CI: 0.27–1.14).[26] However, most of the studies providing relevant data noted that administration of antimicrobial agents, as opposed to placebo or no treatment, in patients with VAT was associated with lower frequency of subsequent pneumonia and more ventilator-free days, but without shorter length of ICU stay or shorter duration of mechanical ventilation.

Conclusion

One could argue that patients with high amounts of bacteria in respiratory specimens could benefit from antimicrobial treatment. However, positive respiratory specimen should be considered as colonization in patients without local and systemic signs of infection. Previous studies demonstrated beneficial effects of systemic and aerosolized antibiotics in preventing VAP in critically ill patients.[27–29] However, antibiotic treatment is a recognized risk factor for the emergence of multidrug-resistant bacteria.[30,31] Infections related to these bacteria are associated with increased morbidity, mortality, and cost.[32] Therefore, a large well-designed study is warranted to determine whether patients with VAT should receive antimicrobials. Furthermore, a short course of antimicrobials could be sufficient in these patients.

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Pharmacokinetic/Pharmacodynamics-Optimized Antimicrobial Therapy in Patients with Hospital-Acquired Pneumonia/Ventilator-Associated Pneumonia

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Abstract

Hospital-acquired pneumonia and ventilator-associated pneumonia continue to cause significant morbidity and mortality. With increasing rates of antimicrobial resistance, the importance of optimizing antibiotic treatment is key to maximize treatment outcomes. This is especially important in critically ill patients in intensive care units, in whom the infection is usually caused by less susceptible organisms. In addition, the marked physiological changes that can occur in these patients can cause serious changes in antibiotic pharmacokinetics which in turn alter the attainment of therapeutic drug exposures. This article reviews the various aspects of the pharmacokinetic changes that can occur in the critically ill patients, the barriers to achieving therapeutic drug exposures in pneumonia for systemically delivered antibiotics, the optimization for commonly used antibiotics in hospital- and ventilator-associated pneumonia, the agents that should be avoided in the treatment regimen, as well as the use of adjunctive therapy in the form of nebulized antibiotics.

Keywords

- hospital-acquired pneumonia
- ventilator-associated pneumonia
- antibiotics
- critically ill patients
- pharmacokinetics
- pharmacodynamics
- optimization
- nebulized antibiotic

Hospital-acquired pneumonia (HAP) and ventilator-associated pneumonia (VAP) remain a major cause of death in critically ill patients with attributable mortality rates as high as 30 to 50%.[1] The offending pathogens for this infection depend on the host risk factors as well as geography. Gram-negative bacilli (GNB) predominates with *Pseudomonas aeruginosa* and *Acinetobacter baumannii* leading this group followed by *Klebsiella pneumoniae* and other non-fermenting GNB such as *Stenotrophomonas maltophilia*.[2–4] Interestingly, the incidence of severe pneumonia caused by gram-positive microorganisms has reduced over the years in some parts of the world, perhaps reflecting an improvement in infection control measures.[5–7] Based on the etiologies, the empiric antimicrobials selected for HAP/VAP should have activity against the common gram-negative pathogens as defined by local data.

Most of the dosing regimens for antibiotics in adults are currently stratified only by the level of renal function of the patient. The regimens are derived from in vitro and animal in

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vivo infection models as well as tolerability studies performed in healthy adults. Additionally, most clinical trials are typically performed in heterogeneous groups of noncritically ill patients. However, numerous clinical data have described the myriad of pathophysiological changes that can occur in critically ill patients which in turn affect antibiotic concentrations and, therefore, dosing requirements.[8–15] These primarily include increases in volume of distribution of an antibiotic as well as increases or decreases in organ function, both of which can influence the clearance of antibiotics.

This article aims to discuss (1) pharmacokinetic (PK) changes in the critically ill patients including PK/pharmacodynamics (PD) targets of commonly used antibiotics for HAP/VAP; (2) penetration of systemically administered antibiotics into the lungs (i.e., the site of infection in pneumonia); (3) commonly used antibiotics for HAP/VAP in terms of PK/PD challenges and their optimization; (4) antibiotics that should be avoided for use in HAP/VAP; and (5) the current position for nebulized antibiotics.

Pharmacokinetics and Pharmacodynamics of Antibiotics

PK is the study of antimicrobial exposure in the body over time that includes absorption, distribution, metabolism, and excretion. PD on the other hand describes the activity of the antimicrobial against the organisms at the site of infection. The parameter used to account for this antimicrobial potency is expressed in the form of the minimum inhibitory concentration (MIC). MIC is a semiquantitative measure that captures the lowest concentration of antimicrobial that renders no visible growth of organisms after 16 to 20 hours of incubation under specifically described conditions. The PK/PD index describes the concentration–time curve associated with maximal bacterial killing, with MIC being the common denominator across all classifications. Generally, antimicrobials can be classified into three categories based on their modes of bacterial killing: (1) concentration-dependent antibiotics (e.g., aminoglycosides); (2) time-dependent antibiotics (e.g., β-lactams); and (3) both concentration and time-dependent antibiotics (e.g., vancomycin and fluoroquinolones). These fundamental concepts of bacterial killing characteristics of antimicrobials are illustrated in ►**Fig. 1**. The relevant PK/PD indices that have been shown to correlate with maximal bacterial killing are presented in ►**Table 1**.

One of the principal challenges for optimal antimicrobial dosing in these patients are severe pathophysiological derangements that can alter most PK parameters; the most important alterations being the primary PK parameters, namely, volume of distribution (V_d) and clearance, which predominantly influence dosing requirements. Changes in V_d and clearance can, to some extent, be predicted by the physiochemical properties of the drug and pathophysiological changes in the patient leading to altered plasma and target site drug concentrations. These have been increasingly reported in critically ill patients,[8,10–12,15,16] and the relevance of the phenomena in determining optimal antibiotic exposure has been described in detail elsewhere.[17,18]

Antibiotic Penetration

The use of plasma sampling has greatly assisted the characterization of antibiotics' PK. However, most infections do not occur within, or are not limited to, the intravascular compartment. For lung infections such as pneumonia, the site of infection is the lung parenchyma. Given that antibiotics do not distribute evenly throughout the body, knowledge of concentrations at the site of infection are very

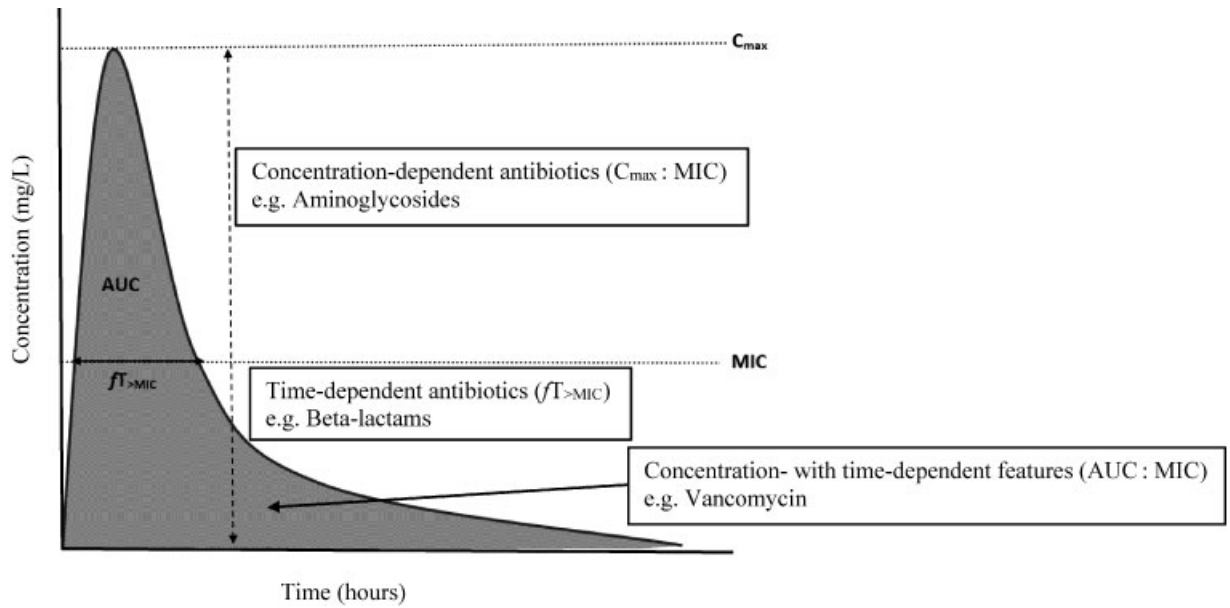

Fig. 1 Fundamental concepts of bacterial killing characteristics of antimicrobials based on pharmacokinetic/pharmacodynamic parameters. AUC, area under the concentration–time curve; C_{max}, maximal concentration; $fT_{>MIC}$, duration of time that drug concentration remains above the minimum inhibitory concentration during a dosing interval; MIC, minimum inhibitory concentration.

Table 1 The PK/PD index and the optimal magnitude for commonly used antibiotics in hospital- and ventilator-associated pneumonia

Antibiotic	Optimal PK/PD index	Optimal PK/PD magnitude for clinical response	Reference
Piperacillin–tazobactam	$\%fT_{>MIC}$	50	50–53
Ceftazidime	$\%fT_{>MIC}$	60	
Imipenem	$\%fT_{>MIC}$	40	
Meropenem	$\%fT_{>MIC}$	40	
Doripenem	$\%fT_{>MIC}$	40	
Colistin/polymyxin	AUC_{0-24}/MIC	20	80,84
Vancomycin	AUC_{0-24}/MIC	350–400	97,99
Levofloxacin	AUC_{0-24}/MIC	80[a]	112–114
Ciprofloxacin	AUC_{0-24}/MIC	>125[a]	
Linezolid	AUC_{0-24}/MIC and $\%fT_{>MIC}$	80–100 85	123,126
Tigecycline	AUC_{0-24}/MIC	> 17.9	137,138

Abbreviations: AUC_{0-24}/MIC, the ratio of the area under the concentration–time curve during a 24-hour period to MIC; $\%fT_{>MIC}$, percentage of time that the free drug concentration remains above the MIC of an offending pathogen during a dosing interval; PK/PD, pharmacokinetic/pharmacodynamics.
[a]PD target for gram-negative bacteria.

important to ensure that maximal antimicrobial effects are being achieved.[19] There are numerous sites in the lungs where antibiotic concentrations could be measured to describe antibiotic penetration including sputum, bronchial secretions, lung interstitial fluid, epithelial lining fluid (ELF), alveolar macrophages, and tissue biopsies. However, as ELF is considered to be the most representative sampling matrix for pneumonia, knowledge of antibiotic concentrations in ELF could be used to develop more effective drug doses.[19–21]

The ELF antibiotic concentration is dependent on antibiotic distribution across the alveolar capillary membrane, an anatomical barrier that separates the blood and the target site compartments.[22,23] While the capillary membrane is rather permeable, the alveolar membrane is relatively impervious with tight junctions called *zonula occludens* that do not allow easy access of antibiotics into the lung parenchyma.[24] This factor becomes important as only free unbound drug can cross these layers with lipophilicity enabling higher penetration too. Between these two layers is the transit area for the drugs to dwell in, before they traverse through zona occludens. Unfortunately, active clearance by the lymphatic system undermines both the drug availability in this area and the maintenance of a concentration gradient.[25]

The physiochemical properties of an antibiotic also influence the degree of ELF penetration. Lipophilic antibiotics are considered to have high ELF penetration, where the ELF-to-plasma concentration ratio (C_{ELF}:C_{Plasma}) usually is ≥1.0.[21,26,27] However, hydrophilic antibiotics can have poorer and more variable ELF penetration; the C_{ELF}:C_{Plasma} is mostly reported to be less than 1.[22,25,28–37] This will be further explored in the later sections that describe individual antibiotic classes and the corresponding ELF penetration data. ►**Table 2** summarizes the data on antibiotic penetration into the ELF in detail.

Increased Minimum Inhibitory Concentration in HAP/VAP Organisms

Pathogens that cause HAP/VAP differ significantly between the isolates recovered from other infections, as they tend to be less susceptible to commonly used antibiotics.[38–40] For example, the MIC of these pathogens are often higher when compared with those isolated from community-acquired pneumonia, as HAP/VAP is commonly caused by nosocomial pathogens that can possess multiple resistance genes.[41] The MIC difference in pathogens isolated in the intensive care unit (ICU) can be up to eightfold when compared with those isolated from the general wards.[42] When considering HAP and VAP separately, the susceptibility of the offending pathogens can vary with higher MICs observed in VAP-causing isolates.[43] Additionally, Ambrose et al showed that the PK/PD target attainment (i.e., achievement of therapeutic concentrations) of patients with VAP was lower when compared with the HAP cohort.[44] As MIC is the common denominator for PK/PD indices, clinicians need to understand that fixed dosing may not be applicable in these patients, as a higher MIC necessitates a higher PK exposure to ensure the optimal PK/PD index is achieved.[45] Indeed, antibiotic dosing that does not account for these physiological differences and clinical features may likely lead to therapeutic failure. Below we discuss the PK/PD data relating to different antibiotic classes in the context of treating HAP/VAP.

Beta-Lactams

The β-lactam antibiotics include penicillins, cephalosporins, carbapenems, and monobactams. The spectrum of antibiotic activity is variable with some having only a narrow spectrum

Table 2 Penetration into ELF in various patient populations for antibiotics that are commonly used for hospital- and ventilator-acquired pneumonia

Antibiotic (reference)	Dosing regimen	Included population (M/F)	Mean age (y)	Participant division (*n*)	Sampling time (*h*)	Plasma concentration (mg/L)	ELF concentration (mg/L)	C_{ELF}:C_{Plasma}
Piperacillin/tazobactam[48]	IV 4 g piperacillin + 0.5 g tazobactam over 30 min × Q8H	10 with VAP (6/4)	61	10	Steady state	Piperacillin = 24.0 Tazobactam = 2.4	Piperacillin = 13.6 Tazobactam = 2.1	Piperacillin = 0.57 Tazobactam = 0.91
Ceftazidime[30]	IM 1 g × 1 dose	25 with acute exacerbation of chronic bronchitis (NS)	NS	5	1	39.9	7.2	NS
				5	2	36.0	2.7	NS
				5	4	13.3	1.3	NS
				5	8	6.1	0.7	NS
				5	12	1.1	0.1	NS
Ceftazidime[29]	IV 2 g over 30 min × 1 dose then CI 4 g over 24 h	15 with severe VAP (9/6)	57	15	8, 12, 18	39.6	8.2	0.21
Ceftazidime[28]	Patients were divided into 2 groups. Group A received CI (IB of 20 mg/kg over 30 min, followed by CI 60 mg/kg/d) Group B patients were treated by IB 20 mg/kg × Q8H	34 patients with VAP (27/7)	Group A = 70	17	Total of 13 blood samples	6–95[a]	12.0	0.42
			Group B = 61	17	Total of 18 blood samples	27.0[b]	6.0	0.44
Cefepime[48]	IB 2 g over 30 min × 1 dose then CI 4 g over 24 h	20 adults with severe VAP (13/7)	65	7	8	13.5	13.7	1.01
				7	12	13.7	13.5	0.99
				6	18	13.3	13.9	1.17
Ceftobiprole[49]	IV 0.5 g over 2 h × Q8H × 4 doses	24 healthy adults (nonsmoking)	54.0	6	2.5	17.7	2.6	0.26[c]
				6	4	12.8	2.0	
				6	6	6.9	4.6	
				6	8	3.65	1.51	
Meropenem[32]	IV 1 g over 30 min × 1 dose	30 adults with no pneumonia	45.8	Nil	0.5	25.96	5.04	0.19
					1	14.98	7.07	0.51
					2	12.01	3.86	0.33
					4	2.51	2.20	1.04
					6	0.57	0.59	0.82
					8	0.29	NR	NA

Table 2 (*Continued*)

Antibiotic (reference)	Dosing regimen	Included population (M/F)	Mean age (y)	Participant division (*n*)	Sampling time (*h*)	Plasma concentration (mg/L)	ELF concentration (mg/L)	C_{ELF}:C_{Plasma}
Meropenem[31]	IV 0.5 g over 30 min × Q8H	20 healthy adults (11/9)	33	4	1	10.9	5.3	0.49–0.80 (range for all sampling points)
				4	2	5.2	2.7	
				4	3	2.4	1.9	
				4	5	0.3	0.7	
				4	8	0.0	0.2	
	IV 1 g over 30 min × Q8H × 4 doses	20 healthy adults (11/9)	29	4	1	19.0	7.7	0.32–0.53 (range for all sampling points)
				4	2	7.5	4.0	
				4	3	5.3	1.7	
				4	5	2.0	0.8	
				4	8	0	0.03	
	IV 2 g over 30 min × Q8H × 4 doses	8 healthy adults (5/3)	33	4	1	60.9	2.9	0.04
				4	3	12.8	2.8	0.22
Meropenem/ RPX7009[47]	IV 2 g × Q8H × 3 doses in combination RPX7009 (2 g)	25 healthy, nonsmoking adults (18/7)	39.0	5	1.5	41.2	21.4	NS
				3	3.25	47.7	28.3	
				5	4	23.8	16.1	
				3	6	7.24	7.51	
				2	8	1.36	2.51	
Ertapenem[37]	IV 1 g over 30 min × 1 dose	15 adults undergoing thoracotomy and most suspected of lung cancer (15/0)	61.8	Nil	1	63.1	4.1	0.06
					3	39.7	2.6	0.07
					5	27.2	2.1	0.09
Biapenem[36]	IV 0.3 g over 30 min × 1 dose	6 healthy nonsmoking adults (5/1)	23.8	This was a crossover study and the same 6 subjects were recruited in both the arms	0.5	18.1	3.48	0.20
	IV 0.3 g over 3 h × 1 dose				3	6.8	1.33	0.20
Colistin[92]	A single dose of neb. 2 MU 8 IV followed by 2 MU Q8H	12 adults with VAP (6/6)	54	Nil	Multiple time points	0.15–4.7	1.48–28.9	NS

(*Continued*)

Table 2 (*Continued*)

Antibiotic (reference)	Dosing regimen	Included population (M/F)	Mean age (y)	Participant division (*n*)	Sampling time (*h*)	Plasma concentration (mg/L)	ELF concentration (mg/L)	C_{ELF}:C_{Plasma}
Vancomycin[35]	IV 15 mg/kg over 2 h and adjusted to achieve C_{min} of 15–20 mg/L (treated for 5 d)	14 critically ill patients infected with gram-positive pathogens and who were mechanically ventilated (11/3)	60 (± 16)	Nil	18.4	24	4.5	0.18
Vancomycin[34]	IV 30 mg/kg per day	10 critically ill patients with MRSA pneumonia and were mechanically ventilated (6/4)	65.6 (± 8.4)	Nil	24	16.3	ELF levels were detected in only 4 patients with the mean of 2.03	NS
Vancomycin[102]	IV vancomycin 1 g × Q12H × 9 doses	10 healthy subjects (5/5)	24 (20–39)	5	4	19.8	5.3	NS
				5	12	5.1	2.4	NS

Abbreviations: C_{ELF}:C_{Plasma}, ELF to plasma concentration ratio; CI, continuous infusion; C_{min}, trough concentration; ELF, epithelial lining fluid; F, female; IB, intermittent bolus; IM, intramuscular; IV, intravenous; M, male; MRSA, methicillin-resistant *Staphylococcus aureus*; NS, not stated; Q12H, every 12 hours; Q8H, every 8 hours; VAP, ventilator-associated pneumonia.

[a]Expressed as minimum concentration to the maximum concentration at steady state.

[b]Steady-state concentration.

[c]Mean AUC_{ELF}:AUC_{Plasma}.

of activity and others having broad activities against anaerobes and gram-positive and gram-negative bacteria including those that express β-lactamase enzymes. The introduction of the existing β-lactams with the new β-lactamase inhibitors such as ceftolozane–tazobactam, ceftazidime–avibactam, aztreonam–avibactam, and meropenem–vaborbactam further expands the antibiotic coverage of this class to cover most of these enzymes conferring resistance including some classes of carbapenemase-producing Enterobacteriaceae (CRE).

Pharmacokinetic Issues and Challenges

Beta-lactams are hydrophilic antibiotics that are primarily distributed within the extracellular fluid compartment.[46] These antibiotics demonstrate variable ELF penetration (C_{ELF}:C_{Plasma} of 0.06–1.0).[31,32,36,37,47–49] ►**Table 2** highlights that most β-lactams (including carbapenems) demonstrate variable, but generally low ELF penetration, except for cefepime when it was delivered via continuous infusion (CI).[28–30,50] Carbapenems also show the same pattern, whereby all carbapenems tested failed to reach 100% penetration into the ELF, except in one study that showed meropenem reached more than 100% penetration following a single dose of 1 g meropenem, 4 hours after the end of its 30 minutes of infusion.[32] This corroborates the notion that alternative dosing strategies may be required to achieve therapeutic exposures in patients with HAP/VAP. Interestingly, even with CI, ceftazidime penetration into ELF was relatively poor (C_{ELF}:C_{Plasma} of 0.21–0.44),[28,29] despite achieving optimal PK/PD exposure against *P. aeruginosa* in the plasma. This further emphasizes that plasma concentrations do not always reflect concentrations in the ELF and as such, aggressive dosing regimens may be needed to ensure effective PK/PD target attainment in infected lung tissues.[28]

PK/PD Optimization and Challenges

The PK/PD target that best predicts bacterial killing activity by β-lactams is the duration of time that the free (unbound) drug stays above the MIC during a dosing interval ($fT_{>MIC}$), specifically the percentage (%) of $fT_{>MIC}$ needed for optimal bacterial killing, which is 60 to 70%, 50%, and 40% for cephalosporins, penicillins, and carbapenems, respectively.[51] However, a more aggressive target might be needed in critically ill patients who may be immunocompromised and are at risk of higher burden of infection. A target of 100% $fT_{>MIC}$ or 100% $fT_{>4\times MIC}$ has been suggested for such patients.[52] Aggressive PK/PD targets are also justified in patients with HAP/VAP, as antibiotic dosing that achieves PK/PD target in plasma is unlikely to achieve the same target in ELF. However, these aggressive targets are rarely achieved with standard β-lactam dosing in daily practice. This was described by Roberts et al in a large multinational PK point-prevalence study in which one in every five patients in the ICU cohort failed to even achieve the conservative PK/PD target (i.e., 50% $fT_{>MIC}$) and the failure rates increased to almost half of the population studied (40%) when the target was aimed at 100% $fT_{>MIC}$.[53] The implication of these findings is profound, as those that did not achieve the conservative PK/PD target were three times more likely to manifest negative clinical outcomes. To overcome this, extended infusion and CI, which can also be referred to as prolonged infusion (PI), have been advocated as a means of achieving optimal PK/PD targets in critically ill patients.[46,54–58] Numerous PK/PD modeling and simulation analyses have shown that an improved β-lactam exposure can be achieved via PI administration, particularly when less susceptible pathogens are present.[59–62]

Despite strong PK/PD data supporting PI of β-lactam antibiotics over intermittent bolus (IB) dosing, there are currently no convincing data on clinical outcomes that differentiate the two dosing methods. Clinical evidence supporting PI dosing has been heterogeneous, varying from no significant effects to significant clinical cure benefits.[55,63] Meta-analyses of clinical studies have also generally not found any significant patient benefits favoring PI over IB dosing.[64–68] This paradox might have stemmed from the methodological flaws associated with the available clinical studies and these inconsistencies have been reviewed in detail elsewhere.[54] Furthermore, it has been suggested that PI administration of β-lactam antibiotics may not benefit all critically ill patients but only in those with a high level of illness severity who are infected with less susceptible pathogens. This was shown in an individual patient level meta-analysis which specifically compared CI and IB dosing of β-lactam antibiotics, in which higher Acute Physiology and Chronic Health Evaluation (APACHE) II scores and infection by nonfermenting GNB (they generally have higher MIC values when compared with fermenting GNB) were among the factors that were associated with a higher mortality rate.[69]

Alternatively, a protocolized approach to dosing that is institution specific using PK/PD modeling and fractional target attainment (FTA) derived from the probability of target attainment of a specific dosing regimen versus a MIC distribution can be used. Such a method was used and reported by Hartford Hospital (Hartford, CT), where the physicians used β-lactams with the highest FTA based on the MIC distribution of three different ICUs.[70] The result was that these drugs were all given as extended infusion (3- or 4-hour infusion) for the treatment of VAP. Following this method, the infection-related mortality in all ICUs was reduced significantly when compared with pre-protocol period. The three ICUs used the specific β-lactam with the best FTA empirically against *P. aeruginosa* which therefore allowed maximal PK/PD attainment even before culture results were known to the physicians. Via this approach, the time to appropriate antibiotics within 24 hours was improved and so was the achievement of shorter antibiotic course and lower superinfection rate.

Polymyxins

Polymyxins are an "old" class of antibiotics that are made up of cationic antimicrobial peptides and consist of polymyxin B and polymyxin E (colistin). There is a major gap in knowledge concerning the pharmacological and PK/PD properties of

polymyxins, as these antibiotics were not previously subjected to rigorous preclinical and clinical evaluation. Much of the contemporary clinical data are on colistin rather than polymyxin B. Polymyxins act on the lipopolysaccharide and as such their spectrum of activities is limited to gram-negative bacteria. Interestingly, polymyxins might also possess antifungal activities that include activity against *Candida* spp. and *Cryptococcus neoformans*. The rampant spread and burden of multidrug-resistant gram-negative bacteria worldwide is the main catalyst for their resurrection in clinical practice. The ensuing overzealous use of these agents, especially in agriculture industry, appears to be a significant driver of its resistance seen in the current era.[71]

Pharmacokinetic Issues and Challenges

Despite a single amino acid difference between colistin and polymyxin B, the two antimicrobials are different clinically as colistin is administered as a prodrug called colistin methanesulfonate (CMS), whereas polymyxin B is administered in its original form, as sulfate salt.[72] Reconstitution of CMS vials would lead to hydrolysis of CMS into colistin and as such should ideally be given immediately after preparation. There are 32 possible chemically divergent compounds that can be found within a reconstituted vial of CMS (ranging from colistin to partially sulfomethylated or fully sulfomethylated CMS),[73] causing large inter- and intra-batch differences accounting for a very wide interpatient PK variabilities in vivo.[74]

Polymyxin B on the other hand is given in its active form and as such does not require prior hydrolysis.[75,76] Nevertheless, both of these drugs attain delayed serum steady-state concentrations (C_{ss}) up to 48 to 72 hours necessitating an upfront loading dose, particularly for colistin.[76,77] CMS is predominantly cleared via the renal route, whereas colistin and polymyxin B are mainly cleared nonrenally. As such, polymyxin B concentrations are similar across varying degrees of renal function and should not be modified in those with renal impairment,[76] unlike CMS, in which its clearance will be impaired in those with kidney failure, leading to increased plasma conversion into colistin, and dose reduction is essential in such cases.[77] Polymyxins B have a high degree of protein binding that range from 78.5 to 92.4%.[75] Interestingly, this might become substantially higher in the critically ill following an increase in acute phase reactant, α_1-acid glycoprotein.[75]

Polymyxins demonstrate poor and variable ELF penetration which is possibly due to their polarity (►**Table 2**). Additionally, conflicting reports of colistin lung penetration have been published. For example, Imberti et al showed that no detectable bronchoalveolar lavage (BAL) concentration was observed following an IV administration of 2 million international units (MIU; 174 mg CMS) of colistin every 8 hours,[78] while Markou et al reported detectable BAL colistin concentration in two patients who received IV CMS (C_{BAL} was 0.36 and 0.42, respectively).[79] The authors of the later study proposed this discrepancy was the result of dilution effect of normal saline during BAL by Imberti et al, which led to the undetectable concentrations in their subjects. Currently, there is lack of data for polymyxin B in terms of lung penetration, as colistin is used much more widely compared with polymyxin B. Notwithstanding, as the in vivo polymyxin B level is more predictable with less complexity, it is perhaps a better agent for clinical use, including HAP/VAP except in urinary tract infection where CMS is concentrated.

PK/PD Optimization and Challenges

Polymyxins demonstrate concentration-dependent killing with a variable postantibiotic effect (PAE) against gram-negative pathogens, and AUC/MIC_{0-24} ratio of 20 has been suggested as the optimal PK/PD index which predicts optimal killing in both murine thigh and lung infection models.[80–83] Most reports highlight the need for an initial loading dose with higher polymyxin doses necessary to treat critically ill patients with severe pneumonia, particularly for colistin.[77,84–86] However, the safety of such an approach is still being debated, as emerging clinical data are disputing the value of using higher polymyxin doses.[87,88] Data from two prospective cohort studies have shown that the use of high colistin dosing did not improve patient survival with the approach being associated with more nephrotoxicity when compared with other colistin dosing regimens.[87] Notwithstanding, the lack of high-quality data especially from randomized controlled trials has made it difficult to define optimal dosing of colistin for patients with HAP/VAP. In addition, due to their limited penetration into the lungs (C_{ELF}:C_{Plasma} of 0.0–7.42) and the narrow therapeutic window, the use of combination therapy is commonly advocated against gram-negative pathogens as well as minimizing the development of resistance.[89] This is especially important when the MIC is $\geq$1 mg/L, as the plasma steady state that is achievable with currently approved dose is only approximately 2 to 2.5 mg/L.[76,77]

The presence of a high inoculum which is common to pneumonia is another argument for combination therapy as polymyxin efficacy gets attenuated in the absence of high burden infection.[90] Weight based or fixed loading doses can enable more rapid C_{ss} achievement.[76,77] Another method that could be employed to overcome their limited penetration into lung parenchyma is the use of nebulized/aerosolized route which will be discussed below. In a study of 12 critically ill patients, where the subjects were given a single nebulized dose of 2 MIU of CMS delivered via vibrating mesh nebulizers followed by the same dose of IV CMS Q8H given 8 hours later, the observed ELF concentrations were 100 to 1,000 times that observed when CMS was given via IV route alone.[91]

Recently, both the European Medicine Agency (EMA) and the U.S. Food and Drug Administration (FDA) released dosing recommendations for colistin.[92,93] The EMA proposes the use of loading dose of 9 MIU of colistin in all critically ill patients, whereas FDA did not make any recommendation on this. Both the maintenance regimens by EMA and FDA are stratified by the renal function, but FDA took one step further by using a weight-based adjustment for CMS dose calculation unlike EMA that proposed the use of specific and finite dosing range for respective renal function groups. The

performance of the two regimens was tested recently by Nation et al in a population PK analysis of 162 patients.[94] The study was performed to test the steady-state average concentration ($C_{ss\ avg}$) of colistin following daily maintenance dose without the use of loading dose. In both the regimens, the $C_{ss\ avg}$ was poor when the creatinine clearance was ≥80 mL/min. When tested against patients with low body weight with creatinine clearance <50 mL/min, the FDA-approved dosing fared poorly against EMA-approved regimens. In addition, the issue of wide interpatient variability was apparent among the subjects.

Vancomycin

Vancomycin is a large and complex tricyclic glycopeptide that exerts its activity by inhibiting the incorporation of murein monomers into the growing peptidoglycan that is important for the cell wall.[95] It is active against gram-positive bacteria including staphylococci, streptococci, enterococcus and species of bacillus, clostridium, and Corynebacterium.[96] It is primarily used for invasive MRSA infections and is still regarded by many as the gold standard for therapy in HAP/VAP despite issues with its PK/PD.[25,97,98]

Pharmacokinetics Issues

Vancomycin is a hydrophilic antibiotic with limited ELF penetration.[25,99–101] In healthy volunteers, the C_{ELF}:C_{plasma} ratio was approximately 50% of the plasma levels into the lungs.[33] However, despite the homogenous and healthy population in this study, there was a huge variability seen in the C_{ELF}:C_{plasma} (0.24–4.77). Studies recruiting critically ill patients with VAP showed a lower penetration ratio. Georges et al reported detectable ELF vancomycin concentrations in only 6 out of 10 patients, although the mean plasma concentration was 12.5 mg/L.[34] Another study by Lamer et al performed in 14 critically ill patients showed only 21% penetration into ELF, despite the maintenance of the vancomycin trough concentration at 15 to 20 mg/L.[35]

PK/PD Optimization

Vancomycin is a time-dependent antibiotic and achievement of an AUC_{0-24}/MIC ratio of ≥350 has been generally accepted as its PK/PD target that predicts clinical success.[102] Trough concentrations (C_{min}) of 15 to 20 mg/L have been proposed as a surrogate marker for this PK/PD target.[98,102] However, based on PK/PD simulation studies performed by Patel et al, the probability of target attainment using this standard C_{min} falters with standard dosing when the MRSA MIC against vancomycin increases above 1 mg/L.[103] The use of CI dosing albeit appealing only showed lower nephrotoxicity rate without improving patient survival.[104] This was in spite of achieving a mean plasma concentration of 24 to 26 mg/L, which is higher than the MIC susceptibility breakpoint of 2 mg/L. Interestingly, a multicenter study involving 75 VAP patients reported lower mortality rates with CI dosing.[105] Despite the PK limitations, there is lack of clinical data that show superiority of comparator agents for MRSA pneumonia.[98,106,107]

Currently, doses of 15 to 20 mg/kg (as actual body weight) is recommended to be given every 8 to 12 hours for most patients with normal renal function.[102] In the critically ill, loading dose of 25 to 35 mg/kg is advocated to ensure rapid attainment of steady state and target trough concentrations. For therapeutic drug monitoring (TDM), the guideline suggests that the first trough to be taken prior to the fourth dose which is the estimated time for the steady-state condition.

Other Agents for HAP/VAP

Fluoroquinolones

Extensive PK/PD data are available on fluoroquinolones spanning from community- to hospital-acquired infections and they were among the first to undergo PK/PD analysis and robust dosing simulations before marketing.[108] This class of antibiotic shows moderate to excellent oral bioavailability as well as excellent tissue penetration due to its moderate lipophilicity and protein binding.[109–114] Fluoroquinolones display concentration-dependent killing characteristics with some time-dependent features. AUC_{0-24}/MIC ratio best predicts its bactericidal effect with different thresholds suggested for optimal patient outcomes in the treatment of gram-positive and gram-negative infections: 30 and 125, respectively.[115,116] An alternative target of C_{max}/MIC of ≥10 has also been used against GNB.[117] However, conventional doses of fluoroquinolones rarely achieve these PK/PD targets, particularly in severely ill patients who are infected with pathogens with high MICs.

In critically ill patients with *P. aeruginosa* pneumonia, a higher dosing of ciprofloxacin (i.e., 400 mg thrice daily) was needed to attain the AUC_{0-24}/MIC target of ≥125.[118] Concentrations below this threshold would likely lead to treatment failure as well rapid emergence of bacterial resistance.[119] An isolates' MIC helps identify likely achievement of a PK/PD target with an MIC >0.5 mg/L associated with lower success.[118] Another therapeutic approach that can be employed is the use of combination therapy with agents such as the β-lactams, to optimize antimicrobial coverage and avoid selection of resistant pathogens.[120] Notwithstanding these data and practices, fluoroquinolone consumption has been linked to recent emergence of resistance.[121,122] They are also now one of the four classes of antibiotics targeted for reduction in use to control the incidence of antimicrobial resistance as well as *Clostridium difficile* infection.[123]

Linezolid

Linezolid belongs to a new antibiotic class called *oxazolidinones* and acts on the ribosomal P site that leads to the interference of bacterial protein synthesis.[124] Its activity is limited to the gram-positive organisms that include MRSA, penicillin-resistant Streptococcus as well as vancomycin-resistant enterococcus species.[125] Linezolid has high bioavailability (100%) with low protein binding of less than 30%.[126] It is associated with high interpatient PK variability as shown in a study by Meagher et al, where AUC_{0-24} were reported from 57 to 871 mg/L.[127] The PK/PD target that best

explains its bacterial activity is $\%f_{T>MIC}$ of 85% as well as AUC_{0-24}/MIC of 80 to 100.[128]

A standard dose of 600 mg 12 hourly is likely to achieve optimal PK/PD targets in the ELF as linezolid demonstrates extensive ELF penetration.[129,130] As such, the use of this antibiotic has been increasingly advocated for the treatment of MRSA pneumonia. However, the results of several meta-analyses have not demonstrated any clinical advantage of linezolid over vancomycin.[106,131–133] Perhaps, the lack of TDM in previous studies to adjust the inherently variable linezolid concentrations may have contributed to these results. Notwithstanding, linezolid and vancomycin are both considered first-line treatments of MRSA HAP/VAP with the choice of agent based on the cell counts, baseline kidney function, cost, as well as the concomitant use of serotonin-reuptake inhibitors.[98]

Tigecycline

Tigecycline is derived from minocycline with a broad spectrum of antimicrobial activity against the gram-positive and gram-negative bacteria including the multidrug-resistant phenotypes as well as anaerobes and atypical organisms. It has little activity against *P. aeruginosa* and *Proteus* species.[134] It exhibits bacteriostatic effect via the ribosomal 30s inhibition with bactericidal effect eclipsing this, as the duration of treatment approaches the 24-hour duration.[135,136] It has negligible oral absorption with extensive V_d (7–10 L/kg). It rapidly attains therapeutic tissue concentrations following IV dose with high penetration into lung tissue, bile, gallbladder, blister fluid, as well as infected and noninfected tissues in diabetic patients.[134,137–139] Interestingly, it shows an atypical and nonlinear protein binding.[138] The primary route for its clearance is via fecal excretion and to some extent by renal route (13%).

The PK/PD index describing tigecycline activity is the AUC/MIC index.[140,141] Interestingly, tigecycline fared poorly against imipenem for treatment of HAP in a landmark clinical trial with increased mortality in the tigecycline treatment arm.[142] As such, a higher than standard dose is recommended to be given to optimize tigecycline exposure (dosed at 200 mg loading dose and 100 mg 12 hourly) for lung infections as suggested by a phase II trial (although there is an increased risk of gastrointestinal side effects).[143] Clinicians are cautioned against using this antibiotic for HAP/VAP, as it is not FDA approved and it carries a black box warning of increased mortality.[144] Notwithstanding this recommendation, its use as part of a combination regimen might be unavoidable in CRE pneumonia because of limited options.[145,146]

Antibiotics to Avoid in HAP/VAP

Aminoglycosides

Aminoglycosides are broad-spectrum antibiotics that are active against Enterobacteriaceae family, non–lactose-fermenting organisms: for example, *A. baumannii* complex and *P. aeruginosa* as well as gram-positive organisms such as *S. aureus*. They also have notable activity against mycobacterium as well as agents for tularemia and plague.[147] They are highly polar and dwell primarily in the extracellular compartment due to their hydrophilicity.[95] Their low protein binding (~10%) allows some distribution from the vascular compartment into the interstitium and extracellular compartment.[95] Maximal bactericidal activity of aminoglycosides depends on the C_{max}/MIC ratio with a common target being 8 to 10, with AUC_{0-24}/MIC also being important.[148,149]

Aminoglycosides are hydrophilic in nature and as such, this antibiotic class demonstrates low and variable penetration into ELF (C_{ELF}:C_{Plasma} of 0.32–1.0).[150,151] Panidis et al observed only 32% penetration into ELF when gentamicin was given to 24 patients with VAP.[150] The significance of the finding may be profound with conventional aminoglycoside dosing highly likely to lead to suboptimal PK/PD target attainment in the ELF, and consequently therapeutic failure in patients with HAP/VAP. The recent ATS/IDSA guidelines on treatment of HAP/VAP has also suggested avoidance of these agents if alternative agents with adequate coverage against GNB are available.[98]

Daptomycin

Daptomycin is a cyclic lipopeptide and it exerts its activity by disrupting the electrochemical gradient of gram-positive organisms that leads to potassium efflux and cell death.[152,153] It is active against the clinically relevant gram-positive pathogens: *S. aureus*, *Streptococcus* species, and *Enterococcus* including those that are resistant to penicillin, methicillin, linezolid, and vancomycin.[154,155]

Daptomycin demonstrates linear PK following infusion (either single or multiple doses) with a high degree of protein binding of up to 96.4%.[156,157] Its major route of elimination is via renal pathway.[109] Animal studies showed that it is a concentration-dependent antibiotic and the optimal PK/PD target is AUC_{0-24}/MIC (bacteriostatic and bactericidal AUC_{0-24}/MIC are 388–537 and 788–1,460, respectively).[158–160] In vitro experiments have shown that daptomycin interacts with lung surfactant which inhibits daptomycin activity.[161] This was subsequently confirmed in two phase III randomized controlled trials that compared daptomycin to ceftriaxone for community-acquired pneumonia.[162] In the clinically evaluable population, daptomycin showed significantly lower cure rates in these studies. Daptomycin is therefore not recommended for treatment of HAP or VAP.

Nebulized Antibiotics

Nebulization of antibiotics has been increasingly used over the years as an approach to maximize concentrations in infected lung tissues.[23] Previous attempts to deliver antibiotics via nebulization including neomycin, polymyxin, and penicillin have failed due to the complex lung anatomy that hinders optimal antibiotic exposure to be achieved in lung tissues.[163] However, refinement of this dosing method over the years has improved the dose of antibiotics to the lower airways. Several antibiotics have been studied as nebulized agents, including polymyxins, vancomycin, aztreonam,

aminoglycosides (i.e., tobramycin, gentamicin, and amikacin), fosfomycin, cephalosporins (i.e., ceftazidime), carbapenems (i.e., imipenem), and penicillins (i.e., ampicillin sulbactam).[164,165]

Direct lung delivery has the potential for reducing systemic toxicity compared with parenteral administration, as the amount of drug absorbed from the lungs into the systemic circulation is minimized. Moreover, supranormal concentrations of antibiotics that may exceed MIC breakpoints by more than 100-fold can be achieved in lung tissues, which may allow the use of those antibiotics even when they test resistant in vitro. This delivery method also promises theoretical activity against biofilms that are associated with endotracheal tubes and which can cause VAP.[166]

However, there are several important issues that need to be considered in antibiotic nebulization. First, the antibiotic particle size is important and it should be between 2 and 5 um.[167,168] Larger particles are more likely to be trapped in the upper airways, whereas smaller particles will be expelled during expiration before they reach the target site for activity.[169] Particle size depends on the aerosol generator as well as the ventilator settings of mechanically ventilated patients. There are currently three types of nebulizing device used in delivering antibiotics, namely, jet, ultrasonic, and vibrating mesh nebulizers.[164] Jet nebulizer is relatively inexpensive and easy to use, but the drug delivery rarely exceeds 15% of the nominal antibiotic dose due to various issues including impaction of the particles onto the delivery limb system.[23,164] Ultrasonic nebulizers are expensive and may have undesirable heating during nebulization, which may damage the antibiotic.[23,164,170] Vibrating mesh nebulizers are also more expensive but are more efficient.[170] The relative advantages/disadvantages of these nebulizers have been reviewed elsewhere.[23,164,165,167,170]

Patient-related factors also play a significant role in influencing the dose of antibiotic that reaches the target site after nebulization. High mucus secretions, preexisting bronchospasm, the use of positive end-expiratory pressure may all impair delivery of antibiotic to the lower airways.[164] In conclusion, these complexities and barriers for optimal antibiotic delivery via nebulized route stand in the way between clinicians and offending organisms.

Conclusion

Given the marked PK variability of antibiotics in critically ill patients with HAP/VAP, including the differing extents of lung penetration, use of fixed antibiotic dosing regimens is likely to be problematic. Furthermore, the reduced susceptibility of pathogens causing HAP/VAP in critically ill patients also supports the use of a different approach to antibiotic dosing, particularly in the form of use of maximal doses. Ideally, antibiotic TDM combined with knowledge of the isolate's MIC is required to ensure optimal therapy is provided. However, given the limited availability of antibiotic TDM and MIC data, clinicians are forced to make "best-guesses" regarding the optimal dose needed for an individual patient.

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How Should We Treat Hospital-Acquired and Ventilator-Associated Pneumonia Caused by Extended-Spectrum β-Lactamase–Producing *Enterobacteriaceae*?

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Abstract

Hospital-acquired and ventilator-associated pneumonia (HAP/VAP) due to extended-spectrum β-lactamase–producing *Enterobacteriaceae* (ESBL-PE) represent a growing problem. Indeed, ESBL-PE is endemic in many countries, and 5 to 25% of intensive care unit (ICU) patients are ESBL-PE carrier on ICU admission. ESBL-PE HAP/VAP is associated with a higher mortality than HAP/VAP due to susceptible *Enterobacteriaceae* because the resistance profile decreases the adequacy rate of empiric therapy. ESBL-PE should be considered in the empirical treatment in case of the high burden of ESBL-PE in the unit, in the case of previous ESBL-PE colonization, when the HAP/VAP occurs late, and in patients with shock. A negative active systematic surveillance culture on rectal swab reduced the risk of ESBL-PE VAP to less than 1%. Rapid diagnostic tests are now able to confirm the presence of ESBL-PE in VAP within 24 hours; new molecular methods will provide results within few hours.Adequate treatment usually required carbapenems. The alternative β-lactams such as β-lactams/β-lactamases inhibitor combinations could be proposed as a step-down therapy according to the antibiotic susceptibility result. Optimization of pharmacokinetics requires high dosage and continuous or prolonged infusions for β-lactams. When the patient is stabilized, a therapy of duration 7 to 8 days is recommended.

Keywords

- extended spectrum β-lactamases
- ventilator-associated pneumonia
- carbapenem
- pharmacokinetic
- antibiotics
- sepsis

Ventilator-associated pneumonia (VAP) is the most commonly acquired infection in intensive care units (ICUs) and is associated with high morbidity and mortality rates.[1–5] The clinical outcomes of these infections are associated with multiple factors such as the underlying host condition, severity of infection (septic shock), and antibiotic appropriateness within the first 24 hours.[6–8] The choice of empirical antimicrobial therapy is a challenge in ICU patients because the incidence of infections related to multidrug-resistant (MDR) bacteria is high in this population while the appropriateness of the therapy can only be validated a posteriori. In recent studies, 36% of microorganisms identified in patients with confirmed infection were MDR bacteria.[9] Current guidelines recommend the administration of broad-

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spectrum antimicrobial therapy if MDR bacterial species are suspected.[10,11] Extended-spectrum β-lactamase–producing *Enterobacteriaceae* (ESBL-PE) are increasingly encountered in patients with hospital-acquired infections, including VAP, with additional mortality and cost.[12–15] Adequate treatment usually requires carbapenems. Prompt identification of patients at risk for ESBL-PE-related VAP is important to initiate appropriate antimicrobial therapy early and avoid overuse of carbapenems when not necessary.

Epidemiology

Since the 1980s, ESBL-PE has spread worldwide.[16,17] *Enterobacteriaceae* are involved in approximately 22 to 35% of the VAP in ventilated patients reported in large multicenter databases.[18–21] Third generation cephalosporin-resistant *Enterobacteriaceae* responsible for HAP/VAP represents 19 to 61% of the episodes, varying according to species and to countries.[22,23] VAP is divided into early-onset or late-onset (early, less than 5 days; late, more than 5 days after ICU stay). In previous guidelines, this classification has been related to bacteriology and empiric therapy choices, but recently, the bacteriological differences between early- and late-onset VAP have been less clear, with some early-onset patients infected with MDR pathogens, while certain patients in both groups can be infected with sensitive pathogens. Traditionally, early-onset VAP is caused by drug-sensitive pathogens, such as wild-type *Enterobacteriaceae*, *Streptococcus pneumoniae*, *Haemophilus influenzae*, and methicillin-sensitive *Staphylococcus aureus*, while late-onset VAP is caused by antibiotic-resistant pathogens, such as *Pseudomonas aeruginosa*, *Acinetobacter* spp., methicillin-resistant *S. aureus*, and ESBL-PE. Recent studies have challenged these concepts and found a similar rate of MDR pathogens between early- and late-onset VAP (27.8 and 32.3%, respectively, $p = 0.33$).[24,25] This may be related to the worldwide rise in MDR pathogens and suggests that the local ICU ecology might be the most important risk factor for acquiring MDR pathogens, irrespective of the length of intubation.

ESBL-PE Carriage: A Risk Factor for Infection

The overall incidence of ESBL-PE is increasing worldwide. Many studies highlighted that prior ESBL-PE rectal colonization is a risk factor for ESBL-PE infections. In a French study conducted between 2010 and 2011, ESBL-PE digestive colonization was identified in 15% of patients admitted in ICU.[26] In another study, ESBL-PE digestive colonization increased with the duration of ICU stay, from 15.6% for stays shorter than 5 days, to 36.8% for longer stays.[27] Most studies conducted in the past decade reported an increasing incidence of ESBL-PE isolates recovered from both clinical and surveillance samples. However, recent studies of colonization rates in ICU patients are sparse, with rates varying according to the regional area and patient populations studied, from 2%[28] to as high as 49%.[29] Furthermore, the link between ESBL-PE rectal colonization and ESBL-PE–related VAP is based on a debatable hypothesis, suggesting a contamination from digestive flora to the respiratory tract.[30]

Risk Factors for Carriage

Several studies have addressed the risk factors associated with ESBL-PE carriage. Older age, and previous hospitalization, urinary tract infection and antibiotic therapy, are well-known risk factors for rectal colonization. Carriage of ESBL-PE has spread into the community makes the identification difficult of all ESBL-PE–colonized patients. Indeed, in a recent study conducted in North Europe, 5% of healthy people were colonized with ESBL-PE.[31] In the community, risk factors for fecal colonization with ESBL-PE in adults include comorbid conditions (i.e., diabetes mellitus, Charlson index > 3), previous hospital admission, recurrent or obstructive urinary tract infections, antibiotic exposure, consumption of meat related to agricultural antibiotic use, and international travel from high endemic area such as Eastern Mediterranean countries, and South-East Asia.[32–35] In the hospital, risk factors seem to be better defined, such as local prevalence, prolonged hospitalization, recent use of β-lactams (and specifically cephalosporins) or fluoroquinolones, transfer from the health care facility, the recent history of a urinary catheter, and immunosuppression.[36] In liver transplant patients, independent predictors of fecal carriage in multivariate logistic regression were exposure to a β-lactam agent in the month preceding transplantation (odds ratio [OR]: 7.8, 95% confidence interval [CI]: 4–15.5; $p < 0.001$), and a history of spontaneous bacterial peritonitis (OR: 2.4, 95% CI = 1.1–4.9; $p = 0.02$).[37] In ICU, the data are scarce. Harris et al conducted a multivariate analysis on a prospective 3.5-year cohort study of patients admitted to medical and surgical ICUs at the University of Maryland Medical Center. The following factors were statistically associated with ESBL-PE colonization at admission: piperacillin-tazobactam (OR: 2.05, 95% CI: 1.36–3.10), vancomycin (OR: 2.11, 95% CI: 1.34–3.31), age >60 years (OR: 1.79, 95% CI: 1.24–2.60), and chronic disease score (OR: 1.15, 95% CI: 1.04–1.27).[28] Thus, coexisting conditions and previous antimicrobial drug exposure were predictive of colonization. In an 8-month prospective study conducted in a French medical ICU,[27] 15% patients were ESBL-PE carriers. Six independent risk factors were associated with ESBL-PE carriage: surgery within the past year (OR: 2.28, 95% CI: 1.34–3.86), hospital admission in another country (OR: 5.28, 95% CI: 1.56–17.8), prior neurological disease (OR: 2.09, 95% CI: 1.10–4.00), transfer from another ICU (OR: 2.56, 95% CI: 1.26–5.22), and use of third-generation cephalosporins (OR: 3.05, 95% CI: 1.21–7.68) or fluoroquinolones (OR: 1.95, 95% CI: 0.96–3.95) within the previous 3 months. When focusing on the specific subset of patients admitted directly from the community, the risk factors associated with ESBL-PE carriage were hospitalization within the last year (OR: 2.83, 95% CI: 1.46–5.45), prior urinary tract disease (OR: 6.03, 95% CI: 1.44–25.1), use of fluoroquinolones (OR: 2.59, 95% CI: 0.90–7.45), and third-generation cephalosporins (OR: 3.58, 95% CI: 1.18–10.8).

Who is Prone to be Infected?

Several studies conducted outside of the ICU suggested that previous colonization and antibiotic therapy were the most important risk factors associated with ESBL-PE-related infection. In a recent prospective cohort study aiming to identify risk factors associated with ESBL-positive strains in case of community onset of bacteremia due to *Enterobacteriaceae*, a high incidence in the regional area, history of travel to a high-risk country within past 3 years, and previous antianaerobic antibiotic administration were associated with health care-associated bloodstream infection caused by ESBL-PE.[38]

In hospitalized patients, the risk of infection in patients previously known to be colonized with ESBL-positive *Escherichia coli is* less than 9%.[39] In multivariate analysis in previously colonized patients, the risk factors associated with secondary infections were the use of β-lactam/β-lactamase inhibitor (BL/BLI) before infection (OR: 3.2, 95% CI: 1.073–9.864); $p = 0.037$ and urinary catheterization (OR: 5.2, 95% CI: 1.984–13.569).[39] A study was recently conducted at the John Hopkins hospital aiming to develop a user-friendly decision tree to predict which organisms are ESBL producing, to guide appropriate antibiotic therapy. Among 1,288 patients with bacteremia, 194 (15%) was due to ESBL-positive pathogens. The final classification tree for predicting ESBL-positive bacteremia included five predictors: a history of ESBL-PE colonization/infection, chronic indwelling vascular hardware, age $\geq$ 43 years, recent hospitalization in an ESBL high-burden region, and $\geq$ 6 days of antibiotic exposure in the prior 6 months. The decision tree's positive and negative predictive values were 90.8 and 91.9%, respectively.[40] More recently, to develop a risk score to predict the probability of bloodstream infections (BSIs) due to ESBL-PE, Augustine et al[41] designed a retrospective case–control study in two large community hospitals. Among 910 patients with *Enterobacteriaceae* BSI, 42 (4.6%) had ESBL-PE bloodstream isolates. Most ESBL-PE BSIs were community onset (33 of 42; 79%), and 25 (60%) were due to *E. coli*. Independent risk factors for ESBL-PE BSI, and their associated point allocation in the ESBL-PE BSI prediction score, included outpatient procedures within 1 month (adjusted odds ratio [aOR]: 8.7, 95% CI: 3.1–22.9, 1 point), prior infections or colonization with ESBL-PE within 12 months (aOR: 26.8, 95% CI: 7.0–108.2, 4 points), and number of prior courses of β-lactams and/or fluoroquinolones within 3 months before BSI: 1 course (aOR: 6.3, 95% CI: 2.7–14.7, 1 point), $\geq$2 courses (aOR: 22.0, 95% CI: 8.6–57.1, 3 points).[41]

A retrospective study conducted in a medical ICU suggested that ESBL-PE infection was rare even in previously colonized patients. In this study, less than 7% of hospitalized patients had an ESBL-PE-related infection. Other studies suggested that ESBL-PE related infection occurred in 0.5 to 10% in ICU patients, even in those previously colonized.[26,42,43] However, the prevalence was higher in immunocompromized patients, up to 50% of previously colonized patients.[26]

Two studies recently conducted in ICU[42,44] highlighted that ESBL-PE represented less than 1% of episodes among all infected patients, and reached 4% in patients previously known to be ESBL-PE carriers.[42,43] In a medical ICU, less than 10% of the first episode of infection, of patients known to be ESBL-PE carriers were related to ESBL-PE, whereas 50% of the second episodes of infections were related to ESBL-PE.[26] In another study involving 16,734 ICU patients, 594 (3.5%) were ESBL-PE carriers and only 98 (16.4%) developed 118 ESBL-PE infections during the ICU stay. Among the 98 patients, VAP occurred in 43 (36.5%) cases.[42] Only one study focused on the risk of ESBL-PE VAP in ICU. Among 587 patients with suspected VAP, 40 (6.8%) were colonized with ESBL-PE. Over the study period, 20 patients (3.4%) had VAP caused by ESBL-PE, of whom 17 were previously colonized with ESBL-PE. These results suggest positive and negative values of 41.5 and 99.4%, respectively, with a positive likelihood ratio of 19.8 (►**Table 1**).[44]

When to Take into Account ESBL-PE in Empirical Therapy of VAP?

The decision to take into account ESBL-PE in the initial treatment of VAP depends on risk factors previously described and on the targeted negative predictive value. For the most severely ill patients, a very high negative predictive value will be required for accepting this risk.

Table 1 Risk factors for ESBL-producing *Enterobacteriaceae* isolation in ICU patients

Risk factors for ESBL-PE carriage	Risk factors for ESBL-PE infections on previously colonized patients
- Travel in high-prevalence countries - Recent hospitalization - Previous antibiotic therapy within 90 d with β-lactams and/or fluoroquinolones - Charlson comorbidity index > 3 - Chronic dialysis - High colonization pressure in your unit - Duration of previous hospital and ICU stay	- Immunocompromised status - High SAPS II - Admission with shock - Previous colonization with ESBL-positive *Enterobacter cloacae* or *Klebsiella pneumoniae* (versus ESBL-positive *Escherichia coli*) - β-lactam/β-lactamase inhibitor before infection - Urinary catheterization - Intravenous catheterization

Abbreviations: ESBL-PE, extended spectrum β-lactamase-producing *Enterobacteriaceae*; ICU, intensive care unit; SAPS, simplified acute physiological score.

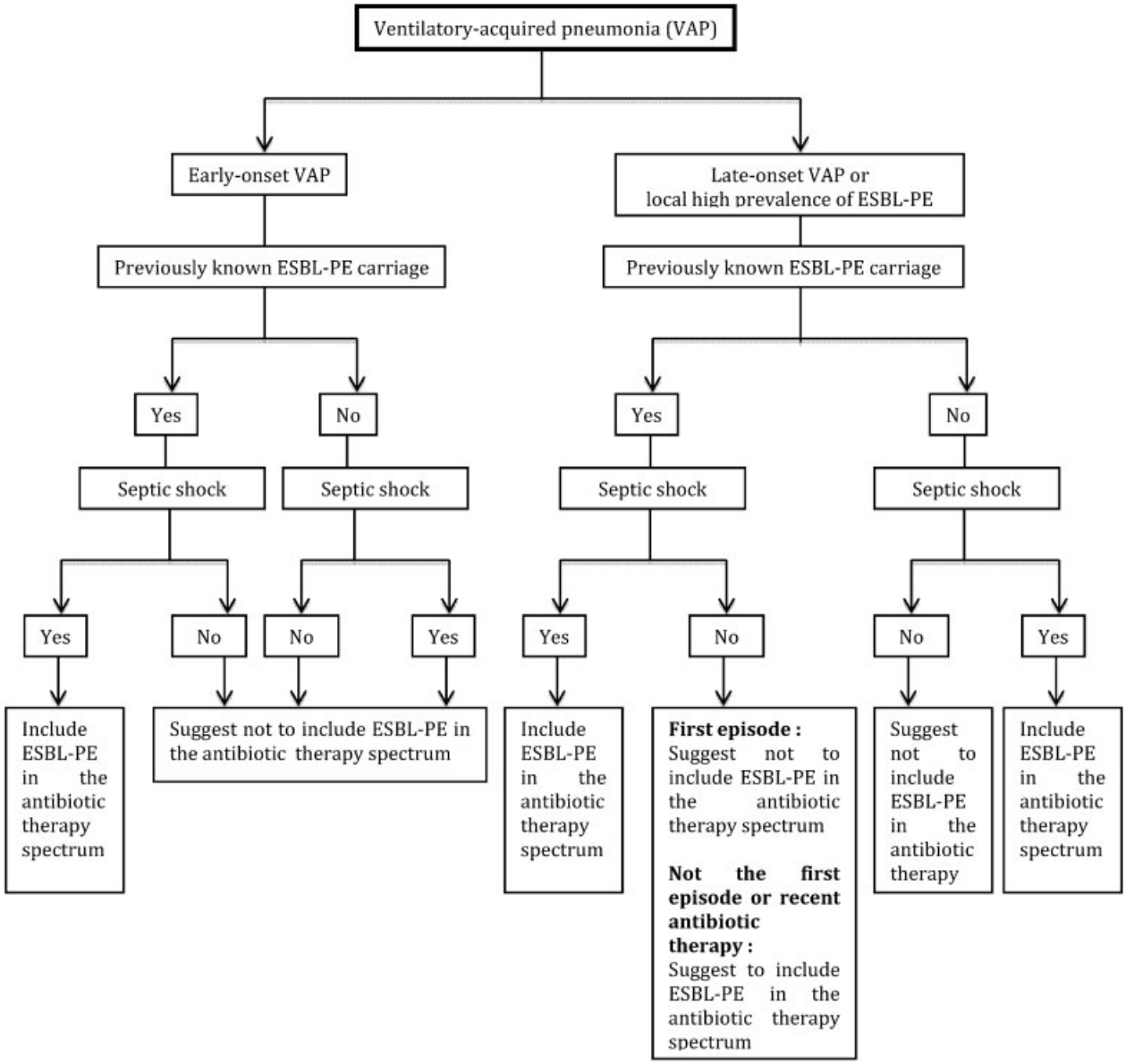

Fig. 1 Proposed algorithm for the treatment of VAP in ICU patients according to early- or late-onset VAP, local prevalence of ESBL-PE, previous known ESBL-PE carriage, and severity of the infection. ESBL-PE, extended spectrum β-lactamase-producing *Enterobacteriaceae*; ICU, intensive care unit; VAP, ventilator-associated pneumonia.

ESBL-PE-related infections are most commonly late-onset infections that occurred after the first course of antibiotic therapy. When active surveillance by rectal swab was performed at ICU admission, and weekly after that, patients' previous colonization with ESBL-PE was associated with a risk of ESBL-PE VAP of approximately 40% if VAP is suspected. On the opposite, if active surveillance is negative, the risk is lower than 1%.[44]

It is recommended to avoid the use of carbapenem in patients without previously known colonization unless there are clinical signs of severity such as septic shock. In case of doubt, the use of a combination therapy that includes an aminoglycoside should reduce this risk of inadequate antibiotic therapy. A suggestion for including an evaluation of the risk of ESBL-PE in the empirical therapy of VAP is proposed in ►**Fig. 1**.

Rapid Diagnostic Tests for Selecting Adequate Antimicrobials in Severe HAP/VAP

The challenge for intensivists is to start adequate antimicrobial therapy that will be immediately effective on ESBL-PE VAP while avoiding any overuse of carbapenems. Classical microbiological tests require at least 24 to 48 hours for microorganism identification and 48 to 72 hours for antibiotic susceptibility profile determination. Furthermore, the early detection of microorganisms may lack sensitivity, especially if patients received previous antimicrobial therapy.

To solve this issue, new rapid diagnostic tests have been developed.[45] Many novel rapid nucleic acid amplification or mass spectrometry-based techniques provide rapid identification of targeted microorganisms (see their description in another article of the same issue). Some of these new tests

are also able to detect resistance genes. However, their use is made complex by a wide variety of ESBL enzymes. The most frequent are those from the CTX-M, TEM and SHV families. Molecular detections are directed against the most frequent ones, but none of the available tests are able to detect all the ESBL enzymes.

Recent two-step multiplex polymerase chain reaction (PCR)/hybridization is also able to detect a large panel of respiratory pathogens and genes of ESBL such as CTX-M, SHV and TEM in turnaround time of 4 to 5 hours.[46] Preliminary results in nosocomial pneumonia are encouraging but require further confirmation. Of note, these new techniques only detect the presence of genes of the pathogen and resistance but are neither able to differentiate alive from dead pathogens and do not provide information regarding phenotypic antimicrobial susceptibility.

Another possible way to optimize the treatment choice is to obtain a very rapid antibiotic susceptibility test. Fluorescence in situ hybridization-based microscopy identification and antibiotic susceptibility test (ID/AST) systems can evaluate antibiotic susceptibility from blood cultures or respiratory secretions on a previously defined panel of phenotypic growth pattern analysis. One recent pilot study reported data from a new accelerate ID/AST automated microscopy system was able to detect MDR in bronchoalveolar lavage after 5 ± 7 hours of culture and 5 hours of analysis with a 100% sensitivity and a 97% specificity.[47] However, the pattern of resistance is not able to detect genes coding for extended broad-spectrum β-lactamases.

Further studies with a better selection of pathogens more adapted to the clinical situation and a quantification of the detected DNA are warranted.

In the meantime, one should keep in mind that rapid antimicrobial susceptibility testing combined with mass spectrometry could give identification and accurate antibiotic susceptibility results within 1 day of sampling.[48]

It is also possible, on the bronchial specimen culture (i.e., after 24 hours), to obtain rapid detection of enzymes such as extended-spectrum β-lactamases, AmpC, and carbapenemases within 15 minutes to 2 hours using biochemical techniques (~90% sensitivity and ~90% specificity).[45,49]

Available Targeted Treatment for Severe ESBL-PE Infections

The Standard of Treatment Remains Carbapenems

The presence of ESBL-PE complicates the selection of antibiotics, particularly in patients with serious infections such as HAP/VAP. The treatment must (1) be effective in vitro against the microorganism, (2) be effective even if the initial inoculum is high, (3) reach sufficient concentration both in serum and in the lung even in ICU patients with increased volume of distribution, (4) have proven effectiveness in clinical studies (5) have demonstrated safety in terms of risk of failure, emergence of resistant organisms and adverse events.

Considering the above requirement, carbapenems should remain the first choice antimicrobials for early treatment of severe infections, including VAP, due to ESBL-PE. However, other β-lactams might be considered for streamlining if the patient's condition improves (►**Table 2**).[50]

Indeed carbapenems are almost always active on ESBL *Enterobacteriaceae* and have been successfully tested in many clinical studies involving ICU patients with HAP/VAP. Therefore, alternatives are seldom used in clinical practice for treating serious infections caused by ESBL-PE.

Table 2 Potential advantages of carbapenems and of alternatives for ESBL-PE infections

Support alternative to carbapenem	Support carbapenem use
• β-lactamases inhibitors such as clavulanate or tazobactam can inhibit Ambler class A β-lactamases • ESBL-producers are frequently susceptible in vitro to other β-lactams, such as cefoxitin, temocillin, piperacillin-tazobactam, or ceftolozane-tazobactam (especially ESBL-producing *E. coli*) • Emerging data from some large cohort studies and a meta-analysis support the safety and efficacy of BL/BLIs for urinary tract infections and if MICs > 4 mg/L • Few clinical studies clearly show inferiority of BL/BLIs when compared with carbapenems in the treatment of susceptible ESBL producers • A combination therapy with another antimicrobial effective on ESBL *Enterobacteriaceae* (e.g., aminoglycosides) may limit the risk of treatment failure • Carbapenems should be reserved for specific situations in which no other drugs are available • Carbapenem use is linked to a rapid increase of carbapenem-resistant gram-negative bacteria in the gut microbiota	• Carbapenems remain stable to ESBLs and are recommended as first-line therapy for severe infections • Carbapenems are only slightly affected by the inoculum size • Alternative β-lactams are not always effective on ESBL-PE • The inoculum effect limits the efficacy of other β-lactams particularly cefoxitin, temocillin, and BL/BLIs in ESBL-PE. It is clearly an issue in HAP/VAP where inoculum is high at the time of therapy initiation • Scarce published clinical experience on the efficacy of BL/BLIs against ESBL producers causing infections outside the urinary tract • Overexpression of β-lactamases (including by other non-ESBL-PE bacteria) may overwhelm the inhibitor component • No head-to-head randomized trials to assess BL/BLIs in comparison with carbapenems • Poor drug concentration attainment with standard doses of piperacillin–tazobactam for isolates with high minimum inhibitory concentrations but still within the CLSI susceptible range (i.e., 8–16 mg/L) • Complex coresistance mechanisms, including other enzymes not well inhibited by tazobactam or clavulanate (e.g., plasmid-derived AmpC) or development of inhibitor-resistant enzymes

Abbreviations: BL/BLI, β-lactams/β-lactamase inhibitor; CLSI, Clinical and Laboratory Standard Institute.

However, carbapenem use is associated with the emergence of carbapenem-resistant gram-negative bacteria in the gut microbiota of ICU patients.[51] Moreover, the extensive use of carbapenems may favor selection of carbapenem-resistant gram-negative bacteria and favor the rapid worldwide spread of carbapenemase-producer gram-negative bacteria. Conversely, effective and safe strategies designed to spare carbapenems are welcomed.[52,53]

Most studies evaluated imipenem and meropenem with similar results. Limited experience has been reported with ertapenem which may represent a valid alternative for targeted therapies, to avoid selective pressure on *Pseudomonas aeruginosa* and *Acinetobacter baumannii*, as ertapenem is not active against these species.[54] In this large cohort study, after adjustment for confounders, ertapenem was as effective as other carbapenems for treating ESBL-PE bloodstream infections. It was especially true for *E. coli* infections. However, there was a trend for other carbapenems for *Enterobacteriaceae* other than *E. coli* and patients with septic shock. This trend may be related to higher minimum inhibitory concentrations (MICs) as compared with drug concentration obtained. The use of this drug is, therefore, possible at high dosages and if MIC $\leq$0.25 mg/L.[55]

Other Drugs That Should Be Discussed to Spare Carbapenems Using Complete Susceptibility Results

β-Lactams

ESBLs possess variable activities on cephalosporins and β-lactam-β-lactamase inhibitor(BL/BLI) combinations. ESBLs are inhibited in vitro by β-lactamase inhibitors. Strains of ESBL-P *E. coli* recovered from pneumonia remained susceptible in vitro to piperacillin/tazobactam (PIP/TAZ) in 69%[23] to 84%[56] of the cases worldwide. Conversely, only 26.9% of ESBL-producing *Klebsiella* species. Isolates from patients with pneumonia were susceptible to PIP/TAZ.[23]

Several clinical studies have suggested the use of BL/BLIs such as PIP/TAZ as a carbapenem-sparing strategy for the treatment of ESBL-PE related infections.[57–60]

One retrospective study examines the clinical impact of an alternative to carbapenems in 56 episodes of ESBL-E VAP.[60] VAP was due to other *Enterobacteriaceae* than *E. coli* in more than 80% of the cases. Drugs used were PIP/TAZ combination or third generation cephalosporins administered at high doses by continuous infusion after a loading dose, to improve pharmacodynamics (PDs). Monotherapy was used in 61% of the cases. Alternative antimicrobial therapy was not associated with differences in failures, relapses duration of mechanical ventilation and death.

Other studies compared carbapenems and alternatives in bloodstream infections with less encouraging results. Ofer-Friedman et al conducted a multicenter observational study including 79 episodes of nonurinary BSI and compared PIP/TAZ to carbapenem for the treatment of ESBL-PE infections.[61] In this study, *E. coli* accounted for only half of the bloodstream infections; the median PIP/TAZ MIC was 4 mg/L, higher than in other studies, but reflecting those seen in usual practices. Half of the patients required ICU care. In this study, the mortality was significantly higher in the PIP/TAZ group (OR: 7.9, 95% CI: 1.2–53). Thus, BL/BLIs may lead to a poorer outcome than carbapenem therapy for critically ill patients with ESBL-PE infection from non-urinary sources, which confirmed the results from previous systematic reviews.[62]

However, for ESBL-P *E. coli*, 2 studies suggested that BL/BLI could be successfully used for bloodstream infections when the MIC to PIP/TAZ is $\leq$ 4 mg/L.[58,63] If de-escalation to PIP/TAZ is decided, in stable patients, the use of prolonged infusion to optimize pharmacokinetic (PK) should be recommended.[64] When MIC to PIP/TAZ is 8 or 16 mg/L, the use of PIP/TAZ is also suggested by recent guidelines,[10] but the doubt persists about the potential efficacy in severe VAP patients.

Ceftolozane-tazobactam (C/T) has been recently approved for treatment of urinary tract infections and intra-abdominal infection.[65] Its activity on ESBL-PE is better than that of PIP/TAZ, especially for ESBL-P *E. coli* infection.[66,67] There are no available data on VAP due to ESBL-P *E. coli*. The PKs of C/T in ICU patients is not known. A study using 2 g/1 g ceftolozane/tazobactam three times a day versus meropenem for treating ventilated HAP/VAP is ongoing (ASPECT-NP clinicaltrials.gov NCT02070757).

Ceftazidime-avibactam is active against ESBL-PE *Enterobacteriaceae*.[68,69] In a recent randomized trial, ceftazidime-avibactam (2 g/500 mg $\times$ 3) was non-inferior to meropenem (1 g $\times$ 3) for HAP/VAP (REPROVE NCT01808092 results available on clinicaltrials.gov), even in the subgroup of HAP/VAP due to gram-negative bacilli resistant to ceftazidime. However, this drug is the only available β-lactam most of the time effective on Ambler A and D carbapenemase-producer *Enterobacteriaceae*. Considering the risk of selection pressure with the emergence of ceftazidime avibactam-resistant *Enterobacteriaceae*,[70,71] this drug should be used only when carbapenemase-producer *Enterobacteriaceae* is also suspected.

Temocillin is a ticarcillin derivate that resists to hydrolysis of ESBL-PE. It has been used in Belgium and UK since decade to treat ESBL-PE infections. A concentration of free temocillin in the serum higher than 16 mg/L was obtained using 2 g $\times$ 3 daily or 6 g in continuous infusion.[72] Temocillin is susceptible to inoculum effect making its use hazardous as a first therapy, but, if the MIC of the ESBL-PE is low ($\leq$ 8 mg/L), temocillin could be used as step-down therapy.[73]

One study suggested that cefepime may be used against ESBL-PE infections if the MICs are within susceptible ranges, preferably $\leq$ 1 mg/L.[74]

Cephamycins have shown to be stable against hydrolysis of ESBL-P organism[75] and less susceptible to inoculum effect than other β-lactams. However, acquired resistance and failures have been described.[76] If MICs are lower or equal than 4 g/L, the use of high dosage (i.e., 8 g/d) in continuous infusions as a step-down therapy is, therefore, possible in stable patients.[77] Newer Cephamycins such as cefmetazole and flomoxef seems promising and need further investigations.[78]

Other Antibiotics

Tigecycline is effective in severe infections due to *Enterobacteriaceae*, including ESBL-P strains, especially when its MIC is $\leq$ 1mg/L. However, the data available for treating ESBL-PE infections are scarce.[79–81] For HAP/VAP, dosage as high as 200 mg loading dose followed by 100 mg bid, must be used.[82] However, as tigecycline could be effective to treat carbapenemase-producing *Enterobacteriaceae*, it should be preserved, and de-escalation from carbapenem to tigecycline for ESBL-PE VAP should be limited to specific situations (i.e., co-infections with *S. aureus*, carbapenem allergy).

Fosfomycin (intravenous) is frequently effective against ESBL-PE infection; it diffuses well into body tissues, including lung. However, it should always be used in combination in case of severe infections as the risk of resistance acquisition during treatment is high. Its use in VAP had never been investigated.

Aminoglycosides, in particular, amikacin, are effective against approximately 80% of ESBL-PE and their combination with β-lactams displays synergy in vitro.[83] It increases the probability to receive adequate antimicrobial therapy in ESBL-PE bacteremia with septic shock (►**Table 3**).[84]

Rules for Conducting Antimicrobial Therapy in ESBL VAP

Considering available molecules, the use of carbapenem as the first-line therapy should remain the rule in ICU patients with VAP. An alternative might be considered for step-down therapy if the patient is stabilized (►**Fig. 2**).

For patients with HAP/VAP due to ESBL-PE, the choice of an antibiotic for definitive (not empiric) therapy is based on the results of antimicrobial susceptibility testing.[10]

The ability of an antimicrobial to kill bacteria depends on the MIC of the bacteria and the concentration of the antimicrobial. The MICs of ESBL-PE is most of the time higher than the MICs of wild strains.

Considerable recent literature suggests that the concentration of antimicrobial both at the infectious site and in the plasma is decreased in severe ICU patients during the first day of therapy. The ability to deliver sufficient concentration of antimicrobial is of particular importance when considering the treatment of infections due to microorganisms with relatively high MICs, when the concentration of bacteria is high and when there is no possibility of removing the infectious source. All these unfavorable conditions are met in VAP.[85]

Therefore any pharmacokinetic (PK) optimization decided for increasing the serum free concentration, and the tissue diffusion of antimicrobial is of particular importance for severe VAP due to ESBL-PE.[86,87] It is now suggested by recent Infectious Diseases Society of America (IDSA) recommendations.[10]

The targeted ELF/plasma ratio is lower than 1 (often lower than 0.5) for hydrophilic antimicrobials such as β-lactams and aminoglycosides, around 1 for tigecycline, and higher than 1 for lipophilic antimicrobials such as fluoroquinolones.[88] For all the molecules, the diffusion into tissue will be improved by an important concentration gradient between plasma and the lung. The initial concentration obtained is independent of the antimicrobial clearance.

A first key consequence is that a loading dose of antimicrobial is always required for improving treatment efficacy, even in patients with altered clearance.

For β-lactam antibiotic, bacterial killing depends on the duration of the time above the MIC. It is recommended to reach a time above the MIC of 100% and even more. The application of an aggressive PK/PD target is also justified in patients with HAP/VAP infections because antibiotic dosing that achieves the PK/PD target in plasma is unlikely to achieve the same target in the epithelium lining fluid.

In general, the use of a prolonged or continuous infusion of β-lactams after the loading dose increases the propensity to reach the adequate PK goals,[89] especially in the case of glomerular hyperfiltration.[90] It also increases the probability to reach the optimal PK/PD target in ELF.[85] When discussing the treatment of infection due to resistant gram-negative bacteria, there is only one randomized study that compared prolonged infusion to intermittent infusion of β-lactam antimicrobials (meropenem or piperacillin/tazobactam or cefepime); it enrolled nonhemodialyzed patients in a country where the rate of gram-negative bacilli is high.[91] In this study, prolonged infusion increased the fraction of patients with 100% free drug over the MIC and increased the proportion of clinical success, especially in patients with a lung infection. Recent post hoc analysis of the DALI cohort study also found that in the subgroup of patients who had respiratory infection, patients receiving β-lactams (meropenem or piperacillin-tazobactam) via prolonged infusion demonstrated significantly better 30-day survival when compared with intermittent bolus patients (86.2% [25/29] vs. 56.7% [17/30]; $p = 0.012$). It was especially the case in severe patients with a sequential organ failure assessment (SOFA) score of $\geq$9.[92] Finally, in a meta-analysis of individual patient data from 632 critically ill patients with severe sepsis, half of them with pneumonia, continuous infusion dosing reduced the in-hospital mortality.[93] Potential drug toxicity associated with the use of high dosing could be reduced by appropriate therapeutic drug monitoring and appropriate decrease of the daily dosing in case of impaired clearance.[94]

A combination of the pivotal antibiotic with an aminoglycoside increased the proportion of adequate empirical antimicrobial therapy but should be stopped after 3 to 5 days.

A Cmax/MIC ratio of 10 to 12 and an area under the curve of the inhibitory concentrations of 80 to 160 are the best predictors of aminoglycoside efficacy. The PKs of aminoglycosides is strongly altered in severe infections, leading to suboptimal plasma drug exposure. A high initial dose of more than 25 mg/kg of amikacin or 8 mg/kg of gentamicin is, therefore, necessary to reach sufficient plasma concentrations.[85,95]

A combination of the pivotal antimicrobial with a fluoroquinolone could also be proposed for the initial therapy.

ESBL-PE are inconsistently susceptible to fluoroquinolones (►**Table 3**). However, fluoroquinolones demonstrate excellent penetration into the alveolar compartments. This

Table 3 Usual breakpoints and proposed dose of antimicrobial for ESBLE ventilator-associated pneumonia

	Susceptibility (%)	Breakpoints (mg/L)	Dosage (IV)[a]	Comments
3 G cephalosporins	*Escherichia coli*: <10% *Klebsiella* species: 3% *Enterobacter* species	EUCAST: S ≤ 1 CLSI: S ≤1	2 g × 3/d	Only for targeted therapy or de-escalation if susceptible strains MIC required
Cefepime	*E. coli*: 5–30% *Klebsiella pneumoniae*: 5–60%	EUCAST: S ≤ 1 CLSI: S ≤ 2	2 g × 3 (extended infusion may be appropriate)	Frequent failure in BSI if MICs > 1 mg/L MIC required
Cefoxitin	*E. coli*: 80% *K. pneumoniae*	EUCAST: NA (CA-SFM: S ≤ 8)	6 (8) g daily continuous infusion	PK optimization is needed
Piperacillin-tazobactam	68–85% ESBL *E. coli* 40% ESBL *Klebsiella* species[1,2]	EUCAST: S ≤8 CLSI: S ≤ 16	4 g/0.5 g × 4/d	Only for targeted therapy or de-escalation if susceptible strains MIC required Probably safe if ≤4 mg/L Optimization of PK using prolonged infusion probably preferable after a loading dose MIC preferable
Temocillin	*E. coli*: 60% *K. pneumoniae*: 60%	EUCAST: S ≤ 8	2 g × 3 (6 g daily continuous infusion)	Optimization of PK is preferable if used for targeted therapy in VAP. MIC required
Ceftolozane-tazobactam	*E. coli*: 85–95% *K. pneumoniae*: 40–60%	EUCAST: S ≤ 1 CLSI: S ≤ 8	2 g/1 g × 3/d	Given PK model, the dosage needs to be doubled for VAP Data on prolonged infusions and PK optimization are scarce but suggests its possible use. MIC measure required
Ceftazidime-avibactam	*E. coli*: 98–100% *K. pneumoniae*: 90–100%	EUCAST: S ≤ 8 CLSI: S ≤ 8	2 g/0.5 g × 3	Probably as effective as carbapenems. Should be reserved for the treatment of carbapenem-resistant GNB
Ertapenem	*E. coli*: 98% *K pneumoniae*: 75%	EUCAST: S ≤ 0.5 CLSI: S ≤ 0.5	0.5 g × 4 or 1 g × 2 (3) daily	MIC ≤ 0.25 preferable for use in VAP
Imipenem–meropenem	*E. coli*: 98–100% *K. pneumoniae*: 90–100%	EUCAST: S ≤2 CLSI: S ≤1	Imipenem: 1 g × 3 Meropenem: 1 g × 4	Clearly the pivotal β-lactam for ESBL-PE VAP Continuous infusion or prolonged infusion of imipenem not recommended (unstable)
Tigecycline	*E. coli*: 95–100% *K. pneumoniae*	EUCAST: S ≤ 1	200 mg loading dose followed by 100 mg × 2	Doubling the dose to 200 mg is mandatory. Should be considered for de-escalation or in case of severe allergy to carbapenems
Proposals for antimicrobial that can be combined with the pivotal antimicrobial				
Amikacin (the % of susceptible strains is usually lower for gentamycin)	*E. coli*: 70–80% *K pneumoniae*: 70%	EUCAST: S ≤ 8	25 (30) mg/kg 1 h infusion once a day	Should not be given alone The first dose is not affected by the altered renal clearance. Therapeutic drug monitoring in necessary to decide reinjection. A short treatment (< 5 d) is sufficient

Abbreviations: 3G cephalosporins, third generation cephalosporins; BSI, blood stream infection; CA-SFM, French committee for antibiotic susceptibility testing; CLSI, Clinical and Laboratory Standard Institute; ESBL, extended spectrum β-lactamase–producing *Enterobacteriaceae*; EUCAST, EUropean Committee on Antimicrobial Susceptibility Testing; GNB, gram-negative bacteria; MIC, minimum inhibitory concentration; NA, not applicable; PK, pharmacokinetic; VAP, ventilator-associated pneumonia.

[a]Suggested dosages are often higher than those approved, to optimize pharmacokinetic (PK)/ pharmacodynamic parameters according to the modified PK of antibacterial agents in intensive care unit patients. An early adaptation based on plasma levels is recommended, particularly in patients with impaired renal and/or liver function.

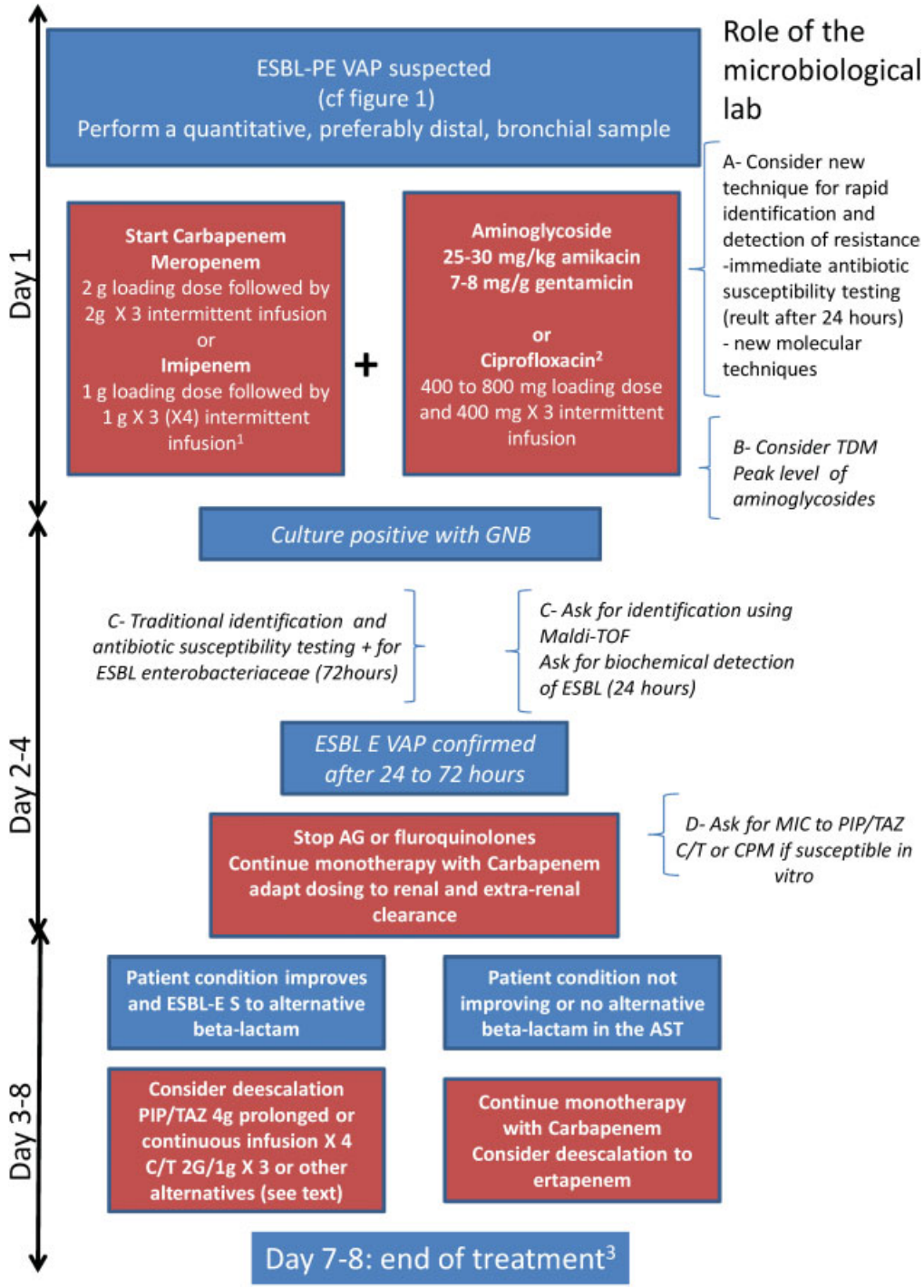

Fig. 2 Suggested empirical and targeted therapy to treat ESBL-PE VAP. (1) Imipenem is not stable after reconstitution and should not be used for prolonged infusion. (2) Ciprofloxacin is very inconsistently effective on ESBL-PE (~20%) and is suggested here to enlarge the spectrum to other gram-negative bacilli such as *Pseudomonas aeruginosa*. (3) Around 7 to 8 days treatment is sufficient if the clinical status is stabilized except in the case of lung abscesses or empyema. Of note, the suggested dosages are often higher than those approved, to optimize pharmacokinetic (PK)/pharmacodynamic parameters according to modified PK of antibacterial agents in ICU patients. An early adaptation based on plasma levels is recommended, particularly in patients with impaired renal and/or liver function. C/T, ceftolozane/tazobactam; ESBL-PE, extended spectrum β-lactamase-producing *Enterobacteriaceae*; ICU, intensive care unit; PIP/TAZ, piperacillin/tazobactam; VAP, ventilator-associated pneumonia.

antibiotic class displays concentration-dependent kill characteristics with some time-dependent features largely. The area under the concentration–time curve over a 24-hour period (AUC0–24)/MIC best predicts its bactericidal effect and a ratio of at least 125 is required for optimal patient outcomes in the treatment of gram-negative infections.[96] Importantly, this PK target will be very difficult to reach if MIC is greater than 0.5 mg/L.

Role of Inhaled Antibiotics in ESBL-PE VAP

Intravenous antibiotics are currently the standard of care for pneumonia; however, increasing rates of multidrug resistance and limited penetration of some classes of antimicrobials[88] into the lungs reduce the effectiveness of this treatment option, and current clinical cure rates are variable, while recurrence rates remain high. Moreover, in vitro studies suggested that antibiotic concentrations below a specific threshold termed the mutation prevention concentration can be associated with a greater emergence of antibiotic resistance.

Inhalation allowed delivery of considerable local concentrations of antimicrobials[97,98]; inhaled amikacin may be of added value in ESBL-PE VAP, especially if another drug than carbapenem is chosen. However, there is no available specifically formulated solutions for inhalation, and a limited number of devices are designed for the nebulization of antibiotics.[99,100] The role of inhaled antimicrobial will be extensively discussed in chapter 11 by Drs. Palmer and Rello in this issue. Despite the possible advantages in term of microbiological eradication and emergence of resistance,[101] available studies did not demonstrate any impact on patients' prognosis.[98,101–103]

Duration of Antimicrobial Therapy

One meta-analysis[104] and two large randomized controlled trials[105,106] clearly showed that an 8-day therapy did not affect the relapse rate, prognosis, duration of stay and duration of mechanical ventilation of VAP patients compared with a 15-day course. Short course therapy significantly reduced antimicrobial consumption. In the study from Chastre et al, similar results were obtained in a subgroup of late-onset pneumonia due to *Enterobacteriaceae*.

However, it should be noticed that these studies referred to immunocompetent patients without cystic fibrosis and for whom the empirical antibiotic therapy was adequate. In the study from Chastre et al, combination therapy was used most of the time (70% with an aminoglycoside for at least 2 days). Also, the most severe patients and patients with lung abscess or empyema were excluded. Although no study specifically addressed ESBL-PE VAP, a short 8-day course of therapy should be proposed if initial therapy was adequate.

Considering the available data, a short duration of therapy for severe or immunocompromised ESBL-PE patients should be considered only if the patient's status clearly improved. The available data do not allow concluding firmly that a short course therapy is safe for ESBL-PE VAP if the initial treatment was not a carbapenem, or if a combination therapy has not been given for at least 2 days. A short course therapy might also be proposed for non-ventilated HAP without any available data.

Longer courses of antibiotics may be required in patients with inappropriate initial empiric therapy; they should be adapted to the patient's clinical response and serial measurement of procalcitonin level.[107] Indeed, a stopping rule based on a decrease of more than 85% of the procalcitonin level has been shown to reduce the mean duration of therapy of VAP to less than 8 days.[107,108] Treatment should be longer in the case of empyema or lung abscesses.

Conclusion

Active treatments of ESBL-PE HAP/VAP are limited to carbapenem and some alternatives. Given the rapid spread of carbapenem-resistant bacteria in worldwide ICUs, any effort to decrease antibiotic selection pressure and carbapenem use should be made. Carbapenem should be spared by (1) not giving carbapenems for the initial treatment of early onset VAP, and in patients without shock and no previous rectal colonization; (2) using new diagnostic test able to give results about the pathogen and the presence of ESBL within 24 hours; (3) de-escalating carbapenem treatment to alternative if ESBL-PE is confirmed, and the patients stabilized; (4) trying to reduce the duration of treatment as much as possible as soon as the clinical situation is stabilized.

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How Should We Treat HAP/VAP Caused by Carbapenemase-Producing Enterobacteriaceae?

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Abstract

Hospital-acquired pneumonia (HAP) and ventilator-associated pneumonia (VAP) represent a common problem in hospital setting worldwide. Infections caused by carbapenem-resistant *Enterobacteriaceae* (CRE) are an emergent problem due to the lack of therapeutic options available, leading to significant increases in morbidity and mortality. CRE have frequently been reported both in HAP/VAP, but limited data regarding the optimal treatment strategy in this setting are available. This review focuses on the current epidemiology of CRE, with a specific focus on HAP/VAP. Moreover, we will suggest a possible strategy for the empiric and targeted treatment of HAP and VAP in which the involvement of CRE is suspected or is confirmed.

Keywords

- hospital-acquired pneumonia
- ventilator-acquired pneumonia
- carbapenemase-producing *Enterobacteriaceae*
- antibiotic therapy
- multidrug-resistant gram negative

Hospital-acquired pneumonia (HAP) is defined as a lower respiratory tract infection occurring in patients hospitalized for more than 48 hours.[1] Ventilator-associated pneumonia (VAP) represents a subgroup of HAP developing in mechanically ventilated patients[1]. HAP and VAP represent a major problem worldwide, accounting for up to 20% of all health care-associated infections.[2] Overall, the incidence of HAP ranges from 5 to 20 cases per 1,000 hospital admissions, and approximately one-third of cases are represented by VAP, which occurs in 9 to 40% of intubated patients.[3,4] Both HAP and VAP have been associated with high mortality rates (20–60%) and significant increases in length of stay and overall health care costs.[3]

The microbiological epidemiology of HAP/VAP varies widely, but the role of *Enterobacteriaceae*, mainly represented by *Klebsiella pneumoniae* isolated in up to one-third of cases, is well established.[5–7] In this setting, the emergence of infections caused by carbapenem-resistant *Enterobacteriaceae* (CRE) represent an alarming problem due to the lack of available therapeutic options, leading to inadequate antibiotic treatment and increased mortality.[8,9]

Limited data regarding the optimal antimicrobial regimen for the treatment of HAP/VAP due to CRE are available. Based on recent data, carbapenems might probably play a pivotal role also when the isolate displays a resistant phenotype, but attention must be paid to dose, modality of administration (extended infusion) and plasma drug levels.[10] Colistin and aminoglycosides, which represent possible therapeutic options in this setting, have poor lung penetration when administered intravenously. The use of aerosolized preparations has been recently proposed, but the optimal use in clinical practice has not been fully established so far. Moreover, new promising antimicrobial agents for the treatment of CRE infections have been recently developed (new β-lactam/β-lactamase inhibitors and plazomycin).

In this review, we will describe the current global epidemiology of CRE, with a specific focus on HAP/VAP. Moreover, we will suggest a possible strategy for the empiric and targeted treatment of HAP and VAP in which the involvement of CRE is suspected or confirmed, focusing on the role of both old and new available antimicrobial agents.

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Microbiology

In 2015 the Center for Disease Control (CDC) updated the Facility Guidance for Control of CRE and defined CRE as *Enterobacteriaceae* that are resistant to any carbapenem antimicrobial (i.e., minimum inhibitory concentrations [MIC] of ≥4 μg/mL for doripenem, meropenem, or imipenem or ≥2 μg/mL for ertapenem) or documented to produce a carbapenemase. Also, for bacteria that have intrinsic imipenem nonsusceptibility (i.e., *Morganella morganii*, *Proteus* spp., *Providencia* spp.), resistance to carbapenems other than imipenem is required.[11]

The most common mechanism of carbapenem resistance among *Enterobacteriaceae* is represented by the production of specific β-lactamases enzymes that possess a direct carbapenem-hydrolyzing activity. Among the four classes of β-lactamases defined by the Ambler classification system, the carbapenemases that confer carbapenem resistance in *Enterobacteriaceae* belong to three classes: Class A (*K. pneumoniae* carbapenemases, KPC), class B (metallo-β-lactamases, MBL, including New Delhi metallo-β-lactamases, NDM), and class D (oxacillinases, OXA). Characteristics and global distribution of carbapenemase enzymes are reported in ►**Table 1**.[12] The large majority of carbapenemases are encoded by genes on mobile elements located on plasmids, which represent the most important driver of the spread of CRE. However, carbapenemases are expressed at various levels and are frequently associated with other resistance mechanisms, such as efflux pumps and modifications in membrane permeability, resulting in a wide range of resistance phenotypes. Moreover, a decreased susceptibility to carbapenems can be observed in extended-spectrum-β-lactamase- or Amp-C- producing *Enterobacteriaceae* when a concomitant downregulation of porins is present. Thus, when *Enterobacteriaceae* display a phenotypic carbapenem-resistance pattern, further tests are required to establish whether carbapenem-resistance is due to the production of carbapenemase enzymes or other mechanisms. For this reason, the European Committee on Antimicrobial Susceptibility Testing (EUCAST) established the epidemiological cut-off values and strongly recommends performing specific tests for the detection of carbapenemases when MICs are above a fixed value. The screening cut-off values for carbapenem-producing *Enterobacteriaceae* are MIC > 0.12 for meropenem and ertapenem and MIC > 1 for imipenem. The modified Hodge test is a phenotypic test widely used in clinical practice for the detection of carbapenemase enzymes; however, this test does not allow the identification of the class of carbapenemase.[13] Carba NP is an alternative, rapid test to identify carbapenemases. Many other tests and polymerase chain reaction techniques for the detection of carbapenemases have been recently developed, but have not been validated for the use in the routine clinical practice so far.[13]

Epidemiology of Carbapenemase-Producing *Enterobacteriaceae*

A rapid spread of carbapenem resistance among *Enterobacteriaceae* has been reported worldwide over the past years, although epidemiology is variable across different countries.[14] In the United States, approximately 11% of *K. pneumoniae* and 2% of *Escherichia coli* isolates in health care-associated infections were resistant to carbapenems in 2013, with an estimated number of 9,300 infections per year and a substantial increase in overall health care costs.[15]

In 2012, the European Centre for Disease Prevention and Control (ECDC) launched the "European survey of carbapenemase-producing *Enterobacteriaceae* (EuSCAPE)" project to improve the understanding of the occurrence and epidemiology of CRE. A self-assessment questionnaire was sent to one national expert from each of the 28 EuSCAPE participating countries. Among these, four countries (Italy, Greece, Malta, and Turkey) reported an endemic situation, with most hospitals repeatedly seeing cases admitted from autochthonous sources, and 13 reported a regional- and interregional spread,

Table 1 Characteristics and global distribution of carbapenemase enzymes

Class of carbapenemases	Characteristics	Distribution
Class A KPC (*Klebsiella pneumoniae* carbapenemase)	Serine-carbapenemases The most common cause of carbapenem-resistance among *Enterobacteriaceae*	Worldwide United States South and Central America Europe (mainly Italy and Greece)
Class B NDM (New Delhi metallo-β-lactamase) IMP (Imipenemases) VIM (Verona integron-encoded-β-lactamases)	Zinc-dependent Unable to hydrolyze aztreonam	NDM: Asia (mainly India, Pakistan, and Bangladesh) IMP and VIM: Europe Romania, Poland, and Denmark)
Class D OXA-48-like enzymes (oxacillinases)	Induce a relatively weak hydrolysis of penicillins and carbapenems High-level carbapenem resistance may occur when these enzymes are found in combination with other β-lactamases (ESBL-od Amp-C), or with membrane permeability alteration	Relatively common in Europe (Mediterranean countries) Extremely rare in United States

with multiple outbreaks suggestive of regional autochthonous interregional and interinstitutional transmission.[16] *K. pneumoniae* large intercountry differences in antimicrobial resistance have been observed with higher rates of carbapenem resistance in the southern European countries and lower rates in the northern ones. Overall, alarming increases in carbapenem resistance rates have been observed in Europe between 2011 and 2014 in seven countries (Bulgaria, Croatia, France, Germany, Italy, Portugal, and Spain).[17] Conversely, carbapenem-resistance has been reported in less than 0.5% of isolates of *E. coli* in most European countries, and no statistically significant increasing trend has been observed over the past years.[17] In India, a rapid increase toward carbapenem resistance has been described, with 57% of *K. pneumoniae* and 13% of *E. coli* displaying resistance to carbapenems in 2014.[14]

Conversely, in Latin America resistance of *K. pneumoniae* to carbapenems is low, and ranges from full susceptibility (Dominican Republic) to 28% of isolates showing carbapenem resistance in Guatemala.[17]

A major concern is currently represented by the emergence of colistin resistance in *Enterobacteriaceae*, which has been reported in up to 20% of isolates in carbapenem-resistant *K. pneumoniae* in specific settings (some European countries and Brazil).[18] Colistin resistance has been associated with higher rates of inadequate antibiotic treatment and increased mortality in CRE infections, mainly due to the lack of available therapeutic options.[19,20] Giacobbe et al in a multicenter, retrospective study including 729 cases of bloodstream infections (BSIs) due to KPC-producing *K. pneumoniae* (KPC-Kp), found that colistin-resistant KPC-Kp were more often associated with lower respiratory tract infections and inadequate empirical antibiotic treatment than colistin-susceptible strains, leading to a higher percentage of initial treatment failure and 30-day crude mortality (51 vs. 39.4%).[21] The global epidemiology of CRE and colistin-resistant *K. pneumoniae* is described in ►**Table 2**.

The Role of KPC in HAP and VAP and Mortality

No studies specifically addressing the role of CRE in HAP and VAP are available so far. However, many studies investigated epidemiology, risk factors, and outcome of CRE infections, including respiratory tract infections. In a prospective, single-center, cohort study conducted from March 2011 to December 2012 in Brazil, 127 patients with health-care-associated CRE infections were evaluated. *K. pneumoniae* accounted for the large majority of isolates (89%), followed by *Enterobacter* spp. Infection-related mortality was 34%, and 30-days mortality was 28.3%. The majority of infections (77.2%) occurred in the intensive care unit (ICU). In this cohort, pneumonia was the most common site of infection (52 cases, 42%) and was associated with a significantly higher infection-related mortality compared with other site CRE infections (61 vs. 34.6%).[21] The same results have been confirmed by other studies reporting high mortality rates in CRE respiratory tract infections. Wang et al collected 94 cases of CRE infections from October 2010 to November 2014 in two large teaching hospitals in China. Respiratory tract infections accounted for approximately half of cases, with higher mortality rates compared with respiratory infections due to non-CRE (37 vs. 16.7%, respectively).[22] Similarly, Qureshi et al analyzed 41 cases of bacteraemia due to KPC-Kp; among these, in 10 cases pneumonia was the source of bacteraemia, and 7 out of 10 patients died.[23]

Risk Factors for the Development of HAP/VAP due to KPC-Producing *Enterobacteriaceae*

Risk factors that are similar to those associated with other multidrug-resistant (MDR) bacteria, such as the history of hospitalization, the severity of illness, and prior antimicrobial use have been identified for KPC-Kp. Furthermore, patient mobility from endemic areas across borders has also recently been highlighted as a risk factor for the acquisition of and spread of KPC-Kp.[24] Risk assessment on the spread of carbapenemase-producing *Enterobacteriaceae* through patient transfer between health care facilities, with special emphasis on cross-border transfer.[25]

Factors associated with the development of infections due to KPC-Kp have been mainly analyzed in retrospective studies from countries with elevated rates of the extended spectrum β-lactamase (ESBL)-producing bacteria. None of the reports, however, specifically focused on HAP/VAP and the majority of studies reported factors associated with KPC-Kp BSIs. A Brazilian case–control study comparing KPC-producing with non–KPC-producing Kp bacteremia (including ~60% ESBL-producing strains) identified age, mechanical ventilation, and fluoroquinolones use during hospitalization as independent risk factors associated with KPC isolation at multivariate analysis.[26]

Table 2 Worldwide distribution of carbapenem-resistant and colistin-resistant *Enterobacteriaceae*

Pathogen	United States	North-Centre Europe	Italy-Greece-Romania	Asia	South-America
Carbapenem-resistant *Klebsiella pneumoniae*	11%	1–5%	25–50%	> 50%	0–30%
Colistin-resistant *Klebsiella pneumoniae*	2.7%	8.2% (overall European mean)	15–25%	Not available	Not available
Carbapenem-resistant *Escherichia coli*	2%	< 1%	< 1%	13%	Not available

In a similar study encompassing 47 cases (including 13% patients with tracheal aspirate positivity for KPC-Kp) and 47 controls, length of stay, long-term hospitalization, use of mechanical ventilation, central venous and urinary catheters, and previous surgery were associated with KPC-Kp infections.[27]

A Greek case–control study evaluating BSI caused by KPC and MBL-producing *K. pneumoniae* in ICU identified high Acute Physiology and Chronic Health Evaluation (APACHE) II score as the main risk factor for the development of KPC-Kp BSI. In this cohort, the isolation of KPC-Kp was also an independent predictor of ICU and in-hospital death.[28]

In a large, retrospective Italian cohort encompassing 426 cases of KPC-Kp infections, risk factors for KPC-Kp infection included Charlson index above 3, the presence of indwelling central venous catheter, recent surgery, neutropenia, more than two recent hospitalizations, and fluoroquinolone and/or carbapenem use. Although specific risk factors for HAP/VAP were not specifically analyzed, 120 (18%) of all colonized and infected patients displayed positive sputum or bronchoalveolar lavage fluid for KPC-Kp. Overall, recent carbapenem use was reported as a factor associated with KPC-Kp in both colonized and infected groups.[29]

Prior use of a carbapenem, in particular, has been reported as an independent risk factor for the acquisition of KPC-Kp and other carbapenem-resistant *Enterobacteriaceae* in various studies.[30,31]

Various studies have reported the impact on outcome and factors associated with poor outcomes in KPC-Kp infections. A prospective Brazilian study including 52 (42%) cases of pneumonia due to CRE with 89% KPC-related infections identified highest mortality in respiratory infections compared with all infections (61.4 vs. 34.6%, respectively). Predictors of mortality included severe presentation with shock, old age, and dialysis.[21]

Inadequate initial antimicrobial therapy and high APACHE III scores have also been identified as risk factors for KPC-Kp mortality, highlighting how a timely appropriate therapy is a key for the management of these infections.[9]

Empirical Treatment

Empirical antimicrobial therapy should be imitated promptly in patients with high probability of HAP/VAP especially if the infection originates sepsis or septic shock, because both delayed and inadequate treatments have been associated with increased rate of morbidity and mortality.[32,33]

Beta-lactam antibiotics alone or as part of a combination regimen are the mainstay of empirical antibiotic guideline recommendations.[1] However, given the global increase in antibiotic-resistance rates and the epidemiological variation, antimicrobials used in the empirical regimens should be chosen based on the local distribution of pathogens associated with HAP/VAP and their antimicrobial susceptibilities.[1,34,35]

There is no suitable clinical information on the efficacy and safety of the empiric treatment of severe infections caused by CRE, including HAP/VAP. A multicenter randomized clinical trial (RCT) to assess the safety and efficacy of empiric treatment with colistin versus meropenem in late onset (> 96 hour) VAP caused by MDR gram-negative bacteria (MDR-GNB), including CRE, is currently ongoing, but results are not yet available.[36] The current approach relies on combination regimens containing two or three active drugs, especially for carbapenem-containing regimens, which have demonstrated significant advantages over monotherapies in terms of survival for CRE infections.[9,37,38] Therefore, we believe that for patients with suspected CRE HAP/VAP empirical use of carbapenem associated with colistin and/or tigecycline may be justified.[9,37,38] Ceftazidime-avibactam could be an alternative option for empirical treatment associated with fosfomycin or gentamicin (►**Fig. 1**).[39] Given the consistent high failure rates with even optimized intravenous antibiotic therapy and the increasing incidence of

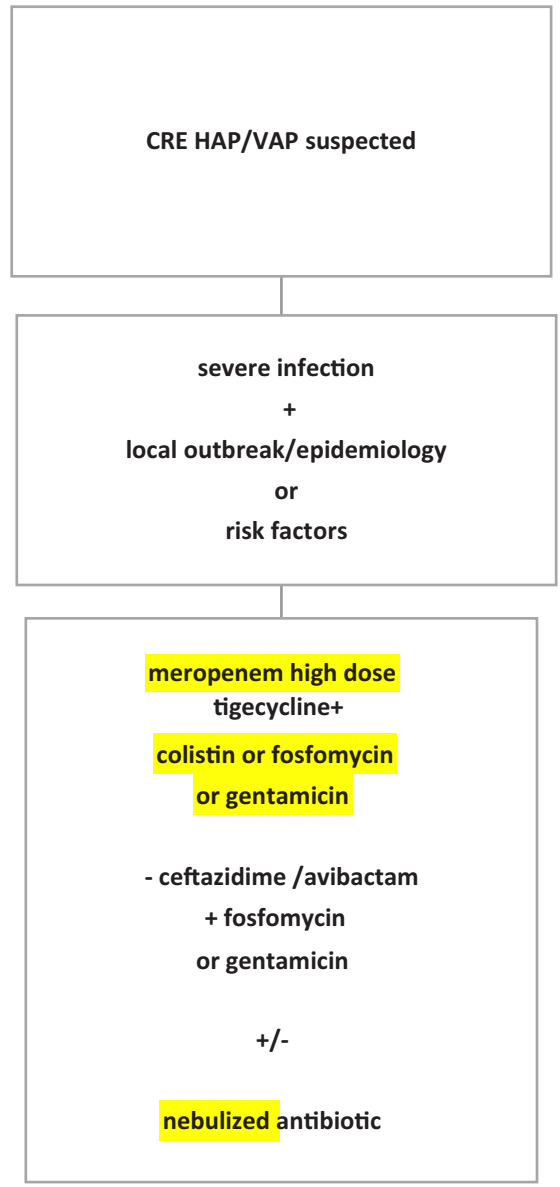

Fig. 1 Empiric treatment in patients with severe infection and risk factors for suspected ESBL and CRE infections. Abbreviations: CRE, carbapenemase-resistant *Enterobacteriaceae*; ESBL, extended spectrum β-lactamase.

MDR-GNB, some authors believe that aerosolized antibiotics should routinely be used as initial empirical therapy for HAP/VAP, since it is likely to lead to substantial bacterial killing even if β-lactam resistance is present.[40] In our opinion, in patients with severe infection with previous CRE colonization and/or multiple risk factors for CRE and/or a local outbreak, nebulized antibiotic should be added to empirical intravenous therapy (►**Fig. 1**). After an optimal empiric therapy against CRE, antibiotic de-escalation 24 to 48 hours after initiation and in vitro synergy testing should be always performed if feasible to improve definitive therapy.[1]

Targeted Treatment

Antibiotic options for treatment of CRE HAP/VAP are limited and the optimal treatment of serious infections caused by KPC-producing *Enterobacteriaceae* remains debatable. Given the limited in vivo data regarding the treatment of CRE infections, appropriate antimicrobial choices for individual isolates should be determined based on susceptibility testing and patient-specific criteria.[35] When considering treatment options, reports of resistance developing during treatment, antimicrobial tissue penetration, and medication-related adverse effects should be taken into account.[35] Overall, colistin, tigecycline, and gentamicin have poor lung penetration, whereas carbapenem and fosfomycin have good distribution achieving clinically relevant concentrations in lungs.[41,42] Combination therapy should be strongly considered (►**Table 3**).[43–45]

Carbapenems

Carbapenem-containing regimens have always constituted a pivotal therapy for VAP and demonstrated a survival benefit, primarily in serious infections caused by CRE, compared with other combinations and could serve as a therapeutic backbone.[34,37,38] Real-time pharmacokinetic/pharmacodynamic optimization of high-dose continuous infusion (extension of the infusion time from 30 minutes up to 6 hours every 6 hour) meropenem may represent a valuable approach for the treatment of disseminated KPC-Kp infections even when

Table 3 Expert opinion target treatment options for KPC-Kp HAP/VAP (Dose adjustment is recommended depending on renal function and antimicrobial susceptibility tests)

KPC-Kp meropenem MIC ≤ 64 mg/L colistin-S + inhaled antibiotic (IA)	KPC-Kp meropenem MIC > 64 mg/L colistin-S + inhaled antibiotic (IA)	KPC-Kp meropenem MIC > 64 mg/L colistin-R + inhaled antibiotic (IA)
• Meropenem 2 g every 8 h iv (B) ± tigecycline 100 mg every 12 h iv (C) ± colistin 4.5 MU every 12 h iv (D) or gentamicin 3–5 mg/kg/d every 24 h iv (E) or fosfomycin 4 g every 4 h iv • Ceftazidime-avibactam 2.5 g every 8 h iv ± gentamicin 3–5 mg/kg/d every 24 h iv (E) or fosfomycin 4 g every 4 h iv + inhaled antibiotic (IA)	• Colistin 4.5 MU every 12 h iv (D) ± tigecycline 100 mg every 12 h iv (C) or gentamicin 3–5 mg/kg/d every 24 h iv (E) ± rifampin 600–900 mg every 24 h iv • Ceftazidime-avibactam 2.5 g every 8 h iv ± gentamicin 3–5 mg/kg/d every 24 h iv (E) or fosfomycin 4 g every 4 h iv + inhaled antibiotic (IA)	• Tigecycline 100 mg every 12 hours iv (C) ± colistin 4.5 MU every 12 h iv (D) ± rifampin 600–900 mg every 24 h iv • Ertapenem 500 mg every 6 h iv (F) ± meropenem 2 g every 8 h iv (B) • Ertapenem 500 mg every 6 h iv (F) ± doripenem 500 mg every 8 h iv (G) • Ceftazidime-avibactam 2.5 g every 8 h iv ± gentamicin 3–5 mg/kg/d every 24 h iv (E) or fosfomycin 4 g every 4 h iv + inhaled antibiotic (IA)

Abbreviations: HAP, hospital-acquired pneumonia; iv, intravenously; KPC-Kp, KPC-producing *Klebsiella pneumoniae*; MIC, minimum inhibitory concentrations; MU, million units; VAP, ventilator-associated pneumonia.

Notes: Antimicrobial susceptibility test:

- Colistin: MIC ≤ 2 mg/L continue colistin; MIC > 2 mg/L consider alternative in vitro active antimicrobial.
- Tigecycline: MIC ≤ 1 mg/L consider tigecycline; MIC > 1 mg/L consider alternative in vitro active antimicrobial.
- Fosfomycin: MIC ≤ 32 mg/L consider fosfomycin; MIC > 32 mg/L consider alternative in vitro active antimicrobial.
- Aminoglycoside: MIC ≤ 2 mg/L for gentamicin/tobramycin or ≤ 4 mg/L for amikacin consider aminoglycoside; MIC > 2 for gentamicin/tobramycin or > 4 mg/L for amikacin consider alternative in vitro active antimicrobial.
- Aztreonam: MIC ≤ 8 mg/L continue aztreonam; MIC > 8 mg/L consider alternative in vitro active antimicrobial.

(A) Inhaled antibiotic depending on susceptibility tests:
-Colistin 2 MU nebulized every 8 h
-Tobramycin 300 mg nebulized every 12 h
-Amikacin 250 mg nebulized every 12 h up to 500 mg every 12 h
-Gentamicin 80 mg nebulized every 12 h
-Aztreonam 75 mg nebulized every 8 h

(B) Meropenem: Loading dose (2 g in 1 h) followed by maintenance doses with continuous infusion (1.5 g every 6 h in 6-h infusion). Therapeutic drug monitoring suggested.
(C) Tigecycline: Loading dose (200 mg) followed by maintenance doses with 100 mg every 12 h.
(D) Colistin: Loading dose (9 MU) followed by maintenance doses with 4.5 MU every 12 h.
(E) Gentamicin: 3–5 mg/kg once a day or Amikacin 15–20 mg/kg/d every 24 h iv
(F) Ertapenem: Maintenance dose with continuous infusion (500 mg every 6 h in 4 h).
(G) Doripenem: Maintenance doses with doripenem 500 mg every 8 h (infusion in 1 h).

caused by meropenem-resistant strains and has been associated with higher rate of clinical cure in VAP.[46] Some studies have ascertained the role of meropenem could be especially relevant when included in combination regimens with other active agents, if the MIC of the pathogen is $\leq$ 16 mg/L.[9,38] However, a recent study demonstrated that high-dose continuous-infusion meropenem optimized in real-time might allow successful clinical outcomes in the treatment of KPC-Kp infections even when caused by meropenem-resistant strains with an MIC $\leq$ 64 mg/L.[10] In this setting the use of meropenem therapeutic drug monitoring (TDM) is highly recommended to adjust the antibiotic dosage depending on the MIC. Of interest that high meropenem concentrations did not result in any relevant drug-related adverse events in previous studies.[10,47]

The double carbapenem regimen including ertapenem and doripenem or meropenem can be a rescue therapy for patients with untreatable infections caused by KPC-Kp with colistin resistance or high carbapenem MIC (meropenem MIC $>$ 8–16 µg/mL), including HAP and VAP.[48,49] Ertapenem due to its higher affinity with the carbapenemase enzyme acts as a suicide inhibitor, thus allowing the more active carbapenem to affect the organism.[50]

Oher Antibiotics

Antibiotics that permeabilize the bacterial cell membrane (polymyxins), interfere with cell wall synthesis (fosfomycin), or inhibit protein synthesis (aminoglycosides or tigecycline) may decrease the MIC sufficiently so that it is exceeded when a carbapenem is coadministered. Colistin is considered the antimicrobial with greater in vitro activity against KPC.[51] The efficacy of colistin in VAP caused by MDR-GNB has been demonstrated in several retrospective and prospective series, but mainly focused on MDR *Acinetobacter* spp. and *Pseudomonas aeruginosa*.[52] Previous studies found that, in critically ill adult patients the intravenous administration of 2 million international units (MIU) every 8 hours resulted in apparently suboptimal plasma concentrations of colistin, which was undetectable in bronchoalveolar lavage (BAL).[53] The current recommended dosage is 9 MIU loading dose followed by 4.5 MIU every 12 hours to rapidly reach therapeutic concentrations.[54] If resistance to colistin is documented, the addition of rifampicin may be considered to exploit synergism.[55]

Tigecycline has not been licensed for the treatment of HAP or VAP but the off-label use of tigecycline is frequent, especially in HAP/VAP due to MDR pathogens, where the therapeutic options are limited. A previous multicenter RCT on HAP, found clinical response of patients treated with standard dose of tigecyline (50 mg every 12 hours; loading dose 100 mg) to be inferior to the imipenem/cilastatin regimen. The increased mortality was observed with tigecycline in the group of patients with VAP.[56] Since standard dose of tigecycline does not achieve adequate concentrations for pulmonary infections, in patients with VAP/HAP caused by KPC it may be advisable to administer high-dose regimens (200 mg followed by 100 mg every 12 hours) always as part of a combination regimen (preferably with a carbapenem or colistin).[57,58]

Aminoglycoside-containing regimens, particularly gentamicin, have also been associated with favorable outcomes and should be encouraged particularly in view of increasing rates of colistin resistance.[38,59] A previous study found that once daily, intravenous administration of gentamicin (240 mg daily) was insufficient to obtain active alveolar concentrations against less-sensitive microorganisms in the treatment of VAP in ICU patients.[60] In our opinion, TDM-guided gentamicin dose can play an important role in the treatment of KPC-Kp in combination therapy usually with carbapenem or tigecycline.

Activity of fosfomycin has been tested in many in vitro studies and has shown synergistic action with other antimicrobials[61] and represents an interesting option to treat a wide range of infections, including HAP/VAP caused by CRE pathogens.[61] However, clinical experience is very limited. A recent study reported an acceptable response in patients with VAP treated with high doses (4 g every 4 hours) of fosfomycin always in combination with other antimicrobials.[62] We believe it should be used in combination regimens aiming to escape resistance development and to enhance the in vivo activity of fosfomycin.[62]

New Antibiotics for CRE VAP/HAP

New drugs in clinical development with activity against CRE and potential indications for HAP/VAP are listed in ►**Table 4**.

Ceftazidime/Avibactam

The treatment is comprised of avibactam, a first-in-class broad-spectrum β-lactamase inhibitor, which protects ceftazidime against degradation by class A, class C, and some class D β-lactamases, and ceftazidime, a third generation cephalosporin with a well-established efficacy and safety profile.[63] Like ceftazidime, avibactam is primarily renally excreted, and clearance correlates with creatinine clearance.

Because of its attractive bactericidal broad-spectrum activity, linear pharmacokinetics with high lung penetration, and low risk of serious adverse events, ceftazidime/avibactam represents a promising option for the treatment of pneumonia caused by MDR-GN pathogens, especially when carbapenem resistance is suspected.[64] The phase III trial assessing the efficacy of ceftazidime/avibactam compared with meropenem in the treatment of adult patients with HAP/VAP is ongoing. Preliminary results from the trial found that the new antibiotic met the primary objective of statistical noninferiority compared with meropenem at the test of cure visit (day 21 from randomization). All-cause mortality rate at day 28 from randomization was also similar in the two groups (available at: www.ClinicalTrials.gov Identifier: NCT01808092).

Ceftazidime/avibactam has been recently approved by the European Medicines Agency (EMA) for use in the treatment of adult patients suffering from HAP, including VAP, as well as complicated intra-abdominal infections, complicated urinary tract infections, the treatment of aerobic GNB infections in adult patients who have limited treatment options.

Table 4 New drugs in clinical development with activity against CRE and potential indications for HAP and VAP

Drug name	Development phase	Spectrum of activity	Dose for patients with normal renal function	Potential indications or clinical trials for HAP/VAP
Cephalosporin				
Cefiderocol	Phase 3	KPC and NDM-1	2 g every 8 h iv (over 3 h)	Ongoing trial including HAP and VAP (https://clinicaltrials.gov/NCT02714595)
Cephalosporin + β-lactamase inhibitor				
Ceftazidime/avibactam	FDA and EMA approved	KPCs and OXA-48 (not active against MBLs)	2/0.5 g every 8 h iv (over 2 h)	Ongoing trial including HAP and VAP (https://clinicaltrials.gov/NCT01808092)
Ceftaroline fosamil-avibactam	Phase 3	KPCs and OXA-48 (not active against MBLs)	600/600 mg every 8 h iv (over 1 h)	No ongoing trials on VAP/HAP
Monobactam + novel β-lactamase inhibitor				
Aztreonam-avibactam	Phase 2	MBLs such as NDM	6,500/2,167 mg on day 1 followed by daily dose of 6,000/2,000 mg iv	No ongoing trials on VAP/HAP
Carbapenem + novel β-lactamase inhibitor				
meropenem/vaborbactam	Phase 3	KPCs	2/2 g every 8 h iv (over 3 h)	Ongoing trial including HAP and VAP
Imipenem/cilastatin-relebactam	Phase 3	Against class A and C β-lactamases	500/250 mg every 6 h iv	Ongoing trial including HAP and VAP (https://clinicaltrials.gov/NCT02452047 and https://clinicaltrials.gov/NCT0249376)
Aminoglycoside				
Plazomicin	Phase 3	Most KPCs (not active against many NDMs)	15 mg/kg/dose every 24 h iv (over 30 min)	Ongoing trial including HAP and VAP (https://clinicaltrials.gov/NCT01970371)
Tetracycline				
Eravacycline	Phase 3	KPCs	1 mg/kg every 12 h	Trial including HAP and VAP finished

Abbreviations: CRE, carbapenem-resistant *Enterobacteriaceae*; EMA, European Agency of Antimicrobials; FDA, Food and Drug Administration; HAP, hospital-acquired pneumonia; iv, intravenously; KPC, *Klebsiella pneumoniae* carbapenemase; MBL, metallo-β-lactamase; NDM, New Delhi metallo-beta lactamase; OXA, oxacillinase; VAP, ventilator-associated pneumonia.

A recent study on bacterial isolates collected from patients hospitalized with pneumonia, including VAP in United States (2011–2015) found ceftazidime/avibactam to be highly active against *Enterobacteriaceae* (99.9% susceptible), including CRE (98.0% susceptible).[65]

A case series on patients with infections (mainly abdominal and respiratory tract infections) by CRE treated with ceftazidime/avibactam salvage therapy on a compassionate-use basis has been recently published. In three-quarters of cases, ceftazidime/avibactam (alone or combined with other antibiotics) cured infections caused by CRE organisms, 95% of which had failed previous therapy.[66] However, despite this promising results, a recent retrospective study reported the alarming emergence of ceftazidime-avibactam resistance in 8% (3/37), including 30% of microbiological failure in patients with CRE infection, after drug exposure as first-line therapy[67]. In our opinion, we believe that that ceftazidime-avibactam is an important addition to the limited antimicrobial armamentarium against CRE infections, which is at least as efficacious as alternative regimens and likely to be better tolerated but combination therapy should be strongly considered both in empirical and target therapy.

Meropenem/Vaborbactam

Vaborbactam (formerly RPX7009) is a β-lactamase inhibitor that displays potent inhibition of KPC enzymes, other Ambler class A and C enzymes. This inhibitor is in clinical development in combination with meropenem.[68] A phase III TANGO 3 trial in the United States and the European Union is ongoing with the purpose to determine the efficacy, safety, tolerability, and pharmacokinetics of meropenem-vaborbactam compared with piperacillin/tazobactam for 7 to 14 days in the treatment of HAP/VAP (available at: www.ClinicalTrials.gov Identifier: NCT03006679).

Imipenem/Relebactam

Relebactam is an investigational, intravenous, class A and C, β-lactamase inhibitor currently being evaluated in combination with imipenem/cilastatin for the treatment of certain complicated GNB infections. Two pivotal phase 3 clinical studies of relebactam in combination with imipenem/cilastatin are currently ongoing and recruiting patients. One study is comparing treatment with imipenem/relebactam, as a fixed-dose combination, with piperacillin/tazobactam in patients with HAP/VAP (available at: www.ClinicalTrials.gov Identifier: NCT02493764). A second study is evaluating the efficacy and safety of imipenem/relebactam versus colistimethate sodium in combination with imipenem in the treatment of imipenem-resistant bacterial infections, including those caused by KPC-producing organisms. Infections evaluated in this study include HAP/VAP (available at: www.ClinicalTrials.gov Identifier: NCT02452047).

Plazomicin

Plazomicin is a new generation aminoglycoside, known as neoglycoside, which inhibits bacterial protein synthesis and exhibits dose-dependent bactericidal activity. No evidence of ototoxicity or nephrotoxicity was observed in healthy subjects administered with escalating single and multiple doses of plazomicin.[39] A phase III clinical trial (CARE) is currently recruiting participants comparing the efficacy and safety of plazomicin with colistin when combined with a second antibiotic (either meropenem or tigecycline) in the treatment of patients with HAP/VAP due to CRE (available at: www.ClinicalTrials.gov, Identifier: NCT01970371).

Nebulized Antibiotics

Another interesting approach for optimizing HAP/VAP therapy involves the delivery of high drug concentrations to the lung via aerosolization.[69,70] Theoretical benefits of local delivery include increased antibiotic concentration at the site of infection and low systemic absorption leading to decreased adverse effects and superinfections.[34] However, a recent report of the prevalence and current practices of administration of nebulized antimicrobial agents in ICUs worldwide found the use of inhaled antibiotics to be common, but with a significant heterogeneity in indications for the use and the choice of drug regimens.[71] Aerosolized antibiotics have been used off-label for the treatment of pneumonia in mechanically ventilated, critically ill patients for around 40 years, but there is still no consensus, guideline or Food and Drug Administration-approved product available for such treatment.

The recent Infectious Diseases Society of America (IDSA) VAP guidelines recommend using nebulized antimicrobial agents and systemic antibiotics, rather than systemic antibiotics alone, particularly in pulmonary infections caused by MDR GNB (susceptible to only aminoglycosides or polymyxins) in spite of limited evidence.[1] Some authors believe that routine use of aerosolized antibiotics is the most rational approach to the current treatment dilemmas for severe HAP/VAP caused by MDR GN.[40]

Available formulations for nebulization which could be treatment options for CRE HAP/VAP include gentamicin, amikacin, tobramycin, aztreonam, and colistin (►**Table 3**).[71] Ongoing, prospective, RCTs with aerosolized antibiotics appear to be promising[71] and are currently focused on a combination of amikacin and fosfomycin (PARI eFlow rapid nebulizer system), inhaled tobramycin (Tobi, Micromedex) and a specially formulated amikacin inhalation solution (Amikacin inhale, Bayer HealthCare and Nektar Therapeutics).[69]

Duration of Treatment

There is no consensus regarding the duration of antibiotic treatment for patients with VAP due to MDR-GNB. A multicenter RCT clearly demonstrated no survival benefit to long course (14–15 days) compared with short course (7–8 days) antibiotic therapy.[72] A higher recurrence rate (40.6 vs. 25.4%) for patients infected with *P. aeruginosa* and other non-fermenters in the 8-day group led some to call for longer treatment despite no difference in overall mortality.[72] A recent meta-analysis also concluded that a short course of antibiotic may be enough to treat VAP although the issue of length of therapy in MDR VAP was not specifically assessed.[73]

The IDSA now recommend a 7-day course of antimicrobial for patients with VAP and HAP (strong recommendation)[1] and duration of antibiotic therapy to be individualized according to the clinical and biohumoral response with procalcitonin (PCT).[1] Multiple studies have shown that antibiotic therapy guided by PCT values, compared with outcomes in standard therapy, are not burdened with a higher mortality rate or treatment failure and allow significant reductions in consumption, toxicity, and selective pressure related to antibiotic therapy.[74] A recent prospective study showed that a PCT-based strategy, stopping antibiotics with PCT < 0.5 ng/mL or decreased by $\geq$80% did not negatively influence outcomes although the subgroup of patients with MDR-GN-VAP has not been specifically evaluated.[75] In our experience for patients with CRE HAP/VAP, we suggest a close monitoring of patient's clinical progression, ventilator support evolution, radiologic resolution, and serial biomarker monitoring to better define and individualize the optimal stopping time of the antibiotic therapy.

Conclusion

Empirical and target treatment of HAP/VAP caused by CRE is a growing cause for concern in daily clinical practice. New therapeutic options are urgently needed. Continued improvements in antibiotic formulations and nebulizer system designs are a promising outlook for the future of inhaled antibiotics.

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Infections Due to *Acinetobacter baumannii* in the ICU: Treatment Options

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Abstract

Bacteria within the genus *Acinetobacter* (principally *A. baumannii-calcoaceticus* complex [ABC]) are gram-negative coccobacilli that may cause nosocomial infections in critically ill or debilitated patients (particularly ventilator-associated pneumonia and infections of the bloodstream, urinary tract, and wounds). Treatment of *Acinetobacter* infections is difficult, as *Acinetobacter* spp. are *intrinsically* resistant to multiple antimicrobial agents, and have a remarkable ability to *acquire new resistance determinants* via mechanisms that include plasmids, transposons, integrons, and resistance islands. Since the 1990s, global resistance to antimicrobials has escalated dramatically among ABC. Global spread of multidrug-resistant (MDR)-*A. baumannii* strains reflects dissemination of a few clones between hospitals, geographic regions, and continents; excessive use of antibiotics amplifies this spread. Many isolates are resistant to all antimicrobials except colistin (polymyxin E) and tigecycline, and some infections are untreatable with existing antimicrobial agents. Antimicrobial resistance poses a serious threat to treat or prevent infections due to ABC. Strategies to curtail environmental colonization with MDR-ABD will require aggressive infection control efforts and cohorting of infected patients. Thoughtful antibiotic strategies are essential to limit the spread of MDR-ABC. Optimal therapy will likely require combination antimicrobial therapy of existing antibiotics as well as development of novel antibiotic classes.

Keywords

- multidrug resistance
- antimicrobial resistance
- *Acinetobacter* spp.
- *Acinetobacter baumannii*
- plasmids
- clonal spread
- carbapenemases

Microbiology

Bacteria within the genus *Acinetobacter* are encapsulated, non–lactose fermenting, oxidase-negative gram-negative coccobacilli that may cause infections in health care or community settings, particularly in patients with comorbidities or skin/soft-tissue injuries.[1–3] More than 20 *Acinetobacter* species have been identified,[1] but the vast majority of clinical infections are caused by organisms within the *A. calcoaceticus-A. baumannii* complex (ABC).[1,4–6] This complex comprises four species; *A. baumannii*, *A. nosocomialis*, and *A. pittii* cause clinical infections in humans, whereas *A. calcoaceticus* is an environmental organism of negligible clinical significance.[1] *A. baumannii* is the most common species in most regions; the prevalence of *A. pittii* and *A. nosocomialis* is higher in Southeast Asia and *A. pittii* may be more common in Scandinavian countries.[6–8] *A. baumannii* has been associated with heightened mortality and a higher degree of antimicrobial resistance compared with other *Acinetobacter* spp.[1,6,9]

Clinical Features

Acinetobacter species (spp.) most frequently cause nosocomial infections in critically ill or debilitated patients,[10,11] including ventilator-associated pneumonia (VAP),[10,12–14] bloodstream infections (BSI),[6,11,15] device-associated

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infections (DAI),[16] wound or skin and soft-tissue infections (SSTI),[1,17] burns,[18,19] urinary tract infections (UTI),[1] intra-abdominal infections (IAI),[17] and meningitis.[1] Additionally, *Acinetobacter* spp. have been implicated in SSTI sustained during disasters, including earthquakes,[20] tsunamis,[21] terrorist attacks,[22] and combat injuries in Vietnam,[23] Iraq and Afghanistan,[24,25] Ukraine,[26] Lebanon, and Syria.[1,27] Infections due to *Acinetobacter* spp. occur more frequently in subtropical or tropical regions; in temperate climates, infections are more common in the summer.[1,24,28] Community-acquired pneumonia (CAP) due to ABC rarely occurs in temperate climates, but fulminant CAP, sometimes with septic shock, has been described in Asian-Pacific regions.[2,3,29–31] Factors predisposing to ABC-associated CAP include alcoholism,[32,33] diabetes mellitus, male gender, renal or pulmonary disease, cirrhosis, advanced age, smoking.[3,31]

Prognosis of Infections Due to *A. Baumannii*

Mortality rates with VAP or BSI due to *Acinetobacter* spp. are 30 to 75%; these high mortality rates in part reflect comorbidities and severity of illness.[1,15,34–37] In the EPIC II study, a multinational study of 14,414 ICU patients, infection with ABC was independently associated with a greater risk for hospital death (odds ratio [OR]: 1.53, $p < 0.001$).[38] Within the past three decades, resistance rates among ABC have escalated globally.[1] Emergence of multidrug-resistant (MDR) strains has undoubtedly contributed to mortality. Not surprisingly, inappropriate initial empiric antibiotic therapy (IET) for pneumonia or sepsis due to ABC has been associated with heightened mortality.[39–41] In a recent retrospective review of 1,423 patients hospitalized with sepsis or pneumonia due to ABC, 82.3% of isolates were MDR.[40] MDR-ABC strongly predicted receipt of IET (OR: 5.5, $p < 0.001$) and IET was associated with higher hospital mortality (OR: 1.8, $p < 0.001$).[40] In light of the rising incidence of MDR-ABC,[42] a multinational consensus statement was recently published regarding the management and prevention of *A. baumannii* infections in the ICU.[43]

Infections Due to ABC in the Hospital Setting

ICU Infections

Most ABC infections occur in hospitalized patients in the ICU, often with multiple comorbidities. Device-related infections (DRI) are typical (i.e., VAP, central venous catheter [CVC]-associated BSI, surgical site infections (SSI), catheter-associated UTIs). The EPIC II point prevalence study in 2007 comprising 75 countries implicated *Acinetobacter* spp. in 8.8% of all ICU infections, with rates of 19% in Asia and 17% in Eastern Europe.[38] In the SENTRY study from January 2009 to December 2011, ABCs were implicated in 7% of ICU infections in the United States and Europe.[44] Even higher rates of ABC infections have been reported in Latin America[45,46] and Asia.[17,47,48] In a review of Vietnamese pediatric ICUs, ABC was implicated in 18.4% of hospital-acquired infections (HAI); 65% of isolates were carbapenem resistant (CPR).[49] In a prospective study from six hospitals in Iran (2011–2012), ABC was implicated in 35% of DRI among hospitalized adults.[16] Importantly, 70.5% were CPR.

Hospital-Acquired Pneumonia

ABC is a common cause of ICU-acquired pneumonia, accounting for 8 to 14% of VAP in the United States[50] and Europe,[51] but much higher rates (19% to >50%) in Asia,[48,52] Latin America,[53] and some Middle Eastern[54] countries. In the United States, rates of VAP due to ABC increased from 4% in 1986 to 7.0% in 2003; no increase was observed for any other gram-negative bacilli.[55] Data from 463 hospitals in the United States from January 2006 to October 2007 implicated *A. baumannii* in 8.4% of VAP.[50] In a study of 411 cases of VAP from nine European countries, *A. baumannii* was implicated in 13.9% of cases.[51] In a cohort of 827 cases of VAP in 27 ICUs in Europe, *A. baumannii* was implicated in 11% of early-onset and 26.5% of late-onset VAP.[56] In Greece and Turkey, ABC was the most common cause of VAP.[56] One prospective study in Turkey implicated ABC in 54% of VAP.[54] Rates of VAP due to ABC are high in tropical or subtropical regions, particularly in Asia. In a series of 621 cases of VAP in Japan from 2005 to 2011, *Acinetobacter* accounted for 54.3% of cases.[52] A prospective study in 10 Asian countries from 2008 to 2009 of HAP in adults ($n = 2{,}554$) implicated *Acinetobacter* spp. in 36.5% of cases.[47] Importantly, 67.3% of *Acinetobacter* spp. isolates were resistant to imipenem.[47]

Risk Factors for Colonization or Infection with *Acinetobacter* spp.

In critically ill patients, *Acinetobacter* spp. may colonize the gastrointestinal (GI) tract, skin, and respiratory tract, and may cause serious infections.[1,24] Risk factors for acquisition of *Acinetobacter* spp. include invasive procedures or devices, prolonged ICU stay, mechanical ventilation (MV), enteral feedings, burns, and recent use of broad-spectrum antibiotics, particularly cephalosporins (CEPHS) or fluoroquinolones (FQs)[1,24,34,57,58] (►**Table 1**). A prospective study identified the following independent risk factors for ICU-acquired *A. baumannii*: (1) prior occupant in that room with *A. baumannii* (OR: 4.2, $p < 0.001$) and (2) MV (OR: 9.3, $p < 0.05$).[59] Diabetes mellitus may increase the risk of recurrent or persistent colonization with ABC.[60] Risk factors for ABC bacteremia among ICU patients include colonization with ABC; high APACHE II scores; MV; presence of an endotracheal tube; recent invasive procedures; CVCs; and prior antimicrobials.[1] In one study, colonization of CVCs with MDR-ABC was associated with a 28% risk of subsequent bacteremia.[61] Studies in patients with malignancies cited the following risk factors for *A. baumannii* infection: CVC and nasogastric tubes,[62] admission to the ICU,[63] dialysis, and prolonged ICU stay[64]; hematological malignancies; use of cefepime; and use of total parenteral nutrition (TPN).[57] In neonatal ICUs, low birth weight, TPN, and presence of CVCs were risk factors for bacteremias due to ABC compared with uninfected infants.[65]

Table 1 Risk factors for *Acinetobacter* acquisition or infection

Risk factor	Reference
Invasive procedures, devices	62,65
ICU admission and/or prolonged stay	1,64,67
Mechanical ventilation and duration of mechanical ventilation	59,64,67
Nasogastric tube	62
Receipt of broad-spectrum antibiotics	57,62,64,67
Receipt of fluconazole	67
Prior hospital room occupant with *A. baumannii*	59
Colonization with *Acinetobacter*	1
Severity of illness score	67
Dialysis	64
Total parenteral nutrition	57,65
Hematologic malignancy	57
Exposure to contaminated fomites	43,66,67
Chronic pulmonary disease	67

Acinetobacter spp. are ubiquitous and may survive for prolonged periods on wet or dry surfaces.[24,34] Contaminated environmental sources and transmission via medical personnel may cause outbreaks of nosocomial infections.[43,66,67] Acquisition and spread of ABC has been noted in hospitals,[66] rehabilitation centers, and long-term care facilities (LTCFs), among pilgrims returning from the Hajj (Makkah)[68] and in the community (particularly among the elderly).[1,2] Colonized or infected patients, selection pressure from antimicrobial use, and incomplete compliance with infection control procedures may facilitate persistence or spread of MDR-ABC within hospital or institutional settings.[1,66] Removal or disinfection and sterilization of contaminated equipment (e.g., ventilator or nebulizer tubing) or fomites may eliminate the problem.[24,66] An outbreak of MDR-ABC in a surgical ICU was linked to aerosolization of ABC during pulsatile lavage of wounds.[67] Multifaceted infection control measures led to control of the outbreak. Interestingly, additional risk factors for acquisition of MDR-ABC included receipt of fluconazole (OR: 73.3), receipt of levofloxacin (OR: 11.5), and chronic pulmonary disease (OR: 11.5).[67]

ABC Virulence Factors and Pathogenesis

The virulence mechanisms and pathogenesis of *A. baumannii* infections have been reviewed elsewhere.[69,70] *A. baumannii* has simple growth requirements and may survive in dry and desiccated conditions for prolonged periods[1,69]; further, *A. baumannii* is able to adhere to living or inert surfaces and form biofilms.[1,2] Additional bacterial factors that may heighten survival and virulence include outer membrane porins, capsule, lipopolysaccharide, regulatory proteins, and iron acquisition systems.[1,2,71]

Mechanisms of Antimicrobial Resistance

Acinetobacter spp. have innate (chromosomal) resistance mechanisms against multiple antimicrobials but also can acquire new resistance determinants via mobile genetic elements such as plasmids, transposons, integrons, insertion sequences, and resistance islands.[1–3,69,72–74] Mechanisms of antimicrobial resistance are numerous and include (1) enzymatic inactivation or modification of antimicrobials; (2) alteration in the bacterial target site(s); (3) permeability barriers to uptake of antimicrobials; (4) active efflux pumps (that extrude antibiotics from bacterial cells); (5) combinations of mechanisms, which may occur as the result of large genomic islands containing multiple resistance genes.[1–3,70,72]

Global Escalation of Antimicrobial Resistance

Within the past three decades, antimicrobial resistance rates among ABC have escalated dramatically worldwide.[17,72,75] In some countries, more than 90% of ABCs are MDR.[17] Molecular-based strain typing by pulse field gel electrophoresis (PFGE) or multilocus sequence typing (MLS) methods has documented global spread of MDR "epidemic clones" between hospitals, regions, and continents.[72] International spread has been extensively documented: for example, between Brazil and Argentina[76]; from Iraq to Germany and the United States among military personnel[77,78]; from northwestern Europe to the Czech Republic and globally[79]; from Turkey to Europe, the Middle East, and the rest of Asia[80]; from southern to northern Europe, the Middle East, rest of Asia, and Latin America[81]; from Europe to multiple continents.[34] The rate of increase may be amplified by selection pressure from antimicrobial use, crowding, lack of hygiene, and increased worldwide travel.[24,34]

Impact of Antimicrobial Use on Antimicrobial Resistance

Not surprisingly, the use of broad-spectrum antimicrobials has been linked to emergence of antimicrobial resistance. In the early 1990s, the use of imipenem against cephalosporin-resistant *Klebsiella pneumoniae* was associated with emergence of imipenem-resistant ABC in one New York hospital.[82] Further, in multiple hospitals in Brooklyn, New York, there was an association between the use of third-generation CEPHS and aztreonam and CP-resistant ABC.[83] In one case–control study in a surgical ICU, risk factors for acquisition of imipenem-resistant (IR) and imipenem-susceptible (IS) strains of *A. baumannii* were assessed.[84] Risk factors for IR-ABC were ICU stay (OR: 21.5), prior exposure to imipenem (OR: 9.2), and prior exposure to third-generation CEPHS (OR: 2.1). Risk factors for IS-ABC include ICU stay (OR: 8.1) and prior exposure to third-generation CEPHS (OR: 2.1). Regionally and globally, selection pressure is the key determinant of emergence of CPR or MDR-ABC.

Resistance to β-Lactams

β-Lactamases

All *A. baumannii* strains possess a chromosomal AmpC cephalosporinase that confers resistance to penicillins and early-generation cephalosporins (CEPHS); however, under normal circumstances, resistance to third- and fourth-generation CEPHS due to AmpC is *clinically insignificant*.[24,85] *Clinically significant* resistance may develop via hyperproduction of the AmpC cephalosporinase,[85] the presence of insertion sequences that promote β-lactamase activity,[46] or incorporation of mobile resistance genes.[86]

β-Lactamases are categorized based on molecular structure into groups A through D and functionally into three groups (1–3) based on the target enzyme they degrade.[87,88] Group 1 (class C) cephalosporinases are relatively narrow spectrum. Group 2 (classes A and D) include serine β-lactamases and extended-spectrum β-lactamases (ESBLs) and have a broader spectrum of activity.[88] Group 3 enzymes include metallo β-lactamases (class B), which are potent hydrolyzers of CP and are not inhibited by β-lactamase inhibitors.[88] β-Lactamases of the IMP, VIM, SIM, and NDM-1 families fall within Group 3.[74]

Extended-Spectrum β-Lactamases

Numerous extended-spectrum β-lactamases (ESBLs) including SHV, TEM, PER, VEB, GES, and CTX-M confer high-grade resistance to all CEPHS.[1,34] ESBL clones (TEM or SHV) were initially described in *Enterobacteriaceae* in France and Belgium in the late 1980s and mid-1990s,[89,90] and rapidly spread globally.[91] By the late 1990s, other plasmid-encoded ESBLs (e.g., PER-1, VEB, CTX-M, and GES) were described among *Enterobacteriaceae*[91] and less commonly among *P. aeruginosa* and *Acinetobacter* spp.[34] ESBL-containing plasmids (PER-1 type) among *A. baumannii* (as well as *P. aeruginosa*, and *Klebsiella* spp.) were first recognized in the late 1990s in Turkey[80] and France[92] and spread globally.[34] Clusters of ABC infections due to VEB-1 type ESBL were noted among French hospitals in 2003.[93] Rapid clonal spread to Belgium,[94] Argentina,[95] Lebanon,[34] and globally[34] ensued. Other ESBLs identified in ABC include TEM-92 and -116 from Italy and the Netherlands, respectively; SHV-12 from China and the Netherlands, CTX-M-2 and CTX-M-43 from Japan and Bolivia, respectively.[4] Later, CTX-M ESBLs were detected in India,[96] Haiti,[97] Brazil,[98] and globally.

Carbapenemases

Many β-lactamases (including ESBLs) may also have hydrolytic activity against CPs via production of carbapenamases (CPE). The emergence of carbapenemases has created a major "hole" in antibiotic coverage against ABC. Carbapenemases include group 2 class D oxacillinases (e.g., OXA enzymes) and class B metallo-β-lactamases (MBLs) (e.g., IMP, VIM, and SIM-1 groups)[34,85] and the newer CPE (i.e., KPC-like; GES-like,[99–102] New Delhi metallo-β-lactamase-1 [NDM-1]).[1,69,103,104]

Class D Serine Carbapenemases

Globally, the most common CPE in *A. baumannii* are the class D serine oxacillinases (OXA), represented by the OXA-23-, OXA-24-, OXA-58-, and OXA-143-like types that can be encoded on *chromosomes* or *plasmids*.[1,46,105–107] The first CPE (an OXA-type enzyme) in ABC was discovered in Scotland 1985.[108] By the mid-1990s, CPR-ABC clones (principally OXA-type CPE) were noted in Latin America,[46,109] the United Kingdom (UK),[110,111] Europe,[1,34,105] North America,[1,34] Australia,[1] Africa, the Middle East, and Asia.[112] In 2003, the OXA-58 oxacillinase (bla_{OXA-58} gene) was isolated from a CPR-*Acinetobacter* strain in Toulouse, France.[105] Subsequently, OXA-58–producing CPR-ABC strains were reported in other Mediterranean countries (e.g., Lebanon, Turkey)[34] and China.[113] After 2009, ABC-producing OXA-23 (bla_{OXA-23} gene) became the dominant OXA in Europe,[114] United States,[115] Latin America,[106] and globally.[69,116] Three clonal lineages (known as Worldwide Clones 1, 2, and 3) dominate among clinical isolates of MDR-ABC globally.[1,34]

KPC, a CPE, first reported in 1996 in *K. pneumoniae* in North Carolina,[117] spreads rapidly within the northeastern United States [118] and to France,[119] Israel, Greece, Italy,[120] and globally.[91] KPC is encoded on plasmids in *Enterobacteriaceae* and *P. aeruginosa*,[119,121] but has not widely disseminated among ABC. KPC-producing ABCs were detected in 10 isolates of *A. baumannii* in Puerto Rico in 2010.[122] To our knowledge, KPC-producing ABCs have *not* been reported in other countries.[121]

A newer group of CPEs termed GES (Guiana extended-spectrum β – lactamases) was first identified in *K. pneumoniae* in 2000, and later reported in *Acinetobacter* spp. in France in 2009[123] followed by rapid spread to Belgium,[100] the Middle East, and Northern Africa.[99,101,102,124–126]

A novel CPE, termed NDM-1, was first detected in a *K. pneumoniae* isolate in a Swedish patient transferred from India.[103] Retrospective studies showed that NDM-1 had been endemic among *K. pneumoniae* and *Escherichia coli* in Indian hospitals since 2006.[127] By 2010, NDM-1-producing *Enterobacteriaceae* had been found on five continents and linked to travel in India or Pakistan.[128] In the United States, three cases of infections due to NDM-1-producing *Enterobacteriaceae* were reported in 2010; all three had recently received medical care in India.[129] From 2010 on, numerous publications cited NDM-1-producing ABC in Europe,[72,126,130–134] the Middle East,[135–138] Africa,[132,139–144] Asia.[145–149] Epidemiological reviews suggest that the majority of infections due to NDM-1-producing ABC occur in India, Asia, the Middle East, and the Balkans.[104] Berrazeg et al reviewed all publications of infections due to NDM-1-producing bacteria from 2009 to December 31, 2012, and identified 950 cases.[104] Only 36 cases (3.8%) were due to ABC. Although infections due to NDM-1-producing ABC have been cited in Brazil,[150] Paraguay,[151] Argentina,[152] and Honduras,[153] NDM-1-producing ABC appears to be rare in the Americas.

Epidemiology and History of Antimicrobial Resistance among *Acinetobacter* spp.

In the 1970s, *Acinetobacter* spp. were usually susceptible to ampicillin, cephalosporins, carbapenems (CPs), and several antibiotic classes.[1] By the 1980s, resistance to various classes of antibiotics appeared, but nearly all isolates remained

susceptible to CPs. In the early 1990s, carbapenem-resistant (CPR) strains emerged.[1] Importantly, CPR-ABCs are often resistant to all classes of antimicrobials except colistin and tigecycline.[1,34] Ominously, strains of *Acinetobacter* resistant to colistin and tigecycline have been reported.[154,155] Drug resistance has an adverse impact on clinical outcomes. Compared with patients with CP-susceptible strains, patients with CPR-ABC infections have increased mortality and increased hospital and ICU length of stay.[1]

In the United States (and globally), CPR-ABCs have escalated dramatically over the past two decades. In the National Nosocomial Infections Surveillance (NNIS) System, CPR-ABC (ICU isolates) in the United States increased from 0% in 1986 to 20% in 2002.[55] In a survey of more than 300 hospitals in the United States, CPR-*A. baumannii* increased from 9% in 1995 to 40% in 2004.[24] The MYSTIC Study surveyed changes in antimicrobial resistance from clinical isolates from 15 U.S. hospitals over a decade; resistance to imipenem increased from 10% in 1999 to 48% in 2008.[156] The Surveillance Network (TSN) database examined more than 55,000 isolates of *Acinetobacter* spp. in the United States from 2002 to 2008; CPR increased from 20.6% in 2002 to 49.2% in 2008.[157] A survey of nine regions in the United States from 2005 to 2011 found that 30% of 2,900 isolates of ABC were MDR.[158] Another study in the United States in 2010 noted that 50% of 514 clinical isolates of ABC were CPR.[159] In the SENTRY study from 2009 to 2011, susceptibility rates to imipenem in the United States were 43% (ICU) and 63% (non-ICU) and in Europe 45% (ICU) and 56% (non-ICU).[44]

Worldwide, rates of CPR-ABC have been highest in Greece, Taiwan, and Latin America,[46,106,160–162] but remarkable differences between countries have been noted.[17,163] A survey of 48 European hospitals (MYSTIC) in 2006 cited CPR in 42.5% of ABC clinical isolates.[164] In the COMPACT study from 2008 to 2009 in Europe, the Middle East, and Africa, 49% of ABC isolates were resistant to imipenem.[163] Resistance rates were higher in Turkey, Greece, Italy, Spain, and England (45–85%) compared with France, Germany, and Sweden (4–20%).[163] In one tertiary care hospital in the United Kingdom, CPR among ABC bloodstream isolates (BSI) rose from 0% in 1998 to 55% in 2006.[111] A survey of 11 countries in Latin America in 2011 found that more than 50% of ABC clinical isolates were CPR.[160] In the SENTRY study of ABC isolates from 2006 to 2009, *global* CPR rates rose from 34.6% in 2006 to 59.8% in 2009.[165] The SMART surveillance study of urinary tract and IAI ABC isolates from 48 countries from 2011 to 2014 cited MDR ranging from 47% in North America to more than 93% in Europe and the Middle East.[17] In China, 58% of blood stream isolates of ABC in 2013 were CPR.[112] The SMART surveillance study, comprising 48 countries from 2001 to 2014, evaluated CPR resistance among ABC isolates from intra-abdominal and UTI.[17] The incidence of MDR-ABC was lowest in North America (47%) and ranged from 77 to 87% in Africa, Asia, and Latin America, and exceeded 93% in Europe and the Middle East.[17] This extraordinary rate of CPR-ABC reflects selection pressure from antibiotic usage. The use of CPs has been associated with increased incidence of CPR-ABC.[162,166] In one study, the prevalence of infections due to MDR-ABC fell 2.24-fold after implementing a policy of restricting CP use in the ICU.[167]

Treatment of Infections Due to *Acinetobacter* spp.

Nosocomial infections due to ABC have been associated with high mortality rates (particularly with BSI or VAP).[24,34,35] Early appropriate antimicrobial therapy is critical.[3,11,35] Optimal therapy for serious ABC infections has not been established,[1] as prospective randomized trials have not been done. For BSI, removal of invasive devices within 48 hours may reduce mortality.[11] For SSTI or SSIs, debridement is an essential part of therapy.[24] Carbapenems, alone or combined with a second agent, has been considered the best therapy for ABC infections.[1,34] However, the emergence of CPR strains limits the use of these agents as monotherapy for *empirical* treatment *when CPR is a consideration*. We believe a combination of a carbapenem plus colistin is appropriate as *initial empirical* therapy for serious *A. baumannii* infections when CPR is suspected.[43] Other agents (e.g., β-lactam/β-lactamase inhibitors, ceftazidime, or FQs) may be used, provided isolates are susceptible.

Advanced Generation Cephalosporins

Third- and fourth-generation cephalosporins (e.g., ceftazidime, cefepime) are not reliable for empirical treatment of infections due to ABC. Globally, only 20 to 40% of ABCs are susceptible to expanded spectrum CEPHS.[17] CEPHS should not be used as empirical treatment for ABC infections, but may be considered for susceptible strains.

Sulbactam

Among β-lactamase inhibitors, sulbactam has the greatest bactericidal activity against ABC.[1] Ampicillin-sulbactam (A/S) (due to the sulbactam component) may be effective therapy for some strains of ABC.[168] High-dose A/S and extended time of infusion may enhance bactericidal activity.[169] Clinical data supporting the use of sulbactam are limited to small series.[168,170] Sulbactam may display synergy against ABC when combined with other antibiotics (e.g., CP, colistin).[171]

Fluoroquinolones

Fluoroquinolones may be active against some strains of ABC, but globally, fewer than 30% of ABCs are susceptible to FQs.[17] FQ resistance can emerge via mutations in the quinolone resistance determining regions (QRDR) of *gyrA* and *parC* genes and/or by overexpression of efflux pumps.[69]

Aminoglycosides

Aminoglycoside resistance among ABCs may emerge via the production of aminoglycoside-modifying enzymes, 16S ribosomal RNA methyltransferase (ArmA), or efflux pumps.[1] In one French study, increased use of amikacin was associated with emergence of amikacin-resistant ABC; decreased amikacin use led to a decrease in case incidence.[172] The

activity of aminoglycosides against ABC is variable, but resistance rates exceed 60% in most countries.[173] See ►**Table 2** for summary of antimicrobial resistance mechanisms among *Acinetobacter* spp.

Treatment of Infections Due to *Acinetobacter* spp.

In view of the high incidence of MDR-ABC, initial empirical therapy with combination therapy (typically CP plus colistin) is often employed while awaiting antimicrobial susceptibility results. Optimal therapy is not clear, as randomized, controlled studies are lacking. In the next sections, we will discuss antibiotics that are often used either as monotherapy or part of combination therapy for MDR-ABC.

Polymyxins (Colistin)

Polymyxins (e.g., polymyxin B and polymyxin E [colistin]) are cationic lipopeptides that disrupt the outer membrane of gram-negative bacteria and are rapidly bactericidal.[155] Polymyxins are usually highly active against MDR-ABC, including isolates resistant to tigecycline.[1] Colistin is administered intravenously as an inactive prodrug (colistimethate sodium [CMS]), whereas polymyxin B is an active drug. CMS is widely available, whereas polymyxin B is infrequently used. Resistance rates to colistin are generally low (< 1%),[174] but colistin resistance among ABCs has been increasing.[155,175] In a survey of 514 ABC isolates from 65 sites in the United States and Puerto Rico in 2010, 5% of isolates were resistant to colistin.[159]

Colistin can be administered by intravenous (IV) or inhaled routes.[1] IV colistin has potential renal toxicity[1] and neurotoxicity (principally paresthesias).[1] Risk factors for nephrotoxicity include colistin dose > 5 mg/kg/day ideal body weight[176] and concomitant use of rifampicin or nephrotoxins.[176] Optimal dosing regimens for IV colistin have not been established.[1,177] Colistin exhibits a concentration-dependent bactericidal activity; therapeutic effect depends on the ratio of peak serum concentration to minimum inhibitory concentration (MIC) or the ratio of the area under the curve (AUC) to MIC.[1] Strategies involving higher doses, longer dosing intervals, loading doses, extended infusions, and pharmacokinetic/pharmacodynamic (PK/PD) principles have been proposed to optimize efficacy and prevent the development of resistance.[178–180] However, colistin has relatively poor PK/PD properties, and it may be difficult to achieve high enough serum concentrations quickly.[155] CMS (a prodrug) has to be converted to the active form (colistin) in the plasma, and concentrations may be suboptimal for 2 to 3 days until a steady state is achieved; thus, a loading dose is recommended.[1] One in vitro study suggested that achievement of serum levels more than 1 mg/L within 1 hour had significant bactericidal activity.[181]

Studies reporting efficacy of colistin *monotherapy* for ABC infections are limited. In a prospective study of 35 episodes of VAP due to MDR-ABC, patients were treated with imipenem ($n = 14$) versus colistin ($n = 21$) based on susceptibility testing.[182] Cure rates were 57% in both groups; in-hospital mortality rates were similar (64 and 62%, respectively). The

Table 2 Common mechanisms of antimicrobial resistance in *Acinetobacter* spp.

Resistance mechanism	Target antimicrobial	References
Enzymatic inactivation or modification of antimicrobials		
AmpC β-lactamase with upstream insertion of IS*Aba1*	Cephalosporins	1,46,70
Non-carbapenemase oxacillinases (OXA)	Penicillins, cephalosporins	1,18,45,68,70
Metallo-β-lactamases (IMP, VIM, SIM, NDM-1)	Penicillins, cephalosporins, carbapenems	1,103,124,130,135,145,150,153
Non-metallo-β-lactamase carbapenemases (OXA, KPC)	Penicillins, cephalosporins, carbapenems, monobactams	1,70,122
Extended-spectrum β − lactamases (SHV, TEM, PER, VEB, GES, CTX-M)	Penicillins, cephalosporins, monobactams	1,70,99,101,102,123–125
Aminoglycoside-modifying enzymes (AAC, APH, AAD)	Aminoglycosides	1,70
Modification of drug target site		
*gyr*A and *par*C mutations	Fluoroquinolones	1,69,70
Alteration of ribosomal-binding site (RmtB, ArmA)	Aminoglycosides	1,70
Altered lipid A of bacterial lipopolysaccharide (PmrAB two-component system mutation)	Colistin	1,70
Loss of lipopolysaccharide (mutated lpxA, lpxC, lpx D)	Colistin	1,70
Altered cell permeability		
Porin/outer membrane protein loss	Carbapenems, aminoglycosides	70
Efflux pumps		
RND efflux pump (AdeABC, AdeFGH, Ade IJK, AbeM)	Fluoroquinolones, β-lactams, aminoglycosides, tetracyclines	1,70

impact of combination therapy has not been elucidated. Turkish investigators retrospectively assessed clinical outcomes in 250 patients with BSI due to extremely resistant ABC.[183] Thirty-six patients received colistin monotherapy; 214 received colistin plus a second agent. All isolates were susceptible to colistin. In-hospital mortality was lower in the combination group compared with monotherapy group (52.3 vs. 72.2%, $p = 0.03$) and rate of microbiological eradication was higher in the combination therapy compared with monotherapy (79.9 vs. 55.6%, $p = 0.001$). By multivariate analysis, Pitt bacteremia score, age, and duration of ICU stay were independent predictors of 14-day mortality. An observational study of 28 Spanish hospitals assessed 30-day mortality rates among 101 patients with serious infections due to MDR-ABC.[184] Pneumonia was present in 50.5%. Sixty-eight patients received monotherapy (MT) (usually a CP or colistin); 33 received combination therapy (CT). Thirty-day mortality rates were similar (23.5% for MT; 24.2% for CT; $p = 0.94$). Another observational study reviewed 69 organ transplant recipients either colonized ($n = 28$) or infected ($n = 41$) with XDR *A. baumannii*.[185] Among 41 patients with infections, 37 received antimicrobial therapy. Clinical success at 28 days was achieved in 18/37 (49%), but clinical recurrence developed within 3 months in 8 of 18 (44%) within 3 months. Further, colistin resistance developed in 5 of 14 patients. The use of combination therapy with colistin and a carbapenem was an independent predictor of survival.[185] These various retrospective studies are inadequate to assess the role or benefit (if any) of combination therapy or the optimal agents to use for serious infections due to ABC.

Aerosolized (inhaled) colistin has been used in patients with cystic fibrosis and as adjunctive therapy for nosocomial pneumonia due to ABC, but data are limited to nonrandomized, retrospective studies.[1,186] One randomized open-label trial compared the efficacy of nebulized CMS (plus IV colistin) for 100 patients with gram-negative VAP, 60% of which were due to ABC. Microbiological outcome was better with nebulized *plus* IV therapy (60.9%) compared with 38.2% among IV CMS *only* group ($p = -0.03$). Importantly, clinical outcomes were similar (51.0 vs. 53.1%, $p = 0.94$). Further, there were more episodes of bronchospasm in the nebulized plus IV therapy group (7.8 vs. 2.0%, respectively, $p = 0.36$). The clinical benefit of nebulized CMS to treat VAP has not been established.

Resistance to colistin may develop.[185] Plasmid-mediated resistance via *mcr-1* gene among *Enterobacteriaceae* was first reported China,[187] and human cases of *E. coli* or *Enterobacteriaceae* expressing *mcr-1* were described shortly thereafter in Switzerland,[188,189] Canada,[190] and Singapore.[191] The *mcr-1* gene has not yet been identified in *Acinetobacter* spp., but it is feasible that in time, MDR *Acinetobacter* could acquire this resistance mechanism. Colistin heteroresistance may also occur.[155] Colistin-resistant ABCs appear to have reduced fitness and less virulence,[192] including a decreased ability to form biofilms.[193]

Tigecycline

Tigecycline, a semisynthetic derivative of minocycline, has excellent in vitro activity against MDR-ABC (including CPR strains).[194,195] However, clinical studies assessing efficacy of tigecycline for serious ABC infections are limited. Favorable clinical responses have been cited with tigecycline (alone or in combination with colistin) in some patients with MDR-ABC infections,[1,196] but large, randomized trials are lacking. In one retrospective study, 266 patients with XDR-ABC infections treated with tigecycline *alone or combined with other agents* (i.e., CP, extended-spectrum CEPH, or piperacillin-tazobactam) were compared with 120 patients who received imipenem *plus* sulbactam to treat XDR-ABC.[197] All isolates were resistant to all antibiotics tested except tigecycline and colistin. Thirty-day mortality rates were similar (44.7 and 46.7%) between the groups. A prospective multicenter phase III trial cited lower cure rates in patients with ABC-VAP treated with tigecycline (68% cure) compared with imipenem (78% cure).[198] Overall mortality rates were similar with tigecycline (14.2%) and imipenem (12.2%). A retrospective study of adults with pneumonia in the ICU due to MDR-ABC matched 84 patients receiving tigecycline to 84 patients receiving colistin.[199] Mortality was higher (60.7%) among patients receiving tigecycline compared with colistin (44% mortality, $p = 0.04$). This excess mortality was significant only for those with MIC greater than 2 μg/mL.[199] Ye et al retrospectively analyzed 168 hospitalized ICU patients with pneumonia due to ABC treated with either sulbactam or ampicillin/sulbactam ($n = 84$) to patients treated with tigecycline ($n = 84$).[200] Clinical responses (66.7% for each group) and mortality rates were similar (17.9% with sulbactam, 25.0% with tigecycline; $p = 0.26$). Microbiological eradication was achieved more often with sulbactam (63.5 vs. 33.3%).

Tigecycline achieves low peak serum concentrations (< 0.8 mg/L) after a standard 100 mg loading dose,[1] a concentration below the MIC of many ABC isolates. Resistance to tigecycline may develop even while on therapy,[194] and persistence of infection (with or without resistance) may occur.[1] Efficacy of tigecycline for BSI due to ABC therefore cannot be assured. Importantly, tigecycline has been associated with an increased risk of death when studied against comparator antibiotics, especially among patients with hospital-acquired pneumonia (HAP).[201] Higher doses of tigecycline (75–100 mg twice daily) have been recommended by some investigators,[43] but randomized trials have not been done. Given the aforementioned limitations, we do not recommend tigecycline monotherapy to treat serious ABC infections.

Eravacycline

Eravacycline is a novel fluorocycline of the tetracycline class with broad-spectrum activity against gram-negative and gram-positive aerobic and anaerobic pathogens.[202] Like tigecycline, eravacycline is not affected by many of the tetracycline-specific resistance mechanisms found in gram-negative bacteria, including acquired efflux systems and ribosomal protection.[202] Eravacycline is two- to fourfold more active (reduced MIC_{90}) than tigecycline versus *A. baumannii*.[203] Whether this increased in vitro activity translates into greater clinical efficacy is not known.

Other Antimicrobial Agents

Rifampin

Rifampin exhibits activity against MDR-ABC in vitro and in animal models.[1] In animal models, the combination of rifampin *plus* colistin may confer additive or synergic bactericidal activity.[1] However, in two randomized trials of serious MDR-ABC infections, the combination of rifampin *plus* colistin was no better than colistin *alone*.[204,205] The role of rifampin as part of combination therapy has not been established.

Other Combination Therapy Using Colistin

Combination therapy has been studied to treat MDR-ABC, particularly with colistin as part of the combination.[171,183–185,206] In vitro studies have shown that synergy may be achieved with combinations of colistin, carbapenems, and rifampicin, in both colistin-S and colistin-R strains of *Acinetobacter* spp.[207,208] In a retrospective multicenter study, Batirel et al evaluated 250 BSIs due to extremely drug resistant (XDR)-ABC (all isolates were susceptible to colistin).[183] Groups included colistin monotherapy ($n = 36$); colistin + CP ($n = 102$); colistin + sulbactam ($n = 69$); and colistin + other agents ($n = 43$). Complete response rates, 14-day and in-hospital survival, and microbiologic eradication were significantly higher in the combination group, but no differences could be seen between the various combinations.[183] A multicenter prospective observational study in Spain of 101 patients with MDR-ABC infections demonstrated no significant difference in 30-day mortality between combination therapy with colistin versus monotherapy with various agents, predominantly a CP.[184] Cheng et al prospectively studied 176 episodes of bacteremia due to XDR-*A. baumannii* in three hospitals in Taiwan.[206] Among infections with tigecycline MIC > 2 mg/L, combination therapy with colistin plus tigecycline was associated with significantly higher 14-day mortality and more breakthrough bacteremias compared with colistin plus CP.[206]

The addition of glycopeptides (agents with gram-positive activity) to colistin has displayed synergy against ABC in vitro.[155] However, clinical studies are limited, and data are conflicting.[209,210]

Novel Agents

It is obvious that new agents are needed to treat ABC infections. Anti-GNB compounds that belong to old classes of agents such as β-lactams, CPs, FQs, and β-lactamase inhibitors are in development, as are novel classes.[211–214] Ceftazidime/avibactam contains an older third-generation CEPH (i.e., ceftazidime), with avibactam, a synthetic non–β-lactam, β-lactamase inhibitor that inhibits the activities of Ambler class A and C β-lactamases and some Ambler class D enzymes.[215–217] Limited data suggest that the addition of avibactam does not improve the activity of ceftazidime against *Acinetobacter* spp.[215] Ceftolozane is a novel cephalosporin with a chemical structure similar to that of ceftazidime, with the exception of a modified side chain at the three-position of the cephem nucleus, which confers potent antipseudomonal activity.[217,218] The addition of tazobactam extends the activity of ceftolozane to include most ESBL producers as well as some anaerobic species.[218] Limited data suggest that ceftolozane/tazobactam is 8- to 16-fold more active than ceftazidime versus *A. baumannii*.[218] Whether this increased in vitro activity translates into greater clinical efficacy is not known.

Plazomicin is a next-generation aminoglycoside that was synthetically derived from sisomicin.[219] Plazomicin demonstrates activity against both gram-negative and gram-positive bacterial pathogens, including isolates harboring all clinically relevant aminoglycoside-modifying enzymes.[212,216,219] Limited data suggest that plazomicin demonstrates approximately eightfold more active than gentamicin versus *A. baumannii*.[220] Whether this increased in vitro activity translates into greater clinical efficacy is not known.

Among the new classes of antimicrobials, bis-indole compounds inhibit DNA and RNA synthesis and some have had very good in vitro activity against MDR ABC.[221] Applying structure-based drug design, pyrrolopyrimidine agents were developed that inhibit both of the bacterial topoisomerases (DNA gyrase and topoisomerase IV) of GNB including ABC, *Pseudomonas aeruginosa,* and *E. coli*.[222] Antimicrobial peptides, naturally occurring molecules of the innate immune systems of all types of living organisms, are potential new treatments for MDR organisms.[223] Some of these, including melittin, indolicidin, and mastoparan, exhibit activity against colistin-susceptible and colistin-resistant ABC isolates in vitro.[224]

Prevention

Hospital outbreaks of *Acinetobacter* infections may reflect environmental contamination[24,66,225–227] or carriage of *A. baumannii* on the hands of health care workers.[66] Aggressive infection-control measures including identifying sources of transmission,[67,225] environmental cleaning, contact precautions, and hand hygiene and isolating or cohorting infected and colonized patients[66,228] may be critical to stop or prevent outbreaks. In one study, daily chlorhexidine baths in ICU patients reduced the development VAP due to *Acinetobacter*.[229]

Conclusion

The dramatic global rise of antimicrobial resistance among ABCs reflects acquisition of novel resistance elements and spread via a few international clones. Many isolates are resistant to all antimicrobials except colistin, and some infections are untreatable with existing agents. Novel approaches including combinations of agents and extended infusion times may be required to optimize therapy. Appropriate use of antimicrobials and infection-control measures are critical to minimize antimicrobial resistance.[43,66]

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Emergence of Antimicrobial Resistance among *Pseudomonas aeruginosa*: Implications for Therapy

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Abstract

Pseudomonas aeruginosa (PA), a nonlactose fermenting gram-negative bacillus, is a common cause of nosocomial infections in critically ill or debilitated patients, particularly ventilator-associated pneumonia (VAP), and infections of bloodstream, urinary tract, intra-abdominal, wounds/skin/soft tissue. PA rarely affects healthy individuals, but may cause serious infections in patients with chronic structural lung disease, comorbidities, advanced age, impaired immune defenses, or with medical devices (e.g., urinary or intravascular catheters, foreign bodies). Treatment of pseudomonal infections is difficult, as PA is intrinsically resistant to multiple antimicrobials, and may acquire new resistance determinants even while on antimicrobial therapy. Mortality associated with pseudomonal VAP or bacteremias is high (> 35%) and optimal therapy is controversial. Over the past three decades, antimicrobial resistance among PA has escalated globally, via dissemination of several international multidrug-resistant "epidemic" clones. We review the emergence of antimicrobial resistance to this pathogen, and discuss approaches to therapy (both empirical and definitive).

Keywords
- multidrug resistance
- antimicrobial resistance
- *Pseudomonas aeruginosa*
- plasmids
- clonal spread
- carbapenemases
- ventilator-associated pneumonia

Pseudomonas aeruginosa (PA), an aerobic, nonlactose fermenting, gram-negative bacillus (►**Fig. 1**) within the order Pseudomonadales, is a common cause of nosocomial infections in critically ill or debilitated patients (particularly ventilator-associated pneumonia [VAP],[1–7] blood stream infections [BSIs],[8–16] infections of the urinary tract,[12,17,18] skin/soft tissue or wounds,[19–21] burns,[22–25] chronic skin ulcers,[26,27] intra-abdominal infections [IAI]).[28] Rare sites of infection include septic arthritis,[29,30] osteomyelitis,[31] sino-orbital disease,[32] endocarditis,[33–35] and meningitis (particularly following neurosurgery).[36] PA rarely causes community-acquired infections in previously healthy individuals but may cause infections in patients with comorbidities,[37] for example, cystic fibrosis (CF)[38]; chronic structural lung disease (e.g., bronchiectasis,[39,40] severe chronic obstructive pulmonary disease [COPD][37,41,42]); impaired immune defenses (e.g., human immunodeficiency virus [HIV] infection,[43–45] primary immunodeficiency syndromes,[46–51] malignancy with neutropenia or recent chemotherapy,[52–55] and organ transplant recipients[56]); diabetes mellitus[57]; hemodialysis,[37,58–60] intracranial, vertebral, or paraspinal infections (particularly postsurgical)[61–63]; chronic cardiovascular or neurological disease[37]; advanced age[64]; debilitation, multiple comorbidities, difficulty swallowing[64–66]; residence in long-term care facility (LTCF)[65,67,68]; and

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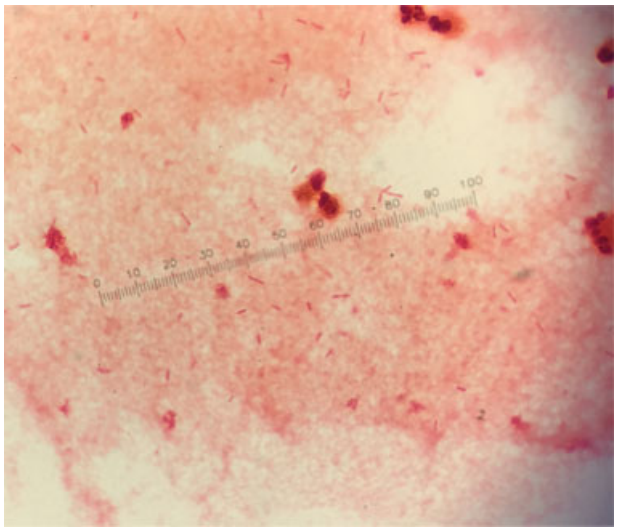

Fig. 1 Gram stain of *Pseudomonas aeruginosa* in body fluid showing long, thin gram-negative rods (×1,000 magnification, scale in microns; photo courtesy of Amanda Harrington, PhD, D(ABMM), Department of Clinical Microbiology, Loyola University Medical Center).

medical devices such as urinary catheters,[69–71] intravascular catheters,[60,72] or endotracheal tubes.[73] In addition, PA may cause the following infections in previously healthy persons in the community: malignant (necrotizing) otitis externa[74,75] (particularly in swimmers),[76] keratitis (often due to contact lens use),[77–79] skin infections (dermatitis, folliculitis) due to contamination of hot tubs or swimming pools,[76,80] and trauma or puncture wounds.[81,82]

Other pseudomonal species (e.g., *Pseudomonas fulva*,[83–85] *Pseudomonas putida*,[84] *Pseudomonas monteilii*,[86] and *Pseudomonas fluorescens*[87]) have rarely been implicated in infections in humans, but may be reservoirs for antimicrobial resistance genes.[88] These species will not be further discussed.

Treatment of pseudomonal infections is difficult, as PA is intrinsically resistant to multiple antimicrobials, and may acquire new resistance determinants by multiple mechanisms even during antimicrobial therapy.[89,90] Mortality of serious pseudomonal infections (i.e., VAP, BSI) is high (≥ 35%), and optimal therapy is controversial. Many physicians advocate the use of combination therapy with agents that act by different mechanisms, but randomized therapeutic trials are sparse,[91] and disparate results have been noted in both retrospective[92] and prospective[93] observational studies.

Epidemiology

PA is ubiquitous in nature, and can be isolated from plants, flowers, soil, water,[94–97] faucets,[98] sinks,[95,99] swimming pools and hot tubs,[76,100,101] wastewater from hospitals,[102] ultrafiltration bags,[99] respiratory equipment (ventilator tubing, tubes, bronchoscopes),[103,104] intravenous (IV) solutions,[95] and colonized medical personnel or patients.[105] However, it is not part of the normal human flora.[106] Colonization rates increase during hospitalization, particularly after trauma, medical procedures, or antimicrobial therapy and can result in infection.[107] PA produces a biofilm that forms on inert surfaces (e.g., endotracheal tubes, vascular catheters), and facilitates survival of the organism against host defenses and antimicrobials.[108] Outbreaks of nosocomial PA infections have been linked to contaminated environmental sources[99,103,104,109] or cross infection from colonized patients or health care workers.[110] In addition, dissemination of resistant bacteria from meat sources, domestic, and companion animals likely contributes to infections in humans.[111]

PA expresses virulence factors,[112,113] such as the classical type III secretion system[114] but additional putative virulence factors, including a novel two-partner secretion system, ExlBA, are responsible for the hypervirulent behavior of some clinical isolates.[115]

Incidence of *Pseudomonas aeruginosa* Infection in Nosocomial Settings

PA is one of the leading causes of nosocomial infections in hospitals worldwide, most commonly causing hospital-acquired pneumonia (HAP),[2,7,95] urinary tract[17,18] or surgical site/wound/soft tissue infections,[116] or bacteremias.[12,13] Point surveillance studies in 2011 implicated PA as a cause of 7.1 and 8.9% of all health care–associated infections in the United States[117] and Europe,[118] respectively.

Infections in Intensive Care Units

PA is particularly relevant in patients residing in intensive care units (ICUs). The European ICU point prevalence study in 1995 reviewed > 10,000 ICU patients from 17 Western European countries, of whom 2,064 (20.6%) had infections (all sites); 28.7% of infections were caused by PA.[119] In 2006, the incidence of infection (all sites) was examined among 3,147 adults in 198 ICUs from 24 European countries; 37.4% had sepsis; PA was implicated in 14% of infections.[120] PA was the only pathogen associated with increased mortality rates.[120] A point prevalence study (EPIC II, European Prevalence of Infection in Intensive Care Unit) in 2007 studied ≥ 14,000 ICU patients from 75 countries; 51% were infected; PA was implicated in 19.9% of infections globally.[121] A survey of 9,043 "device-related infections" in 398 ICUs in Singapore from 2004 to 2009 implicated PA in 17.2%, of infections, second only to *Acinetobacter* spp. (19.1%).[72]

Nosocomial Pneumonia

PA is a major pathogen responsible for nosocomial pneumonias, in part owing to its propensity to colonize the lower respiratory tract in patients in the ICU, particularly among patients requiring mechanical ventilation (MV).[95] In a survey of > 35,000 isolates of aerobic gram-negative bacteria (GNB) from ICUs in the United States (43 states) from 1994 to 2000, PA was the most common bacterium isolated from the respiratory tract (31.6%).[122] PA is consistently in the top 2 or 3 pathogens implicated in VAP in the United States,[4,123] Europe,[6,124–127] Latin America,[1,2,4,128] Asia,[72,127,129–132] and the Middle East.[133,134] In the Global SENTRY Antimicrobial Surveillance Program (1997–2008), PA was implicated in 21.8% of HAP or VAP, second only to *Staphylococcus aureus*

(28%).[4] In the SENTRY program from 2004 to 2008, PA accounted for 28.2% of cases of hospital-acquired bacterial pneumonia in Latin America.[4] In the SENTRY study from 2009 to 2012 in the United States and Europe, comprising > 12,000 patients with pneumonia, PA was the most frequent isolate, implicated in 20.9% of cases in the United States and 20.9% in Europe.[135] French investigators reported 3,837 patients with VAP; PA was the cause in 25%.[6] A 1-day point prevalence study in 2011 of nosocomial infections in the United States (183 hospitals, 10 states) implicated PA in 21.8% of pneumonias and 7.1% of nosocomial infections (all sites).[117] In a meta-analysis of 11 studies of VAP post-cardiac surgery, PA was the causative organism in 23.2%, followed by *S. aureus* (20.2%), *Haemophilus influenzae* (19.5%), and *Acinetobacter* spp. (10.7%).[136] A prospective study in Asia (75 hospitals from 11 countries) from 2008 to 2009 evaluated 2,554 consecutive cases of nosocomial pneumonia (HAP [$n = 1,577$], VAP [$n = 977$]) in adults.[129] In HAP, the most frequent isolates were PA (15.6%), *S. aureus* (15.5%), and *Acinetobacter* spp. (13.6%). In VAP, *Acinetobacter* spp. were most common (36.5%), followed by PA (25.9%) and *Klebsiella pneumoniae* (16.8%).[129] In a meta-analysis of HAP or VAP in China from 2007 to 2012, PA was the most common isolate (19.9%), followed by Acinetobacter *baumannii* complex (13.9%) and *K. pneumoniae* (11.9%).[130] Similarly, in a meta-analysis of 50 publications from China from 2010 to 2014, PA was implicated in 19.4% of cases of VAP.[131] In summary, PA is responsible for 15 to 30% of ICU-acquired pneumonias globally; further, multidrug-resistant (MDR) strains have increased dramatically in frequency over the past three decades[90,137–139] (discussed in detail later).

Risk Factors for *Pseudomonas aeruginosa* Infections

Risk factors for PA infections include prior antimicrobial use[11,95,121,140,141]; recent hospitalization or residence in a health care facility[14,95,112,140] or LTCF[65,68]; advanced age[17,52,53]; immunodeficiency[43,47,56]; use of corticosteroids or immunosuppressive agents[49,95,140,141]; malignancy[11,52,53]; neutropenia[52,55]; intravascular[14,142] or urinary catheters[14]; hemodialysis[58,59]; diabetes mellitus[57]; chronic pulmonary disease[41,42,143,144]; chronic cardiovascular disease[129]; enteral feedings[129]; and debilitation or other comorbidities[64,65] (►**Table 1**). Although all of the earlier risk factors may be associated with PA infections (all sites), BSIs are usually due to contaminated medical devices such as intravascular catheters (particularly central venous catheters),[14,141,142] urinary catheters,[11,17,69,71] endotracheal tubes,[73] percutaneous tubes,[11] hemodialysis,[58,59] or invasive procedures.[11]

Table 1 Common risk factors for *Pseudomonas* infection

Risk factor	Examples
Chronic illness	Diabetes mellitus[57] End-stage renal disease (hemodialysis)[58–60]
Chronic lung disease	Cystic fibrosis[38] Bronchiectasis[39,40] Chronic obstructive lung disease[37,41,42]
Immunodeficiency	Human immunodeficiency virus[43–45] Chemotherapy for cancer[52–55] Primary immunodeficiency[46–51] Corticosteroid/immunosuppressive use[49,95,138,139] Organ transplantation[56]
Surgery	Intracranial or spine surgery[61–63]
Medical devices	Urinary catheters[70,72] Mechanical ventilation[73] Intravascular catheters[14,140]
Community-acquired infection	Swimmers (otitis externa)[74–76] Hot tub exposure (folliculitis)[76,80] Contact lens wearers (keratitis)[77–79] Trauma[81,82]
Other	Prior antibiotic use[11,95,119,138,139] Advanced age[64,66] Debility[64,65] Residence in long-term care facility[64–68] Intensive care unit stay[117,120] *Pseudomonas* colonization[2]

Specific Populations at Risk

Cystic Fibrosis and Noncystic Fibrosis Bronchiectasis

PA (particularly mucoid strains) is the most common respiratory pathogen in CF[145] and has been associated with increased frequency of exacerbations, disease progression, and mortality in both CF[105,146,147] and non-CF bronchiectases.[39,40,148–152] Antimicrobial resistance rates are particularly high in patients with CF[38,153,154] and MDR-PA strains may limit therapeutic options.[155] Several distinct epidemic clones of MDR-PA have disseminated globally among CF patients and centers.[156–159] Epidemic and nonepidemic strains may differ in virulence, biofilm formation, and antimicrobial susceptibility.[160,161] The importance of PA in evolution of the CF lung lesion is fascinating but is beyond the scope of this article and will not be further discussed herein.

Immunodeficiency States

Human Immunodeficiency Virus Infection

PA may cause infection in HIV-infected patients, particularly pneumonia, BSI, and urinary tract infections (UTIs) (often due to intravascular or urinary catheters).[162,163] In one retrospective study of HIV-infected patients, *Pseudomonas* spp. were responsible for 11.6% of 1,933 bacterial infections and 5.4% of 1,072 episodes of sepsis.[162] Among 179 infections, most common sites of involvement were lower respiratory tract ($n = 66$), urinary tract ($n = 53$), and blood ($n = 34$).[162] Before the era of highly active antiretroviral therapy (HAART), PA accounted for 8 to 25% cases of community-acquired pneumonia (CAP) in HIV-infected subjects, second only to *Streptococcus pneumoniae* (35–47%).[164–166]

Similarly, in the pre-HAART era, PA was the most common bacterial pathogen causing HAP in HIV-infected subjects, accounting for 21 to 39% of cases.[43,45] Among HIV-infected subjects in the post-HAART era, PA was implicated in 5 to 6.7% of CAP[165,166] and in up to 33% of HAP.[167] Pseudomonal infections typically occur in patients with advanced HIV and severe CD4+ lymphopenia.[162,163,168]

Hematological Malignancies

Infections due to PA (principally pneumonia and BSI) are more common in neutropenic patients with malignancy,[52,53] particularly acute leukemias,[54] or hematopoietic stem cell transplant recipients.[169–173] In one review of 795 episodes of neutropenic patients with cancer, 55 had pneumonia; PA was implicated in 39.6% of pneumonias, followed by *S. pneumoniae* (20.6%) and *Escherichia coli* (8.6%).[52] Marin et al reported 569 BSI in neutropenic patients with malignancy (hematological [$n = 493$] or solid tumors [$n = 86$]).[53] PA was the most common cause of pneumonia in patients with solid tumors.[53]

Organ Transplant Recipients

Solid organ transplant (SOT) recipients are at increased risk for pneumonia and BSI following transplant.[174] Investigators from the University of Pittsburgh reported 503 cases of PA-BSI over a 10-year period, including 149 SOT recipients[56]; 43% of PA isolates from SOT recipients were MDR compared with 18% of isolates from nontransplant patients ($n = 391$) (odds ratio [OR]: 3.47, $p < 0.001$). Mortality among SOT recipients was 42%, compared with 32% in nontransplant patients (OR: 1.55, $p = 0.108$). For SOT recipients, onset of BSI in the ICU was the only independent predictor of mortality (OR: 8.0, $p = 0.008$).[56] Luo et al reported 61 PA infections among 55 SOT recipients; most common sites were lungs (57%) and blood (28%); mortality was 33%.[175] Brazilian investigators cited PA-BSI in 7 of 83 (8.4%) SOT recipients.[176] In a cohort of 1,935 abdominal SOT recipients, PA infections occurred in 54 (2.8%); most common sites were lung (56%) and blood (24%); crude 30-day mortality was 39%.[177] In a series of 165 consecutive liver transplant recipients, 15 (9.1%) developed PA infections; 47% of PA isolates were MDR.[178] PA-BSI occurred in 8 of 176 (4.8%) lung transplant recipients at the Duke University over a 6-year period.[179] A multicenter study reported 56 BSIs in lung transplant recipients from 2000 to 2004; 13 (23%) were due to PA; 28-day mortality for PA-BSI was 33%.

Primary Immunodeficiency Syndromes

Severe PA-BSI may occur in children and adults with primary immunodeficiency syndromes.[46–50,180]

Sites of Infection

Pneumonia

Community-Acquired Pneumonia

PA rarely causes CAP[95,143,181–184] unless other risk factors are present.[41,123,181,185] In a meta-analysis of 33,148 patients with CAP in 127 study cohorts, PA was implicated in only 18 cases.[186] Hatchette et al reviewed the world's literature of CAP in previously healthy adults using strict criteria and documented only 12 cases.[187] However, comorbidities and age are strong risk factors.[95] In one study, recent hospitalization (OR: 3.8) and pulmonary comorbidity (OR: 5.8) were risk factors for PA as the causative pathogen of CAP.[41] PA has been implicated in 4 to 15% of pneumonias in nursing homes or LTCF[65,67,68] or in the aged.[66] In these settings, debilitation, multiple comorbidities, and difficulty swallowing are major factors responsible for pneumonia and are linked to mortality.[64–66]

Ventilator-Associated Pneumonia

Oropharyngeal or tracheal colonization with PA increases with increased length of hospitalization, prior antibiotic use, and severity of illness, and is an important risk factor for PA pneumonia.[2,188] Colonization of dental plaque risk is a risk factor for lower respiratory tract infection/colonization with PA.[189] Other risk factors for colonization or infection with PA include previous use of antibiotics less effective against PA and COPD.[188,190] In an international study, > 1,800 adults requiring MV for > 48 hours to 7 days from 56 ICUs in 11 countries across four regions were prospectively observed; countries/regions participating in the study included the United States ($n = 502$ patients), Europe ($n = 495$), Latin America ($n = 500$), and Asia Pacific ($n = 376$).[2] Prior antimicrobial use (within 90 days) and duration of hospitalization > 5 days were risk factors for colonization with PA.[2] The odds of developing PA-VAP was eight times higher in patients with prior PA colonization compared with noncolonized patients.[2] French investigators reported 3,837 patients with VAP; PA was implicated in 25%.[6] Risk factors for PA pneumonia included older age, transfer from medical ICU or medical unit, length of MV, antimicrobial use, and admission to a ward with high incidence of PA infections.[6] Endotracheal colonization with PA may increase mortality in intubated patients, even without clinical evidence for pneumonia.[191]

Outcomes of Ventilator-Associated Pneumonia

PA-VAP is associated with attributable mortality rates > 25% and crude mortality rates > 40% in most studies.[3,7] In a retrospective study of 110 patients with PA-VAP from 2008 to 2013, 49.5% died in the ICU.[3] Risk factors for mortality included inadequate initial antimicrobial therapy (IIAT), higher APACHE II scores, older age, and diabetes mellitus.[3] The presence of MDR or IIAT were associated with increased duration of MV postpneumonia. Micek et al reported 740 patients with PA-HAP from five countries; 226 (30.5%) of isolates were MDR.[7] In-hospital mortality was 35.7%. Risk factors for mortality included increased age, MV, MDR, heart failure, and bacteremia.[7]

Blood Stream Infections

Risk factors for BSI include arterial, venous, or bladder catheters,[141] percutaneous tubes[11]; prolonged hospitalization[140]; corticosteroid or immunosuppressive therapy[10]; neutropenia[12]; multiple comorbidities[12,14]; and poor functional scores.[192] BSI due to PA are associated with significant mortality (often > 35%),[9,141,193,194] which in some cases

reflects: presence of shock,[12,141,192,194] pneumonia,[192,194] high APACHE II scores,[194] advanced age,[9] MDR isolate,[10,141,195] and IIAT.[12–14,141,194]

Mechanisms of Antimicrobial Resistance

PA isolates are intrinsically resistant to most antimicrobials[196] via chromosomal AmpC cephalosporinases and low permeability to antimicrobials, and may accumulate additional resistance determinants by acquisition of mobile genetic elements.[90,137,197] PA has a large genome (> 6 MB), a large proportion of regulatory genes and repertoire of virulence determinants.[90] PA is capable of developing resistance to nearly all antimicrobial classes by mutations in chromosomal genes as well as transferable resistance determinants, particularly those encoding metallo-β-lactamases (MLBs) or extended spectrum β-lactamases (ESBLs), often cotransferred with genes encoding resistance to aminoglycosides (AGs) and/or fluoroquinolones (FQs).[90]

Global Escalation of Antimicrobial Resistance

Antimicrobial resistance rates among PA have continued to rise over the past three decades.[89,90,137,138] Clones of MDR (i.e., resistant to at least three of eight antibiotic classes) and extensively drug resistant (XDR) (i.e., susceptible to only one or two antibiotic classes).[198] PA have emerged and disseminated worldwide.[90,199] A few "high-risk" clones (e.g., ST111, ST175, and ST235) account for a significant proportion of MDR/XDR isolates globally.[200–205] A recent study in Spain revealed that 73 of 81 (90%) XDR isolates belonged to these three international clones (ST111, ST175, and ST235).[114] ST235 has the widest distribution present in five continents.[90] In contrast, ST175 is widely distributed in Europe, but outside Europe, it has been detected only in Japan.[90] These "international clones" are associated with transferable resistance; nearly 100 different horizontally acquired resistance elements and up to 39 different acquired β-lactamases have been reported among ST235 isolates.[90] Other clones, such as ST266, are highly prevalent in Brazil but are rare in other countries.[90]

In addition, epidemic clones that confer MDR among individuals with CF (e.g., ST146 [Liverpool epidemic strain, LES]) have disseminated rapidly worldwide.[90] The LES, ST146, originally described in a CF center in the mid-1990s,[206] was detected in Scotland and Wales,[207] Canada,[208] and Spain.[209] These CF epidemic clones are capable of person-to-person spread.[207–209]

Excessive use of antimicrobials, international travel, and dissemination of MDR clones will amplify spread of resistant organisms globally.[90]

Impact of Antimicrobial Use on Antimicrobial Resistance

Not surprisingly, the use of broad-spectrum antimicrobials has been linked to emergence of antimicrobial resistance. López-Dupla et al reviewed PA-BSI from 1997 to 2007; prior use of ciprofloxacin (within 30 days) was an independent predictor of resistance to ciprofloxacin (OR: 2.4) as well as other drug classes (e.g., ceftazidime [OR: 2.0]; piperacillin/tazobactam [P/T] [OR: 2.4]; meropenem [OR: 2.7]).[210] Not surprisingly, prior use of carbapenems (CPs) was a risk factor for CP-resistant (CPR) PA.[211,212] In Europe, in 2007, > 25% of PA isolates were CPR in 6 of 33 countries.[213] The SENTRY survey evaluated > 22,000 clinical isolates of GNB from 101 medical centers in the United States and Europe from 2009 to 2011; resistance rates were much higher in ICU compared with non-ICU patients.[214] Overall, resistance rates of PA to ceftazidime, P/T, FQs, and CPs ranged from 27 to 32% (included ICU and non-ICU isolates).[214] The SENTRY study examined antimicrobial susceptibilities of 12,861 isolates of GNB from 28 medical centers in the United States and 25 centers in Europe and the Mediterranean from 2009 to 2012.[135] Rates of susceptibility in the United States and Europe, respectively, were as follows: ceftazidime (80%/69%), meropenem (76%/66%), and P/T (73%/64%).[135] The Asian Network for Surveillance of Resistant Pathogens Study Group prospectively assessed antimicrobial susceptibilities from 1,897 cases of HAP or VAP from 10 Asian countries (73 hospitals) from 2008 to 2009; 73% of PA isolates were susceptible to imipenem.[129] The International Nosocomial Infection Control Consortium (INICC) prospectively evaluated > 43,000 ICU patients from 98 ICUs in Latin America Europe, Africa, and Asia from 2002 to 2007.[215] Resistance rates among isolates of PA were as follows: ciprofloxacin (52.4%), imipenem (36.6%), ceftazidime (51.7%), piperacillin (50.8%) (these rates of resistance were considerably higher than contemporaneous data from the U.S. Centers for Disease Control and Prevention (CDC) which reported 13.5 to 34.8% resistance to the earlier antimicrobials).[215] In a subsequent study, the INICC prospectively evaluated > 300,000 ICU patients from 36 countries in Latin America, Europe, Africa, and Asia from 2004 to 2009.[216] Among isolates of PA, 47.2% were resistant to imipenem compared with 23.0% resistance in the U.S. CDC data during that time frame.[216] A recent prospective study in India evaluated 98 consecutive clinical isolates of PA: 47.5% were MDR; 2.3% were XRD; none was pan resistant.[217] Resistance rates can vary substantially among geographic regions. Over time, we can expect further increases in antimicrobial resistance, fueled by antibiotic use, international travel, and dissemination of MDR clones globally.[90,218]

Resistance to β-Lactams (Including Carbapenems)

Resistance to β-lactams may occur via hyperexpression of chromosomal AmpC cephalosporinases[219]; loss of outer membrane channel OprD[197,220]; mutations in efflux systems (MexAB-OprM, MexCD-OprJ, MexEF-OprN, and MexXY-OprM)[221,222]; production of carbapenemases (CPEs) or metallo-β-lactamases (MBLs)[223–225] or combinations of mechanisms.[137,205]

β-Lactamases

β-lactamases are categorized based on molecular structure into groups A through D and functionally into three groups (1–3) based on the target enzyme they degrade.[226,227] Group 1 (class C) inducible Amp C cephalosporinases are present in the chromosomes of all PA strains, conferring resistance to penicillin and early generation CEPHs. Two additional chromosomal β-lactamases (PoxB/OXA-50[228] and PA5542[229]) may contribute to β-lactam resistance. Group 2 enzymes (classes A and D) include serine β-lactamases and ESBLs and have a broader spectrum of activity.[226] Group 3 enzymes (class B) are potent hydrolyzers of CPs and are not inhibited by β-lactamase inhibitors.[227]

Extended Spectrum β-Lactamases

ESBLs, initially described in Enterobacteriaceae in the 1980s,[230] spread to PA beginning in the late 1990s.[90,137] ESBLs hydrolyze late generation CEPHs and antipseudomonal penicillins but do not affect CPs. ESBLs encoded in PA include class A (e.g., PER, VEB, Guiana extended-spectrum β-lactamases [GES], KPC, BEL, PME) and class D (OXA) enzymes.[90] ESBLs comprising TEM, SHV, or CTX-M enzymes are common among Enterobacteriaceae but are only occasionally detected in PA.[90] The following brief discussion of several ESBLs underscores the potential for clonal dissemination within and between countries.

PER-1 Type

PER-1 was the first ESBL identified in PA from a Turkish patient hospitalized in France in 1991.[231] PER-1–producing PA were widespread in Turkey[232] and were later detected in Belgium,[233] Italy,[234] Poland,[235] Hungary and Serbia,[236] Japan,[237] Tunisia,[238] China,[239] and globally.[137] Epidemiological studies linked this PER-1 PA to the international clonal complex CC11.[137]

VEB Type

VEB-1–type ESBL was isolated from PA in 1998 in France, from a patient transferred from Thailand.[240] Over the next several years, VEB-1–producing PA were detected in Thailand,[241] Kuwait,[242] India,[243] China,[244] Bulgaria,[245] United Kingdom,[224] Denmark,[246] and globally.[137]

GES Type

A new group of ESBLs termed GES, first detected on PA in 2000 in South Africa[247] and France[248] was soon detected in Greece,[249] Brazil,[250] Argentina,[251] Germany,[252] China,[253] South Africa,[254] Turkey,[255,256] Canada,[31] Mexico,[257] South Korea,[258] Japan,[259] and globally.[31,137] GES are encoded in plasmids and thus are transferrable.[89] Most, but not all, GES display CPE activity.[89]

KPC Type

KPC, a class 1 serine CPE encoded in plasmids, was first detected in Columbia in 2006.[260] Subsequently, KPC-producing PA were found in Puerto Rico,[261] Trinidad and Tobago,[262] South America,[263,264] and China.[265] In 2012, isolates of PA coharboring Verona integrin-encoded MBL (VIM) and KPC CPE[266] and KPC-2 and imipenemase (IMP)-18 CPEs[267] were reported. Clonal spread of VIM and KPC CPEs, fueled by antibiotic selection pressure, was cited in Columbia.[268]

PME-1 Type

A novel ESBL, termed PME-1, was isolated in PA in 2008 at the University of Pittsburgh from a patient who had a prolonged hospitalization in the United Arab Emirates.[269] In 2015, a second PME-1–producing PA was isolated in Qatar; this isolate belonged to the high-risk international clone 654.[270]

Metallo-β-Lactamases

MBLs hydrolyze CPs via production of CPEs.[89] MBLs confer resistance to all β-lactams except aztreonam; MBLs are not inhibited by clavulanic acid or tazobactam.[89] MBLs normally reside in integron gene cassettes, and are linked to mobile genetic elements (i.e., plasmids or transposons) that may facilitate gene transfer to various bacterial species and genera.[89,271] The worldwide emergence of CPR strains with similar mobile genetic elements reflects dissemination of genes encoding CPEs via horizontal gene transfer. In Latin America and the Caribbean, MBLs have escalated dramatically, particularly in Brazil, Columbia, Argentina, and Mexico.[225] Two strains of XDR-CPE-producing PA belonging to international clones ST111 and ST235 harboring VIM-2 and KPC-2 on mobile genetic elements disseminated rapidly in Columbia.[272] A review of CPR-PA collected during 2009 to 2011 in 14 European and Mediterranean countries cited an increase in MBLs from 13.4% in 2009 to 30.6% in 2011.[223] The presence of resistance genes varies among geographic regions, and marked increases in resistance can be anticipated in the future with international travel and spread of specific resistance clones.

Imipenemase and Verona Integrin-Encoded MBL Types

VIM and IMP are the most common MBLs found in PA.[89,90,273,274] The first PA-associated MBL, IMP-1, was discovered in Japan in 1988.[275] Within two decades, more than 40 IMP types were described.[89] In 2013, Japanese investigators reported IMP-43 and IMP-44 in two MDR-PA isolates.[276]

VIM-type MBLs were first described in Italy in 1997[277,278] and France in 1996.[279] Since then, more than 40 VIM types were described in PA.[89,280] Analysis of 267 isolates of MDL-producing PA in the United Kingdom from 2003 to 2012 found that $>$ 91% were VIM; a few produced IMP or NDM (New Delhi MBL [NDM-1]).[274] PA isolates coexpressing more than one MBL have been described, for example, VEB + VIM[224]; VIM + KPC[266]; KPC-2 + IMP-18[267]; and VIM + KPC.[268]

German Imipenemase

In 2002, a novel MBL, termed German imipenemase (GIM)-1, was isolated in a PA isolate in Germany.[252] From 2007 to 2012, isolates of GIM-1 (+) PA and Enterobacteriaceae were reported in Germany.[281] An outbreak of XDR-GIM-1(+)-PA affecting 29 patients in a surgical ICU was linked to contaminated hospital sinks.[282] To our knowledge, GIM-1 PA isolates have not been detected outside Germany.

CTX-M Type

A CTX-M-1–producing PA isolate from a patients with CF was reported in 2006 in the Netherlands.[283] CTX-M-2- and CTX-M-43-positive PA were identified in Bolivia in 2006[284] and Brazil in 2009.[285] Recently, CTX-M-3, CTX-M-14, and CTX-M-15 were identified from several PA isolates from China.[239]

Sao Paulo Metallo-β-Lactamase

Sao Paulo metallo-β-lactamase (SPM)-1 is a novel MBL discovered in Brazil from a PA isolate that was susceptible only to colistin.[286] Epidemic clonal spread of this SPM-1 (+) strain was documented in several regions and hospitals in Brazil.[96,287–291] The first isolate of SPM-1–producing PA outside of Brazil was reported in 2007 from a Swiss patient who received medical treatment in Brazil.[292] In 2013, an SPM-1–producing PA from the pandemic clone SP/ST277 was isolated in the United Kingdom from a patient who recently had surgery in Brazil.[293] Dissemination of clones of MSP-1–producing PA and *Acinetobacter* spp. has resulted in high levels of CPR in Brazil and Latin America.[294,295] This underscores the potential for global dissemination within and across continents.[296]

BEL Type

BEL-1 is a novel ESBL isolated from an isolate of PA in Belgium[297]; a second isolate, BEL-2, clonally related to BEL-1, was described in 2010.[298] Among 2,150 isolates of PA from two Belgian reference laboratories from 2004 to 2008, 48 (2.2%) produced ESBLs; 39/48 produced BEL.[299] Most ESBL (+) isolates belonged to a single clone (ST235, serotype 011).[299]

Florence Imipenemase

A novel MBL, isolated in Florence, Italy in 2007, termed Florence imipenemase-1, was related to the ST235 epidemic clone.[300]

New Delhi Metallo-β-Lactamase

NDM-1 was first described in an isolate of *K. pneumoniae* in 2009.[301] The first PA isolate producing NDM-1 was reported in 2011 from Serbia.[302] In 2012, a NDM-1–producing PA ST235 strain was isolated in France from a patient previously hospitalized in Serbia.[303] Since then, NDM-1-positive PA isolates have been recovered throughout the world including India,[304] Italy,[305] Egypt,[306] and Slovakia.[307]

Other ESBLs and MBLs

Several other ESBLs or MBLs have been reported in PA including oxacillin (OXA) class D ESBL[308–310]; SHV-type ESBL in France[311]; Thailand[312]; Tunisia[313]; Japan[314]; Greece[315]; AIM MBL (Australia)[316]; TEM ESBLs[317–319]; and PIB-1 (France).[229]

Multidrug Resistance and Extensively Drug-Resistant *Pseudomonas aeruginosa*

PA strains that display MDR or XDR[198] have disseminated globally.[90,138,274] Several international clones disseminated from hospitals,[90,138] whereas other clones evolved from CF centers.[153,156–159] In North America, rates of MDR are modest.[320,321] Data from the Eurofins' Surveillance Network evaluated > 205,000 PA isolates from patients with HAP or BSI from 217 hospitals in the United States from 2005 to 2011.[320] Overall, 22.0% of PA isolates from patients with pneumonia were MDR; 14.7% of BSI isolates were MDR.[320] In Canada, in 2008, only 5.9% of isolates of PA from 10 hospitals were MDR.[321] However, globally rates of MDR exceed 30% in some regions.[114,134,215,217,322]

Treatment of Infections Due to *Pseudomonas aeruginosa*

Mortality rates of pseudomonal pneumonia or BSI are high (> 35%)[1,3,141,323,324] and relapses or clinical failures are common.[325] Further, antimicrobial resistance develops in 10 to 53% of patients with serious PA infections, even while receiving appropriate antibiotic therapy.[323,324,326–328] The most active agents against PA include CPs, AGs (particularly amikacin), and colistin.[153] Other agents such as ceftazidime, cefepime, P/T, ciprofloxacin, and levofloxacin are active in 40 to 70% of PA isolates.[134,320] Several studies have shown that inappropriate initial antibiotic therapy (IIAT) or delay in instituting appropriate therapy for PA-BSI[12–14,141,194,329] negatively influences survival. However, numerous nonantimicrobial risk factors for mortality in patients with PA-BSI or PA pneumonia include respiratory failure or shock[12,13,192,194,330]; high comorbidity scores[10,14]; increasing APACHE II score[194]; poor functional status[192]; severity of illness[9]; age[12,192]; corticosteroid use[10]; and cirrhosis.[12] A multicenter prospective study in Israel evaluated 76 adults with PA-BSI within 72 hours of hospital admission.[192] Independent predictors of mortality included severe sepsis or septic shock on admission (OR: 21.9, $p < 0.001$); respiratory or unknown source of bacteremia (OR: 11.5, $p = 0.003$); recent hospitalization (OR: 6.2, $p = 0.032$); and poor functional status (OR: 5.8, $p = 0.029$). IIAT was marginally associated with increased mortality only among patients who presented with severe sepsis or septic shock ($p = 0.051$).[192] Although nonantimicrobial factors may be more important in determining outcomes than specific antimicrobials, we discuss therapeutic options later.

Antimicrobial Options for *Pseudomonas aeruginosa*

Historically, β-lactams have been the cornerstone of therapy for PA. In the 1980s and 1990s, the third or fourth generation cephalosporins (CEPHS), ceftazidime and cefepime, respectively, as well as P/T were used as preferred therapy for PA. These agents are active against 65 to 85% of PA isolates in North America,[320,321,331] but much higher rates of resistance have been reported in Latin America, the Middle East, and some parts of Asia.[114,216,217,322] By the 21st century, emergence of resistance to these β-lactams shifted therapy primarily to the CPs. However, for susceptible isolates, these antipseudomonal CEPHS or P/T may be adequate.

Carbapenems

Over the past decade or more, IV CPs (i.e., imipenem/cilastatin, meropenem, doripenem) have been the agents of choice for severe PA infections. In North America, CPR-PA is relatively low (< 20%),[215,320,321,331] but in some countries or regions, > 40% of PA isolates are CPR.[134,215,322] Among 120 patients with CF in three European countries, high rates of CPR (37–52%) were cited from 2006 to 2012.[153] Monotherapy with a CP can be used for susceptible organisms; however, for empirical therapy (before antimicrobial susceptibilities are available), combining a CP with an agent from another antimicrobial class (e.g., AG or FQ) is reasonable.

New Cephalosporin/β-Lactamase Inhibitor Combinations

Ceftolozane/tazobactam[332,333] and ceftazidime/avibactam[333–337] are new β-lactam/β-lactam inhibitor combinations with excellent activity against PA, including CPR and MDR strains.[332,333,336,338] However, while ceftazidime/avibactam has activity against organisms that produce KPC CPEs, ceftolozane/tazobactam does not, and neither drug has activity against organisms that produce NDM-1.[333] Both agents are Food and Drug Administration approved to treat complicated UTIs and complicated IAI[339,340]; studies to treat VAP are in progress.

Fluoroquinolones

Among the FQs, ciprofloxacin and levofloxacin are the most active agents, but only 40 to 65% of PA isolates are susceptible to these agents.[215,216,341] Further, resistance can develop rapidly following exposure to FQ antimicrobials.[10,327] PA can develop resistance to FQ via chromosomal mutations in the quinolone resistance determining regions of *gyrA* and *parC* genes, decreased cell membrane permeability[90] and/or by overexpression of efflux pumps.[90,137,221,342,343] Factors associated with FQ resistance include prior use of FQ,[122,210] CF,[344] residence in the ICU, monotherapy for pneumonia.[327] In a review of 572 cases of PA-BSI from 1997 to 2007, prior use of ciprofloxacin (within 30 days) was an independent predictor of resistance to ceftazidime (OR: 2.0), imipenem (OR: 2.0); meropenem (OR: 2.7); P/T (OR: 2.4), ciprofloxacin (OR: 2.9), and MDR (OR: 2.5).[210]

Aminoglycosides

More than 80% of PA isolates are susceptible to AGs (particularly amikacin).[216,341] However, AG resistance among PA may emerge via the production of AG-modifying enzymes or efflux pumps[345,346] as well as nonenzymatic mutations.[347,348] Plasmids may produce multiple resistance determinants affecting AGs, β-lactams, FQs, and other drug classes concomitantly.[90,137] AGs are rarely used as the first-line monotherapy for serious PA infections (due to concerns regarding nephrotoxicity), but may be used as combination therapy with a second agent of another class (e.g., β-lactam or FQ).

Colistimethate Sodium (Colistin)

Colistin is the most active antimicrobial against PA (> 98% susceptible)[132] but is usually reserved for MDR or XDR isolates so as to prevent the evolution of resistance to this agent. Colistin-resistant isolates have been detected globally via selection pressure[344,349–356] and may be resistant to all antimicrobial classes. Increases in colistin resistance can be expected in tandem with its use.[137,357] In Brooklyn, NY, in 2003, 25 of 527 (5%) of PA isolates exhibited reduced susceptibility to polymyxin B (MIC > 2 mg/L) compared with 0 of 691 (0%) in 2001.[351]

Combination Therapy

Optimal therapy for serious infections due to PA (particularly BSI or VAP) remains controversial,[91,324] but many physicians advocate combination therapy with agents that act by different mechanisms. Potential advantages of this approach include broadening the spectrum of empiric therapy so that the organisms would be treated by at least one agent, using a possibly more potent synergistic combination and preventing or delaying the development of antimicrobial resistance. Randomized therapeutic trials of combination therapy versus monotherapy are lacking, and disparate results have been noted in both retrospective[92] and prospective[93] observational studies.

Blood Stream Infections

Several nonrandomized observational studies have compared combination therapy with monotherapy for PA-BSI. One multicenter retrospective study evaluated 384 patients with PA-BSI from 2000 to 2010.[358] Thirty-day mortality was higher for patients receiving inappropriate therapy than for those receiving appropriate empirical therapy (mortality rates 43.8 and 21.5%, respectively, $p = 0.03$). However, if empirical therapy was appropriate (i.e., isolates were susceptible to at least one agent), 30-day mortality rates were similar with combination therapy (36.6%) versus monotherapy (28.7%) ($p = 0.17$). Empirical combination therapy did not offer an additional benefit, as long as the isolate was susceptible to at least one agent.[358] Spanish investigators evaluated 593 patients with PA-BSI treated with either combination therapy or monotherapy.[359] Thirty-day mortality was 30.6% for patients receiving adequate empirical combination therapy, 26.5% for patients with adequate empirical monotherapy, and 33.3% for patients receiving inadequate empirical therapy ($p = 0.17$).[359] After adjustment for confounders, 30-day mortality rates were not significantly different between combination therapy and monotherapy. Hu et al performed a meta-analysis comprising 1,239 patients with PA-BSI from eight retrospective and two prospective studies.[360] There were no differences between combination therapy and monotherapy when data were combined (OR = 0.89, $p = 0.61$) or when data were analyzed in subgroups. In a separate study, investigators from the MD Anderson Medical Center retrospectively reviewed 245 cases of PA-BSI in cancer patients between 1991 and 1995; cure rates were similar with monotherapy with a β-lactam as compared with combination therapy ($p = 0.72$).[54] Vidal et al reported 189 consecutive cases of PA-BSI from 1991 to 1994; overall mortality was 18%.[330] Provided the isolate was susceptible, survival rates were similar with combination versus

monotherapy. Mortality rates were higher with pneumonia (47%) or severe sepsis (62%).[330] Israeli investigators reported 123 episodes of PA-BSI, with attributable mortality of 34%.[361] After excluding patients with early mortality (< 48 hours) and inappropriate therapy, mortality rates were similar with combination therapy (6/42 [14%] and monotherapy (2/15 [13%]).[361] Lodise et al retrospectively evaluated the impact of delay in appropriate antibiotic therapy among 100 adult immunocompetent patients with hospital-acquired PA-BSI.[329] Delayed (i.e., > 52 hours) appropriate therapy was associated with a 30-day mortality of 44% compared with 19% with early appropriate therapy. By multivariate analysis, delayed appropriate therapy was independently associated with higher 30-day mortality (OR = 4.1, $p = 0.03$). Antimicrobial resistance to ≥ 3 classes (adjusted OR [AOR] = 4.6, $p = 0.001$) and COPD (AOR = 5.4, $p = 0.01$) were independently associated with delayed appropriate therapy.[329] Chamot et al retrospectively reviewed 110 episodes of PA-BSI treated between 1988 and 1998.[362] Compared with adequate combination therapy, the risk of death at 30 days was higher with inadequate definitive therapy (aOR: 2.6) but not with adequate definitive monotherapy (aOR: 0.70). These various studies are not definitive, but suggest that monotherapy for PA-BSI may be as effective as combination therapy, provided the isolate is susceptible to that agent. These studies also demonstrate the high mortality of PA-BSI, even with adequate therapy.

The use of certain antimicrobial combinations (particularly CPs and FQs) has been shown to limit emergence of resistance in in vitro pharmacodynamic[363–365] models. However, in one study of 200 episodes of PA-BSI, the use of antimicrobial combinations that displayed synergy in vitro did not influence survival.[93] Nonantimicrobial factors (e.g., pneumonia, need for ICU care) were more important predictors of outcome. At present, the value and clinical relevance of combination therapy in human infections remains controversial.

However, combination therapy as initial empirical therapy (before antimicrobial susceptibilities are available) may reduce the likelihood for inappropriate therapy (i.e., treating with agent[s] to which the organism is nonsusceptible). Several studies have shown that inappropriate initial antimicrobial therapy (IIAT) for PA-BSI increases mortality,[12–14,141,194,329] even if treatment is subsequently modified. Although the benefit of combination therapy has not been established for infections due to PA, it is possible that combination therapy may have a role for certain clinical scenarios such as septic shock or pneumonia. A multicenter (28 hospital) trial enrolled 4,662 patients with culture (+) bacterial septic shock (all pathogens); 1,223 propensity-matched pairs were generated (monotherapy or combination therapy).[366] Twenty-eight-day mortality was lower in those receiving combination therapy (29.0%) compared with monotherapy (36.3%), $p = 0.0002$. In a separate study, these investigators performed a meta-analysis of 50 articles that compared combination therapy with monotherapy for sepsis.[367] Combination therapy was associated with substantial benefit only in the most severely ill subset of patients (risk of death ≥ 25%, OR: 0.51, $p < 0.0001$). By contrast, in low-risk patients (predicted risk of death < 15%) treated with combination therapy, mortality was higher than monotherapy (OR: 1.53, $p = 0.003$). These data are not definitive, but raise the possibility that combination therapy may have a role for patients with more severe illness (e.g., septic shock, multilobar pneumonia). Additional studies are required to identify which (if any) subsets of patients with PA infections may benefit from combination therapy. The use of combination therapy adds cost, may add toxicity, and could lead to superinfection by more resistant organisms.[368]

Optimal duration of therapy for pseudomonal infections has not been established. French investigators randomized 401 patients with VAP to either 8 or 15 days of antibiotic therapy (to which the organism was susceptible).[369] Mortality rates were similar (18.8% in 8-day cohort compared with 17.2% in 15-day group [all pathogens]). Among 178 with nonfermenting GNB (NFGNB) as the causative agent, 28-day mortality rates were 23.4% (15/64) in the 8-day group compared with 30.2% (19/63) in the 15-day group (NS, nonsignificant). However,, among those with NFGNB, recurrent infections were more common in the 8-day group (40.6%) compared with 25.4% in the 15-day group.[369] There were no differences in duration of MV, ICU stay, or 60-day mortality between the groups. Hedrick et al retrospectively evaluated 452 cases of VAP from 1996 to 2004 (154 were due to nonfermenters).[370] Among 27 patients receiving short course therapy (mean: 6.4 days, range: 3–8 days), recurrences occurred in 22% of patients compared with 34% recurrence rate among 127 patients receiving > 9 days of therapy (mean: 17.1 days) ($p = 0.29$). Mortality rates were similar (22% with short course; 14% with long course therapy). These studies are inadequate to determine the optimal duration of therapy for PA-VAP. However, we usually recommend a 15-day course of therapy for PA-VAP or BSI.

Pharmacokinetics/Pharmacodynamics

The use of extended or continuous infusion of β-lactam antibiotics (particularly P/T and CPs) compared with intermittent infusion therapy has been associated with improved outcomes in several,[371,372] but not all,[373] studies of PA infections. Randomized controlled trials are limited and the value and indications for extended/continuous infusion remain controversial. This will be discussed in detail by Roberts and co-workers in article "Pharmacokinetic/Pharmacodynamics-Optimized Antimicrobial Therapy in Patients with Hospital-Acquired Pneumonia/Ventilator-Associated Pneumonia" on pp. 271–286.

Inhaled Antibiotics for PA-VAP

Aerosolized (inhaled) aminoglycosides have been used in patients with CF[357,374–376] and as adjunctive therapy for VAP,[148,377,378] but data were gleaned largely from nonrandomized, retrospective studies. Several studies added aerosolized colistin to parenteral antimicrobials for VAP due to MDR-GNB but failed to demonstrate improvement in clinical cure rates or mortality.[379–383] The role of inhaled antibiotics in

severe nosocomial pneumonia (particularly VAP) is controversial[384,385] and will be discussed in detail by Palmer and Rello in article "Is There a Role for Inhaled Antibiotics in the Treatment of Ventilator-Associated Infections?" on pp. 359–370.

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New Strategies Targeting Virulence Factors of *Staphylococcus aureus* and *Pseudomonas aeruginosa*

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Abstract

Morbidity, mortality, and economic burden of nosocomial pneumonia caused by *Staphylococcus aureus* and *Pseudomonas aeruginosa* remain high in mechanically ventilated and hospitalized patients despite the use of empirical antibiotic therapy or antibiotics against specific classes of pathogens and procedures to reduce nosocomial infections in hospital settings. Newer agents that neutralize or inhibit specific *S. aureus* or *P. aeruginosa* virulence factors may eliminate or reduce the risk for developing pneumonia before or during mechanical ventilation and may improve patient outcomes through mechanisms that differ from those of antibiotics. In this article, we review the types, mechanisms of action, potential advantages, and stage of development of antivirulence agents (AVAs) that hold promise as alternative preventive or interventional therapies against *S. aureus*– and *P. aeruginosa*–associated nosocomial pneumonias. We also present and discuss challenges to the effective utilization of AVAs separately from or in addition to antibiotics and the design of clinical trials and meaningful study end points.

Keywords
- antivirulence agents
- *Staphylococcus aureus*
- *Pseudomonas aeruginosa*
- nosocomial pneumonia
- ventilator-associated pneumonia

Nosocomial hospital-acquired pneumonia (HAP) and ventilator-associated pneumonia (VAP) continue to impose a significant burden of disease, as measured by mortality, morbidity, and health care costs on a global scale, despite the availability of broad-spectrum antibiotics and recommendations to contain cross-contamination in health care settings.[1,2] In its most severe form, nosocomial pneumonia is estimated to be directly related to death in 19.6% of hospitalized patients and to contribute to death in 43.9% of hospitalized patients.[3] The highest risk of mortality from hospital-acquired infections occurs in patients with HAP and VAP; this is especially true in old and very old patients, those with contributing comorbidities, and patients receiving inadequate empirical therapy.[4–6]

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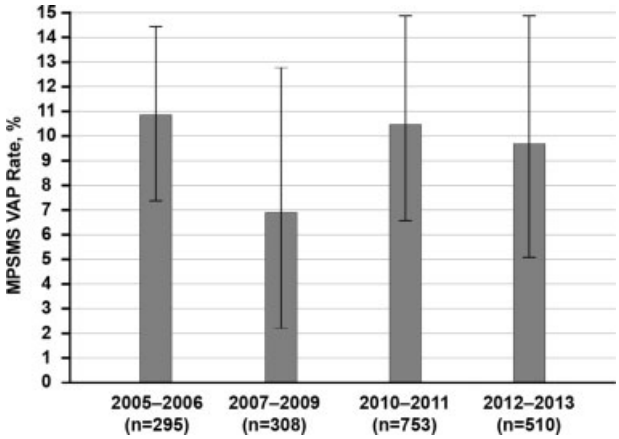

Fig. 1 Adjusted VAP rates among patients ≥ 65 years of age in the MPSMS, 2005 to 2013. MPSMS, Medicare Patient Safety Monitoring System; VAP, ventilator-associated pneumonia. (Reproduced with permission from Metersky et al.[10])

Although some epidemiologic literature indicates that the incidence rates of VAP have decreased in recent years in parallel with decreases in VAP-associated hospital infections and mortality,[7–9] a recent retrospective analysis by the Medicare Patient Safety Monitoring System highlights the persistent incidence of VAP in elderly patients placed on mechanical ventilation for various medical conditions (►**Fig. 1**).[10] These results are supported by a regional U.S. patient database analysis that showed stable or variably increasing rates of VAP from 2002 to 2009.[2]

These data may underestimate the actual prevalence of VAP from factors influencing case reporting, such as clinical standards for possible or probable pneumonia[11] and medical diagnosis classification codes for reimbursement,[12,13] lack of financial incentives for hospitals to incur costs aimed at avoiding resistance, and VAP incidence as a standard of care benchmark for quality health care assessments.[2,13]

Nosocomial VAP and HAP caused by *Staphylococcus aureus* and *Pseudomonas aeruginosa* are especially problematic for their high prevalence compared with other nosocomial pathogens (►**Table 1**).[14] In hospitalized patients with a primary or secondary diagnosis of pneumonia or respiratory failure, both *S. aureus* and *P. aeruginosa* pneumonias are associated with hospitalization rates exceeding those associated with other pathogens, except pneumococcal pneumonia, and have higher odds ratios for all-cause mortality than those for pneumonia caused by *Klebsiella* spp., *Pneumococcus* spp., *Haemophilus influenzae*, and influenza virus.[12] Patients with *S. aureus* and *P. aeruginosa* pneumonias also have significantly longer mean stays in hospital and intensive care unit (ICU) stays, higher rates of mechanical ventilation, higher mortality, greater risk of rehospitalization, and higher mean hospitalization costs than patients not diagnosed with pneumonia (►**Fig. 2**).[15] Although these findings are intuitive for risks associated with virulent *S. aureus* or *P. aeruginosa* pneumonias, data on length of stay in hospital and ICUs and the associated health care costs in these patients are often time biased (i.e., include time from admission to discharge) and may not reflect actual outcomes and costs incurred during the postinfection period in hospital.[16,17]

Table 1 Global incidence of the top six bacterial pathogens in HAP and VAP from the SENTRY Antimicrobial Surveillance Program, 2004 to 2008[14]

Pathogen	Prevalence (% of isolates)
S. aureus	20.1–36.3
P. aeruginosa	19.7–28.2
Klebsiella spp.	8.5–12.1
Enterobacter spp.	6.2–6.5
Acinetobacter spp.	4.8–13.3
E. coli	4.6–10.1

Abbreviations: HAP, hospital-acquired pneumonia; VAP, ventilator-associated pneumonia.

Rationale for Targeted Alternative Therapies against *S. aureus* and *P. aeruginosa*

The continuing high burden of *S. aureus* and *P. aeruginosa* HAP and VAP underscores the need to develop alternative therapies for halting or attenuating the severity and duration of nosocomial pneumonia caused by these pathogens. Alternative therapies may include a variety of antivirulence agents (AVAs) that target specific virulence factors responsible for colonization, tissue and cellular destruction, and evasion of host immune mechanisms. Pathogen-specific AVAs can conceivably reduce or eliminate pathogenesis of pneumonia when used alone or in combination with guideline recommendations for the treatment and prevention of HAP and VAP.[18] The development of AVAs is further justified by the long-standing reliance on broad-spectrum agents for antimicrobial therapy that has led to the spread of cross-species resistance, the deleterious impact of antibiotics on the beneficial microbiome, and the underappreciated impact of antibiotic-susceptible organisms on the incidence and severity of HAP and VAP.[18–20]

Rising Antibiotic Resistance

The increasing emergence of species and cross-species antimicrobial resistance and of multiple drug-resistant (MDR) bacterial pathogens constitutes a significant threat to community populations in general and to patients at risk in particular, including those hospitalized with one or more significant comorbidities, the elderly, mechanically ventilated patients, and immunocompromised patients. In the hospital setting, the known risk factors for MDR VAP include the following[1,4,21]:

- Current hospitalization of ≥ 5 days before onset of VAP
- Intravenous antibiotic use within the preceding 90 days
- High frequency of antibiotic resistance in the specific hospital unit
- Acute respiratory disease syndrome preceding onset of VAP
- Immunosuppressive disease and/or therapy
- Acute renal replacement therapy before onset of VAP.

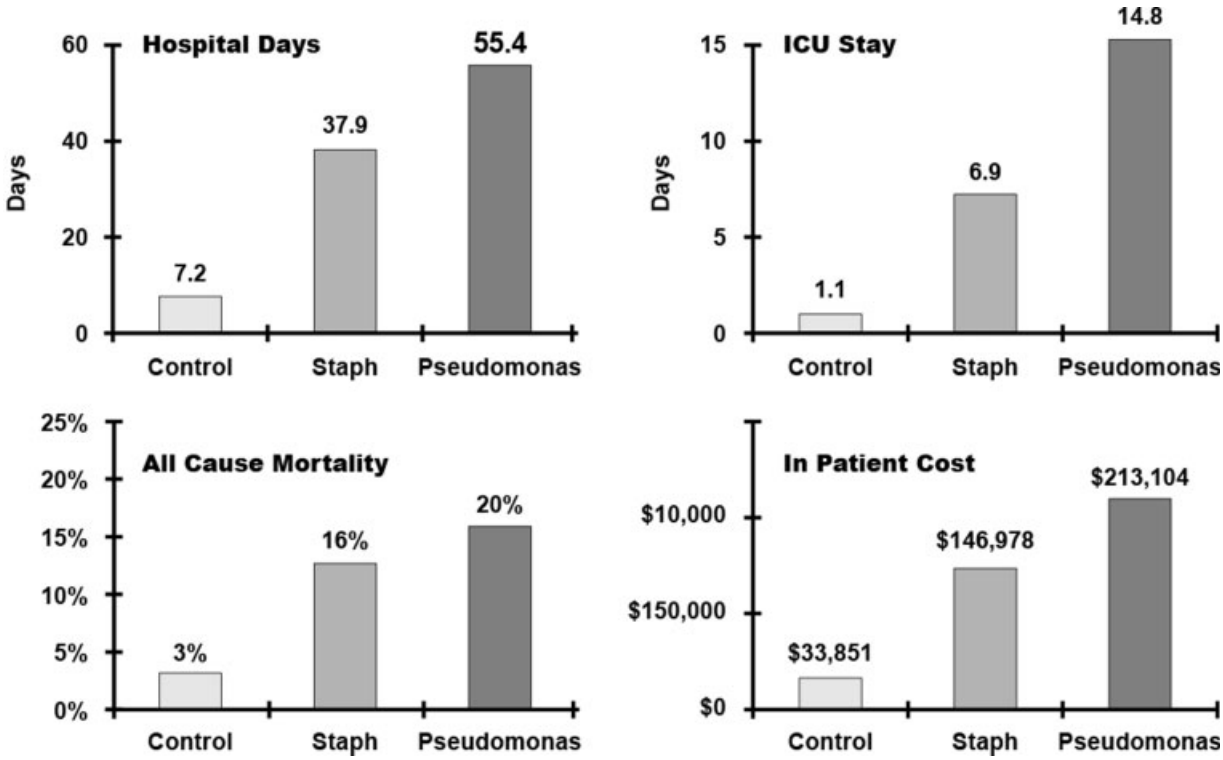

Fig. 2 Increased health care resource utilization for ICU patients with *S. aureus* or *P. aeruginosa* pneumonia versus controls. ICU, intensive care unit. (Data used with permission from Kyaw et al.[15])

Not surprisingly, MDR bacteria, including *P. aeruginosa* and *S. aureus*, are associated with a significantly longer median length of ICU stay (19 vs. 16 days, $p = 0.02$) and duration of mechanical ventilation (18 vs. 14 days, $p = 0.03$) than are antimicrobial-susceptible organisms.[22] The overall prevalence of MDR pathogens such as methicillin-resistant *S. aureus* (MRSA) and MDR *P. aeruginosa* varies across regions and countries.[23–26] Recent global and national epidemiological surveys show that the prevalence of antibiotic-resistant and MDR pathogens has remained stable or, in some pathogens, actually increased.[23,27] For example, data from an Indian surveillance network in 2012 showed that 57 of 66 (86%) pathogens isolated from ventilated patients were MDR, with notably high rates of resistance against various antibiotics among isolates of *Klebsiella pneumoniae* (82%), *P. aeruginosa* (71%), *Staphylococcus* spp. (75%), and 100% of all isolates of *Escherichia coli*, *Citrobacter freundii*, and *Acinetobacter* spp.[28]

The need for combination antimicrobial therapy in high-risk patients and those with antibiotic resistance against first- and second-line antibiotics[29] and the risk of persistent or recurrent infection after treatment for first VAP episode (e.g., recurrent *P. aeruginosa* VAP after fluoroquinolone therapy) highlight the problem encountered in preventing protracted disease with established antibiotic regimens.[30,31] Further complicating effective therapy are the well-known associations between prior antibiotic therapy and the development of drug resistance, the risk for late-onset VAP, and the shift in the ecological distribution of gut microflora.[20,32] In addition, the recent identification of a *mcr-1* mutation conferring colistin resistance in a single case in the United States underscores the ability of microbial pathogens to acquire antibiotic resistance even against very strong antimicrobial agents.[33]

Microbiome Effects of Antibiotics

The changing patterns of antibiotic use (measured as days on therapy) across different agent classes, especially in the U.S. hospitals, probably reflect changes in approaches to therapy that are driven by the prevalence of drug-resistant pathogens, as well as efforts to control antibiotic-mediated depletion of beneficial commensal microflora (dysbiosis), which reduces microbial competition and the immune system "tuning" attributed to the beneficial flora. This microbial dysbiosis can result in the emergence of secondary tissue, respiratory, and bloodstream infections caused by extended-spectrum β-lactamase–producing Enterobacteriaceae, carbapenem-resistant Enterobacteriaceae, vancomycin-resistant enterococci, or *Clostridium difficile*.[31,34,35] Interest in the "colonization resistance" effect of normal commensal aerobic and anaerobic gut bacteria is the basis for studies on recolonization via fecal transplantation in models of antibiotic dysbiosis and infection.[35,36] Different AVAs may be selected on the basis of their lack of impact on commensal flora as compared with antibiotics.

Impact of Antibiotic-Susceptible Infections

Although much focus is currently placed on the impact of antibiotic resistance on the risk of serious morbidity and mortality in patients with HAP or VAP, statistics show the persistent high burden of disease imposed by antibiotic-susceptible pulmonary pathogens in VAP patients. Thus, surveillance numbers in the United States have shown that although

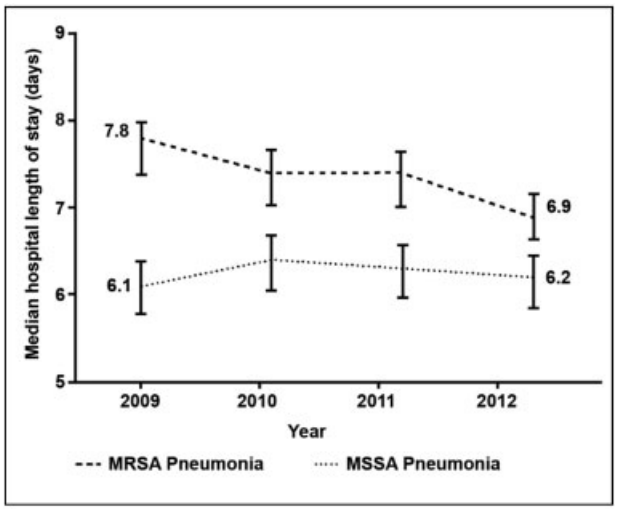

Fig. 3 Median length of hospitalization in adult patients ≥ 18 years of age with a primary diagnosis of *S. aureus*–associated pneumonia in the United States, 2009 to 2012. MRSA, methicillin-resistant *S. aureus*; MSSA, methicillin-sensitive *S. aureus*. (Adapted with permission from Jacobs and Shaver.[39])

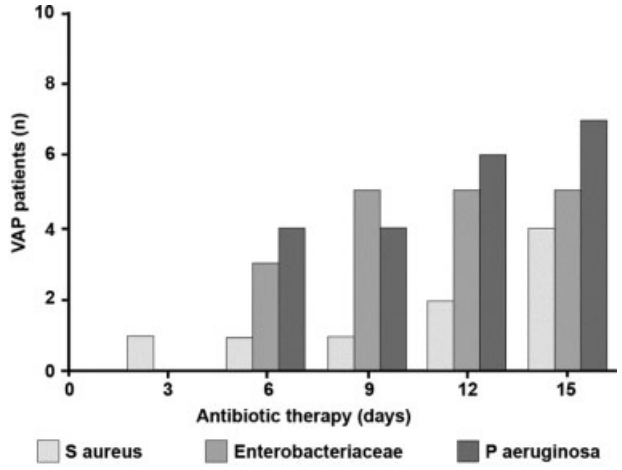

Fig. 4 Number of VAP patients with newly isolated microorganisms from endotracheal aspirates after beginning antibiotic treatment. VAP, ventilator-associated pneumonia. (Reproduced from Dennesen et al[97] with permission from the American Thoracic Society. Copyright © 2017 American Thoracic Society.)

most VAP pathogens are usually susceptible to one or more appropriate antibiotics,[25,37] the burden and severity of disease from these organisms remains high, as measured by hospital length of stay and total attributable health care costs.[38] This is exemplified by data from a U.S. surveillance study showing a sustained median length of stay among patients with methicillin-susceptible *S. aureus* that approaches the more recently observed median length of stay among patients with MRSA pneumonia (►**Fig. 3**)[39] and the appreciable length of stay associated with antibiotic-susceptible organisms in a variety of infections, including HAP and VAP.[13,22,38]

The large number of respiratory nosocomial infections caused by antibiotic-susceptible strains evokes several important considerations relevant to the design of new strategies for prevention of nosocomial pneumonia. First, the use of empirical or pathogen-specific antibiotic regimens does not attenuate the duration or severity of pneumonia in many patients infected with pathogens possessing multidrug resistance or phenotypic characteristics associated with greater virulence (e.g., Exo cytotoxins, lipopolysaccharide [LPS] 011 serotype antigen, *P. aeruginosa* Psl exopolysaccharide, *S. aureus* α toxin [AT], quorum-sensing [QS] molecules).[40] Second, pathogens that are initially susceptible to one or more antibiotics may become resistant to those antibiotics over days or weeks of therapy (►**Fig. 4**),[41] particularly in the absence of competitive nonpathogenic flora or microbiome dysbiosis caused by antibiotics.[42] Third, the potentially toxic physiologic effects of antibiotics and the release of inflammatory or toxic bacterial components during antibiotic therapy (e.g., LPS, Shiga toxins, lipoteichoic acids, peptidoglycans)[43–45] may actually contribute to patient morbidity during hospitalization. This is especially true with the use of antibiotics that target the cell wall components of bacteria (e.g., β-lactams), as opposed to the generally less proinflammatory effects of aminoglycosides or fluoroquinolones.[44,45]

Targeting Pathogen-Specific Virulence Factors

Continuing advances in the understanding of the virulence mechanisms utilized by *S. aureus* and *P. aeruginosa* (►**Table 2**) has opened the door for the development of an array of pathogen-specific AVAs that may effectively cure or curtail disease pathogenesis in various clinical settings of prophylaxis against or treatment of nosocomial pneumonia. Not only are these advances interesting from a strictly microbiological point of view but they may have the potential to augment therapy against both susceptible and drug-resistant organisms in the intensive-care setting. AVAs may exert their antimicrobial effects strategically, via mechanisms dissimilar but not inhibitory to the mechanisms by which antibiotics exert their biological effects. AVAs may also inhibit or halt pathogenesis without exerting the inevitable and often rapid selective pressure for evolutionary adaptation of resistance to one or more antibiotics.[46]

Classes of Antivirulence Agents

A large number of AVAs are currently being developed for prophylaxis and/or treatment of bacterial infections, including nosocomial pneumonia, and a select number of agents are currently entering clinical trials. AVAs targeting one or more pathogen-specific virulence factors include monoclonal antibodies (mAbs) against bacterial toxins, cell invasion mechanisms, immune evasion, and adhesion molecules, as well as antibody–antibiotic conjugates, bacteriophage lysins, and peptidomimetic inhibitors of QS pathways and anchoring enzymes.[40,47,48]

Monoclonal Antibodies

mAb-based AVAs provide multiple immunologic mechanisms of action against pathogens, including (1) direct neutralization of and specificity for virulence-associated epitopes or domains on bacterial toxins such as *S. aureus*

Table 2 Examples of *S. aureus* and *P. aeruginosa* virulence factors[48,66,98–101]

Virulence factor	Mechanism of action
S. aureus	
Autolysins	Enzymes involved in cell–cell cleavage and eDNA release in biofilm production
Adhesins	Polysaccharide intercellular adhesion and fibronectin-binding proteins
Leukocidins	Cell lysis by α-hemolysin (Hla) and leukocidins, HlgAB, HlgCB, LukED, and LukSF Panton–Valentine leukocidin, LukGH (LukAB), and phenol-soluble modulins
Proteases (e.g., GluV8)	Digest IgG antibody components and diminish effector function
Superantigens	Endotoxin B and exfoliative enterotoxin
Quorum-sensing factors	Regulate transcription of RNAII and RNAIII (*arg* locus) and α-hemolysin production
Immunoglobulin-binding factors (protein A, Sbi)	Immobilize IgGs and inhibit engagement of host immune factors
P. aeruginosa	
Pili/flagellum	Attachment to host cells and bacterial motility
LPS (endotoxin)	Attachment to host cell receptor (CD14) and proinflammatory effects
Exopolysaccharides (alginate, Psl, Pel)	Biofilm formation, attachment to mucosal surfaces, microcolony formation, shielding against antibiotics and immune defense mechanisms
Pyocyanin	Induces IL-8, depresses host immune response, induces apoptosis in neutrophils
Pyoverdine	Regulates secretion of *P. aeruginosa* virulence factors exotoxin A and an endoprotease
Alkaline protease	Fibrin-lysing protease
Protease IV	Degradation of surfactant proteins A, D, and B
Elastase	Ruptures epithelial cells' tight junctions
Phospholipase C	Attacks host cell membranes
Exotoxin A	An ADP-ribosyltransferase; inhibits protein synthesis, cell death
Type III secretion system	Includes the PcrV injectisome protein and injected Exo proteins (Exo U, S, T, and Y)
Quorum-sensing factors	Bacteria-to-bacteria cell signaling through small auto-inducing peptides and acyl lactones

Abbreviations: ADP, adenosine phosphate; eDNA, environmental DNA; IgG, immunoglobulin G; IL-8, interleukin 8; LPS, lipopolysaccharide.

hemolysin AT and LPS from gram-negative bacteria, (2) fixed complement-mediated lysis, (3) blocking of adhesion molecules to prevent bacterial attachment, (4) inhibition of QS molecules to prevent cellular aggregation and biofilm formation, and (5) opsonophagocytic killing (►**Fig. 5**).[40,46,49]

The success of vaccines in reducing MDR while significantly reducing or eliminating infection rates speaks to the importance of pathogen-specific immunity in containing the possible emergence of drug resistance.[50] Passive immunization with mAbs targeting bacterial virulence factors offers several potential therapeutic benefits to attenuate disease independent of antimicrobial resistance, including prophylaxis in colonized patients at risk for VAP (►**Table 3**).[51] These benefits may lead to more favorable clinical outcomes during therapy and reduction in the incidence of recurrent pneumonia.[40,46,52–54] Molecular engineering of mAbs also has the potential to further extend serum half-lives of the agents and provide multiple antigen (epitope) recognition on single antibody molecules. mAbs engineered for extended serum half-lives and those with specificity for multiple virulence factors may also increase the therapeutic window against faster growing pathogens in early-onset VAP (e.g., *S. aureus*)[52] as well as slower growing pathogens such as *P. aeruginosa* that are associated with late-onset VAP.[1]

Liposomal Decoys

A unique AVA-based approach to antimicrobial therapy is the use of liposomes made with sphingomyelin and supranormal concentrations of cholesterol, which act as adsorbent decoys for the membrane pore-forming cholesterol-dependent cytolysins (streptolysin O, tetanolysin, pneumolysin), α-hemolysin, and phospholipase C.[55] In a preclinical study, these liposomes effectively neutralized monocytolysis mediated by multiple toxins and provided survival benefit when injected several times within 24 hours after lethal *Streptococcus pneumoniae* pneumonia and bacteremia challenge, as well as *S. aureus* septicemia.[55] In that study, combination therapy with liposomes plus either vancomycin or penicillin significantly improved survival and lowered blood pneumococcal counts in mice compared with either antibiotic alone or placebo.[55] An ongoing randomized, double-blind, phase 1 study (NCT02583373) is evaluating the safety, efficacy, and

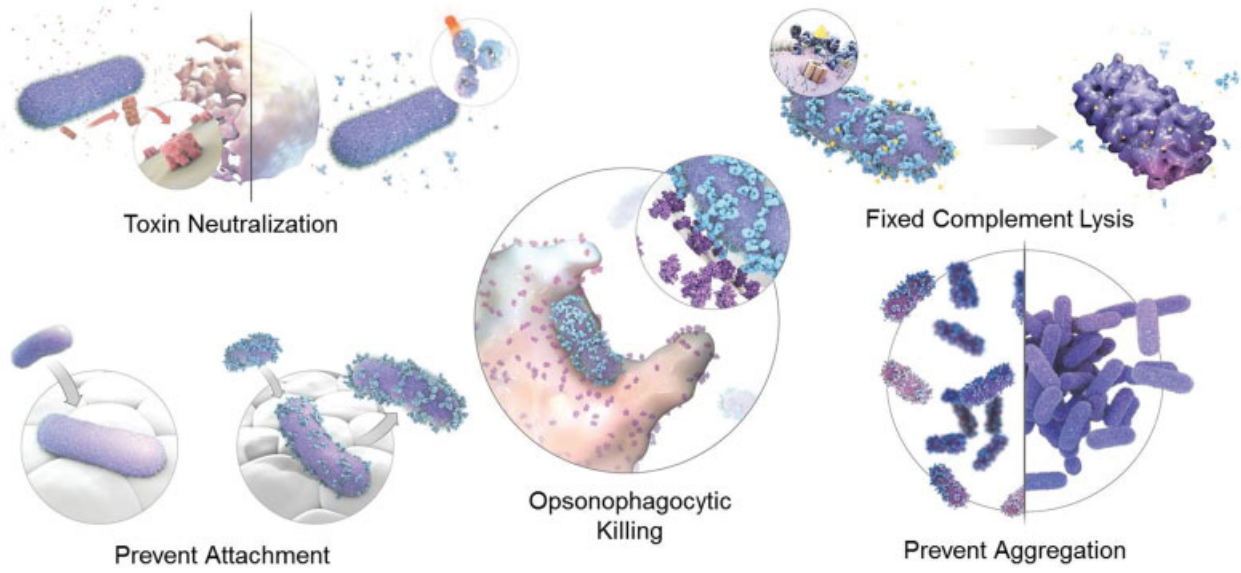

Fig. 5 Antibacterial mechanisms of antibodies.

pharmacodynamics of this liposomal preparation (CAL02; Combioxin) administered intravenously to patients with severe community-acquired pneumonia.

Quorum-Sensing Inhibitors

QS molecules are cell-density–dependent, auto-inducing regulators of bacterial virulence.[40,46,56] Bacteria secrete QS molecules during replication to levels that activate the expression of certain genes, such as the *agr* gene expression pathway in *S. aureus*[57–59] and *lasR* and or *rhlR* genes expression and rhamnolipid production by *P. aeruginosa*.[60] Examples of QS molecules include the *N*-acyl homoserine lactones (AHLs) used by gram-negative species, derivatives of the sugar-like molecule dihydroxypentanedione used by both gram-negative and gram-positive bacteria, auto-inducing oligopeptides used by gram-positive bacteria, and quinolone signaling molecules found in *Pseudomonas* spp.[56] QS inhibitors include AHL-degrading enzymes such as AHL lactonases and acylases, naturally occurring halogenated furanones and several AHL analogues,[40,56,61] and the antibiotic azithromycin, which has preferential inhibitory effects on transcription of *lasR* and *rhlR* codons and reduces rhamnolipid-dependent VAP in patients at high risk for *P. aeruginosa* nosocomial pneumonia.[62] The potential advantages of QS inhibitors include specific inhibition of bacterial virulence and infection without affecting bacterial growth or viability, thus averting selective antibiotic resistance.[63]

Leukocidins and Cytolysins

The cytolytic toxins of *S. aureus*, including α-hemolysin (AT), leukocidins, and phenol-soluble modulins, as well as components of the type 3 secretion system of *P. aeruginosa*, are being actively investigated as major AVA target molecules. In addition to the cytolytic effects of these molecules on host leukocytes and erythrocytes, some cytotoxins (e.g., *S. aureus* phenol-soluble modulins) regulate bacterial cell spreading in culture and *S. aureus* AT expression while also increasing virulence through cell–cell transmission of a plasmid carrying the *mecA* gene encoding methicillin resistance.[64,65] Hence, pathogen-specific inhibitors of bacterial cytolysins

Table 3 Potential therapeutic benefits with mAb-based AVAs[51]

Characteristic	Potential benefit
Specificity and MoA	Target one or more virulence-associated epitopes/domains No impact on the beneficial microbiome or cross-species resistance
Safety	Not targeting host immune mechanisms No drug–drug interactions with small molecules
Long half-life	Potential single-dose protection for 1–6+ mo with mAbs engineered for extended half-lives
Antibiotic preservation	No environmental exposure to select for antibiotic resistance Prophylaxis or treatment could decrease antibiotic use Adjunctive use could reduce resistance
MoAs can complement antibiotics	Synergistic effects with antibiotics increase host defenses and capacity to limit damage

Abbreviations: AVAs, antivirulence agents; mAb, monoclonal antibody; MoA, mechanism of action.

may help reduce longitudinal transmission of virulence and the cellular spreading involved in biofilm formation.[66]

Biofilm Inhibitors

In addition to the direct or indirect roles of QS molecules and cytolysins in bacterial virulence and biofilm formation, three or more exopolysaccharides contribute to the characteristic biofilm formation by *P. aeruginosa* in the lungs of patients with cystic fibrosis: these are alginate, Psl, and Pel. All three of these polysaccharides enhance bacterial virulence via protection (shielding) against antibiotics and immune defense mechanisms, attachment to mucosal surfaces, and microcolony formation.[67,68] Inhibitors of biofilm-forming or biofilm-promoting virulence factors may enhance the antibacterial activities of other AVAs while decreasing bacterial colony formation and spreading. ►**Table 4** lists a number of investigational AVA molecules being assessed in various preclinical models of *S. aureus* and *P. aeruginosa* infections.

Other interesting staphylococcal virulence factors not yet studied in preclinical models of infection include the bacterial glycosyltransferases SdgA and SdgB, which modify certain proteins such as the fibronectin adhesion protein clumping

Table 4 *S. aureus*– and *P. aeruginosa*–specific AVAs in research or preclinical development

AVA type (name)	MoA/specificity	Test or infection model
S. aureus		
mAb combination	Binds AT rim domain (MEDI4893*) and ClfA (mAb 11H10)[102]	Inhibits bacterial aggregation, promotes opsonophagocytic bacterial killing, and survival in mouse bacteremia
Antibody-antibiotic conjugate (THIOMAB)	Antibiotic targeted to *S. aureus* via mAb that binds to cell wall lipoteichoic acid[103]	Rifamycin derivative-antiteichoic acid antibody combination promotes intraphagocytic killing of *S. aureus*
Polyclonal antibodies	Neutralize bicomponent *S. aureus* leukotoxins[104,105]	In vitro cytotoxicity neutralization, mouse *S. aureus* sepsis model, and correlates of antileukotoxin antibody levels in patients with *S. aureus* sepsis
mAb (THP101)	Neutralizes glucosaminidase (Gmd) subunit of *S. aureus* autolysin (Atl)[106]	In vitro bacterial aggregation and murine model of implant-associated osteomyelitis
mAb cocktail	Tripartite mAb cocktail neutralizes ricin, staphylococcal enterotoxin, and *Clostridium perfringens* epsilon toxin[107]	Mouse models of lethal toxemia
mAb	Binds to immunodominant *S. aureus* cell wall transglycosylase autolysin[108]	Mouse bacteremia
Peptidomimetic	Peptidomimetic inhibitor of QS AIPs[109,110]	In vitro inhibition of AIP-induced AgrC activity
P. aeruginosa		
QS inhibitor compounds (M64)	Inhibit the QS MvfR regulon in multidrug-resistant isolates[63]	In vitro bactericidal and antibiotic resistance, macrophage cytotoxicity, and murine models of acute infection (thermal injury and lung infection)
Cell wall lysin (Mul-1867)	Nonspecific attack on the cell walls of MDR *P. aeruginosa*[111]	Inhibits *P. aeruginosa* biofilm formation in vitro
Enzyme inhibitor (compound 14, others)	Inhibits PyrD[59] (a dihydroorotate dehydrogenase)	Bacterial colonization in a mouse model of acute pneumonia
Enzyme inhibitor (NLF20)	Serine proteinase inhibitor heparin cofactor II[112]	Lethal *P. aeruginosa* challenge
Antimicrobial peptide (SB056)	Amphipathic β-stranded peptide disrupts bacterial lipid membranes[113,114]	In vitro antimicrobial activity, hemolysis, membranolytic, and peptide-binding (CD) studies
Anticalins	Engineered lipocalins with broad protein-binding capacity[115]	Tetraspecific anticalins bind four classes of *P. aeruginosa* siderophores (QS-driven iron-scavenging peptides)
Peptidomimetic (L27–11)	Inhibits LPS transport function of outer membrane protein LptD of gram-negative bacteria[116]	In vitro antimicrobial activity

Abbreviations: AIP, autoinducer peptide; AVA, antivirulence agent; LPS, lipopolysaccharide; mAb, monoclonal antibody; MDR, multidrug resistant; MoA, mechanism of action; QS, quorum-sensing.

factor and protein A in *S. aureus* and *S. epidermidis*,[69] and *S. aureus* sortases, which are transpeptidase enzymes involved in anchoring of virulence factors to the bacterium's cell wall.[70]

Antivirulence Agents in Clinical Development

Monoclonal Antibodies

Several mAbs are being investigated as single-agent, passive-immunization prophylaxis against HAP or VAP in patients colonized with either *S. aureus* or *P. aeruginosa* or as adjunctive treatment to standard antibiotic therapy of clinically diagnosed HAP or VAP. Currently, four mAb-based AVAs each have entered into phase 1 or 2 clinical trials in patients with *S. aureus* or *P. aeruginosa* nosocomial pneumonia.

S. aureus Monoclonal Antibodies

Two of four mAb-based AVAs against *S. aureus* target epitopes on the AT rim domain and inhibit the assembly of AT subunits into pore-forming complexes. The first, AR-301 (Aridis Pharmaceuticals), is reported to reduce bacterial load and significantly improve survival in models of localized and systemic *S. aureus* infections. A double-blind, placebo-controlled, four-dose cohort, phase 1/2a clinical trial evaluating the safety, pharmacokinetics, and efficacy of AR-301 in subjects with *S. aureus* HAP and VAP was completed in July 2016.[71] The second AT-specific mAb, MEDI4893 (MedImmune), is an immunoglobulin G1 (IgG1) kappa molecule with a triple–amino-acid substitution, M252Y/S254T/T256E (YTE), engineered into the Fc region of the antibody to extend its serum half-life.[72] MEDI4893 recognizes a highly conserved region of *S. aureus* AT that has been identified in $>$ 97% of *S. aureus* global clinical isolates sequenced to date.[73,74] This mAb exerts its neutralizing activity through the dual mechanisms of sterically blocking binding of AT to its cognate cellular receptor and preventing formation of the pore-forming heptameric AT complex.[72] Subtherapeutic doses of this mAb and vancomycin or linezolid have been shown to synergistically improve survival and extend the antibiotic treatment window against *S. aureus* pneumonia in immunocompromised mice.[54] The safety and pharmacokinetics of MEDI4893 have been studied in a phase 1 dose escalation trial, and it is currently being assessed for its efficacy and safety in an international phase 2 dose-ranging study (SAATELLITE, NCT02296320; EUDRA EudraCT 2014–001097–34) in mechanically ventilated and nonventilated subjects colonized with *S. aureus*.[75]

ASN100 (Arsanis, Waltham, MA) is a combination of two mAbs: the first (ASN1) selected for neutralizing specificity for a common rim domain epitope shared by *S. aureus* AT and four of five leukocidins (HlgAB, HlgCB, LukED, and LukSF) (PVL), and the second mAb (ASN 2) with neutralizing specificity for LukGH (LukAB).[76,77] In a rabbit model of *S. aureus* necrotizing pneumonia, the prototype mAb for ASN-1 (Hla-F#5) provided passive protection against lethal respiratory challenge with the SF8300 MRSA strain and also significantly reduced bacterial counts in lung, spleen, and kidney compared with a monospecific anti-AT mAb and control mAb (motavizumab). A phase 2 study (NCT02940626) is ongoing to assess the safety and efficacy of a single dose of ASN100 for the prevention of *S. aureus* pneumonia (primary end point, clinical symptoms) in heavily colonized, mechanically ventilated subjects.[78]

514G3 (XBiotech, Austin, TX) is an investigational mAb that has been shown to promote opsonophagocytic activity against all forms of *S. aureus* while neutralizing immune evasion mechanism(s).[79] This mAb binds to *S. aureus* protein A in a manner that inhibits protective coating of the bacterium's cell wall with host serum IgG molecules while allowing complement-dependent lysis of *S. aureus* cells.[80] XBiotech has completed enrollment in a phase 1/2, two-arm randomized, placebo-controlled, dose escalation study of 514G3 for the treatment of serious infections (bacteremia) due to *S. aureus* (NCT02357966). Although no published data on this agent are yet available, information provided indicates a direct correlation between the pharmacokinetics of the antibody in treated subjects and whole blood clearance of *S. aureus* in vitro.[79]

P. aeruginosa Monoclonal Antibodies

A total of four mAb-based AVAs are being or have been evaluated in early clinical trials for safety and efficacy against *P. aeruginosa* nosocomial pneumonia. Two of these mAbs are engineered to target the PcrV protein located on the tip of the *P. aeruginosa* T3SS injectisome complex that is responsible for host cell toxicity by the ExoU, ExoT, and ExoS cytotoxins. The first, KB001 (KaloBios, Brisbane, CA), is a pegylated mAb Fab′ fragment that has been evaluated in a phase 1 pilot safety study in mechanically ventilated subjects colonized with *P. aeruginosa* (NCT02940626) and in a phase 2 study in subjects with cystic fibrosis (NCT00638365). Data from the study in mechanically ventilated subjects showed improvements in incidence of clinical pneumonia, catheter-related infection, and 28-day overall and infection-free survival compared with placebo.[81] However, results from the cystic fibrosis trial showed no benefit based on the failure to meet the primary end point of increased time to need for antibiotics for worsening respiratory tract signs and symptoms of infection.[82]

MEDI3902 (MedImmune) is a bispecific mAb engineered to recognize and bind simultaneously to both the PcrV protein and the Psl exopolysaccharide involved in biofilm formation on host tissue substrates and endotracheal tube surfaces.[83,84] The preclinical prototype of MEDI3902 (BiS4αPa) has demonstrated marked neutralization of *P. aeruginosa*-mediated cytotoxicity and protection against lethal pneumonia in immunocompromised mice, thermal injury, and bacteremia.[84] Subtherapeutic levels of this mAb and antibiotics provided synergistic protection against lethal pneumonia in mice, thus providing supporting evidence for the efficacy of a bispecific mAb.[84] This mAb has been studied in a recently completed phase 1 dose escalation study in healthy adult subjects (NCT02696902), with a publication of study results in progress. A European phase 2 dose-ranging study of MEDI3902 (EVADE, NCT02696902; EUDRA EudraCT 2015–001706–34) is currently assessing the efficacy and safety of this mAb in mechanically ventilated and nonventilated subjects colonized with *P. aeruginosa*.[75]

Aerucin (Aridis Pharmaceuticals, San Jose, CA) is an IgG mAb that binds to the *Pseudomonas* alginate exopolysaccharide involved in cellular adhesion. A phase 1 dose-escalation study of this mAb in healthy subjects has been completed (NCT02486770),[85] and a phase 2, placebo-controlled, double-blind study is planned to assess the molecule's safety and efficacy as adjunctive therapy to standard antibiotics in subjects with *P. aeruginosa* HAP/VAP (NCT00851435).

A fourth mAb AVA, panobacumab (Aridis Pharmaceuticals), is a fully humanized IgMκ opsonizing antibody against the LPS serotype 011 antigen that is present on ~20% of *P. aeruginosa* clinical isolates. A phase 1 dose escalation trial demonstrated the molecule's safety and tolerability, linear pharmacokinetic profile, and relatively short serum half-life of 70 to 95 hours (± 20–24 hours).[86] A post hoc analysis of a phase 2a open-label study showed that adjunctive treatment of pneumonia with three doses of panobacumab infused over a period of 7 days plus standard antibiotic therapy ($n = 17$) resulted in significantly shorter time to clinical resolution as compared with subjects not treated with the mAb ($n = 14$).[87]

Bacteriophages

Predating the introduction of antibiotics, bacteriophages are potentially useful therapeutic agents against virulent bacteria in different sites of infection. Their distinguishing characteristics and potential advantages include specificity for particular strains and species of bacteria, lack of infectivity for eukaryotic cells, and no effect on normal microflora. To date, four phage-based AVAs are being evaluated in phase 1 or 2 human subject trials. The first, CF-301 (ContraFect Corporation, Yonkers, NY), is a phage-derived, peptidoglycan-cleaving recombinant hydrolase lysin that has been shown to synergize therapeutically with antibiotics in a murine model of *S. aureus* bacteremia[88] and is currently being assessed in a phase 1 dose escalation study in 20 healthy adult subjects.[89] Another intravenously administered *S. aureus*–specific phage lysin, SAL200 endolysin (N-Rephasin; iNtRON Biotechnology, Seongnam, Korea), has recently completed a phase 2a trial (NCT01855048) in healthy subjects. The toxicology of this agent has been tested in rodents and dogs.[90] Clinical studies with *Pseudomonas*-specific bacteriophages include (1) phase 1 or 2 trials with Biophage-PA (AmpliPhi Biosciences, San Diego, CA), a phage cocktail topical therapy for chronic *Pseudomonas* otitis media[91] and (2) Phagoburn (Pherecydes Pharma, Romainville, France), a phage topical therapy for burn wounds associated with *P. aeruginosa* infection (NCT02116010). The use of bacteriophages as inhaled therapy against *P. aeruginosa* nosocomial pneumonia is currently being tested in preclinical studies.[92]

Challenges in Pathogen-Specific Approaches to Targeted Therapies

In contrast to the potential advantages of pathogen-specific AVAs in alleviating the duration and severity of HAP or VAP, several challenges exist for the development and clinical implementation of AVAs. These challenges include diagnostic considerations, evolution of clinical practice, and trial design and subject enrollment.

Diagnostic Considerations

Optimum utilization of AVAs may rely in part on the ability of clinicians to perform rapid bedside diagnostics to quickly identify the specific pathogens causing disease in individual patients.[93] Advances in molecular diagnostics, such as multivalent polymerase chain reaction analysis or automated microscopy, offer the ability to perform rapid real-time identification of pathogens, which can be confirmed with companion microbiological methods to measure antibiotic susceptibility profiles and the spectrum of pathogens.[94–96] In conjunction with rapid diagnosis, targeting specific virulence factors with AVAs may provide increased potential for individualized therapy in a bench-to-bedside approach to therapy. Early diagnosis may also open the door for prophylaxis and the potential to avoid inappropriate use of broad-spectrum antibiotics before or at the time of clinical diagnosis of pneumonia. However, current reliance on conventional microbiological identification of causative pathogens and generally limited use of rapid diagnostic methods may represent barriers to the therapeutic use of AVAs in settings of early intervention for pneumonia.

Evolution of Clinical Practice

A significant impediment to acceptance and usage of AVAs may be the need for a paradigm shift in the way physicians, hospitals, and payers view the utility of these agents against the backdrop of established clinical practice.[46] In addition, the greater health care costs associated with newer agents that work differently from antibiotics may cause some hesitancy for their use if the long-term outcomes are not as clearly defined as the known and expected effects of antibiotics.

Trial Design and Enrollment

Designing clinical trials to assess the safety and efficacy of AVAs is challenging from several standpoints. These can include (1) the need to determine whether the trial design is relevant to the actual clinical scenario of pneumonia in HAP and VAP; (2) difficulties in recruitment of appropriate trial subjects, which can significantly and negatively impact clinical development timelines and substantially increase costs; (3) access to and proper use of rapid diagnostic platforms at clinical sites; (4) specimen collection and analysis; (5) subject population size and statistical considerations; and (6) identification of the most important and critical primary clinical end points and secondary end points.

Defining appropriate and clinically meaningful study end points is an important component of trial design for newer agents. For example, to assess the efficacy of AVAs that are amenable to preventive prophylaxis, subjects enrolled in trials may be required to meet the criteria for a quantitative threshold of bacterial colonization that supports therapy before a clinical diagnosis has been made on the basis of signs and symptoms of disease. Primary end points should be designed to be objective and reproducible, according to

guidance from the U.S. Food and Drug Administration, the European Medicines Agency, and the Infectious Diseases Society of America, including clinical, radiographic, and microbiologic findings consistent with new-onset pneumonia in mechanically ventilated and nonventilated patients. In light of the possible challenges to patient enrollment that may negatively affect clinical trial design and execution, it may be necessary to base regulatory approval of AVAs on a collection of small, randomized phases 2 and 3 studies that, taken together, provide enough clinical evidence for sufficient regulatory review.

Summary

In the era of emerging MDR strains of bacterial pathogens and the remaining high morbidity and mortality associated with nosocomial pneumonia, newer strategies need to be explored for control of life-threatening pneumonia. The rationale for utilizing pathogen-specific AVAs against *S. aureus* and *P. aeruginosa* virulence factors is supported by the continuing emergence and high rates of antimicrobial-resistant and MDR strains, the deleterious microbiome effects of antibiotics, inappropriate antibiotic usage, and high burden of disease in VAP caused by antibiotic-susceptible pathogens.

Fundamental reasons for developing AVAs revolve around the concept of inhibiting or attenuating pathogen virulence associated with the severity of pneumonia without altering the host microbiome and avoiding risks for antimicrobial resistance, drug–drug interactions, and antibiotic toxicities. Advances in research and the clinical effectiveness of pathogen-specific AVAs such as mAbs, bacteriophage cocktails and cell wall lysins, QS inhibitors, and antimicrobial peptides will ultimately determine their appropriate and optimal use in patients with nosocomial pneumonia, with a focus on the overarching medical need in patients with HAP or VAP.

Advantages of mAb-based agents include target specificity, infrequent or single administration, low immunogenicity, potential for prophylactic use in colonized patients at risk for pneumonia or as adjunctive therapy to standard-of-care antibiotic regimens, and ability to engineer multispecific and extended half-life mAbs against different virulence factors, including common antigens. Non–mAb-based AVAs offer therapeutic selectivity and specificity based on molecular mimicry of virulence factors, direct bactericidal effects, or inhibition of virulence factors associated with bacterial colonization and immune evasion. Data from ongoing clinical trials will help determine whether the positive results that have been observed with various AVAs in experimental models of pneumonia, in particular, as well as in other tissue infections, can be translated into positive outcomes in hospitalized patients. Depending on clinical study results, some AVAs may become an integral part of individualized therapy for HAP and VAP, which will be supported by greater utilization of rapid molecular diagnostics. Despite the potential advantages of AVAs in the treatment and prevention of pneumonia, several challenges exist for their uptake and utilization in clinical practice and in clinical trial design.

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Is There a Role for Inhaled Antibiotics in the Treatment of Ventilator-Associated Infections?

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Abstract

The increasing emergence of multidrug-resistant organisms creates a therapeutic challenge for physicians treating ventilator-associated respiratory infections. As the production of new systemic antibiotics lags far behind the emergence of worsening antibiotic resistance, intensivists are turning to inhaled antibiotics to use as adjunctive therapy. When given properly, these drugs can provide high concentrations of drug in the lung that could not be achieved with intravenous antibiotics without significant systemic toxicity. This review summarizes current evidence describing the use of inhaled antibiotics for the treatment of bacterial ventilator-associated infections. Inhaled adjunctive therapy has been described in numerous small nonrandomized studies and in six recent randomized placebo-controlled trials. Inhaled therapy has also been used to treat ventilator-associated tracheobronchitis. These preliminary data suggest aerosolized delivery of antimicrobials may effectively treat resistant pathogens with high minimum inhibitory concentrations when used in time-limited protocols and delivered with devices known to deposit antibiotics in the area of infection. Large, multisite, clinical, randomized placebo-controlled studies are needed to confirm these data.

Keywords

- inhaled antibiotics
- ventilator-associated tracheobronchitis
- ventilator-associated pneumonia
- bacterial resistance
- colistin
- amikacin

Ventilator-associated respiratory infections remain the leading cause of death related to nosocomial infection in critically ill patients.[1–3] Equally important, treatment of these infections accounts for more than 50% of the antibiotic use in the intensive care unit (ICU).[4,5] The morbidity and mortality related to respiratory infections remain significant and may vary with the causative organism.[6–8] In a 2009 review of clinical outcomes of health care–related infection in European ICUs, 4,457 patients were identified with ventilator-associated pneumonia (VAP) caused by *Pseudomonas aeruginosa*, *Acinetobacter baumannii*, *Escherichia coli*, or *Staphylococcal aureus*.[5] The excess risk of death from VAP (hazard ratio) was 1.7 (95% confidence interval [CI], 1.4–1.9) for drug-sensitive *Staphylococcal aureus* and 3.5 (95% CI, 2.9–4.2) for ceftazidime-resistant *Pseudomonas*. Multidrug-resistant (MDR) pathogens in the ICU patient change their susceptibility rapidly in the presence of systemic antibiotics and easily outpace Pharma's motivation to create new systemic antibiotics. There is an urgent call for new therapies. Some regions of the world now have gram-negative pathogens that are extensively drug resistant (XDR), that is, resistant to all antibiotics including colistin.[9]

Despite increasing evidence of the clinical resolution rates of ~50% and mortality of 25% with the use of current systemic antibiotics, the role for inhaled antibiotics remains controversial and recent guidelines remain cautious about their use.[1] The 2016 American Thoracic Society (ATS) guidelines suggest, "for patients with VAP due to gram-negative bacilli that are susceptible to only aminoglycosides or

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polymyxins (colistin or polymyxin B), we suggest both inhaled and systemic antibiotics, rather than systemic antibiotics alone" (weak recommendation). Enthusiasm about their use varies, but all intensivists agree that failure rates with intravenous (IV) therapy are high and that new forms of therapy are needed. Inhaled antibiotics may be a useful mode of treatment, but more data are needed about the proper dose and delivery device to ensure efficacy as shown in a recent point counterpoint in chest.[10,11]

Regardless of guidelines and controversy, ICU physicians in regions of the world with endemic MDR or XDR gram negatives are already responding to the lack of effective systemic antibiotics by adding inhaled antibiotics empirically to their VAP treatment regimens.[12–14] Empiric therapy with off the shelf nebulizers and off label use of antibiotics is their only choice as 45 years after the initial instillation of antibiotics into an endotracheal tube or a tracheostomy have no commercially available Food and Drug Administration approved inhaled drugs on the market for ventilated patients.[15–24]

In this article, we review the literature with emphasis on the most recent data concerning inhaled antibiotics including:

- Rationale for this mode of delivery
- Clinical outcomes and their relationship to delivery device
- Microbial effects of inhaled antibiotics
- Concerns
- Future.

Background

The earliest studies of inhaled antibiotic therapy were driven by the same clinical problem that plagues us now, the emergence of resistance to the currently available systemic antibiotics. Resistant gram-negative organisms, in particular, *Pseudomonas* species, were causing respiratory infections in intubated patients and clinical response to IV therapy was poor.[12–14] At that time, aminoglycosides given intravenously were the primary treatment for gram-negative organisms and treatment failure occurred in up to 60% of patients. These poor outcomes were thought to be due to poor penetration of the aminoglycosides into the lung; therefore, methods of increasing the concentration via direct delivery were investigated with some success.

Now, more than 40 years later, we still have the same problems with resistant MDR gram negatives. The rapid emergence of resistance to β lactams and carbapenems, and the poor penetration of amikacin to the lung are leading to two changes in treatment. One is the use systemic colistin which when given is associated with significant systemic side effects. The other is off label use of inhaled antimicrobials with no well validated dosing or defined devices for most studies. There is one Phase 3 randomized controlled trial (RCT) in ventilated patients for VAP which is currently enrolling patients. A recent Phase 2 trial[25] of amikacin fosfomycin inhalation system (AFIS) failed to show any benefit of the inhaled antibiotic, which we shall address in more detail later.

Rationale for Aerosolized Antibiotic Therapy in the Ventilated Patient

The theoretical reasons for using targeted antimicrobial therapy in mechanically ventilated patients include:

- Direct delivery to the site of infection
- Deposition site can be targeted
- Achievable concentrations in the lung are far higher (> 100–1,000-fold) than would be tolerated if given intravenously
- The microflora of the gut will not be altered, thus reducing the emergence of MDR organisms (MDRO)
- Shortening of the duration of systemic antibiotics.

Of these five rationales, the first three are well proven. It has been shown in multiple studies that antibiotic concentrations achieved in the lung in secretions as well as bronchoalveolar lavage with targeted therapy far exceed the minimum inhibitory concentration (MIC) of pathogens with very low or nondetectable levels in the serum.[26,27] These high concentrations in secretions result in a large ratio of maximum concentration/MIC.[28] This index has been shown to be important for eradication of organisms in the milieu of thick purulent secretions, biofilm, and diminished mucociliary clearance.[29] Also, devices can be designed for proximal or peripheral delivery (►**Fig. 1**).

The data on effects or lack of effects of inhaled therapy on gut flora have not been measured directly. There are data demonstrating a decrease in respiratory MDRO after treatment even when patients are on concomitant systemic therapy. These investigations will be discussed later as will potential effects on systemic antibiotic use.

The fifth rationale, the possibility that the addition of inhaled antimicrobials may decrease the amount or duration of systemic antibiotic therapy needs further investigation. There is only preliminary data at this time. One investigation has shown that less additional systemic antibiotics were added to patients who received inhaled antibiotics as adjunctive therapy, and another trial demonstrated the number of systemic antibiotics used decreased during the trial in the patients receiving adjunctive active drug.[30,31] Investigations designed to test the hypothesis that systemic antibiotic use will be decreased in the presence of inhaled therapy are needed. If this hypothesis were correct, then the driving pressure for new resistance from the use of IV antibiotics would decrease.

Inhaled Antibiotics for Prevention of Ventilator-Associated Pneumonia

The use of inhaled antibiotics, as prophylaxis for VAP, is not well supported at this time. A meta-analysis by Falagas et al reviewed the literature from 1950 to 2005.[32] Of the 12 prophylactic trials, there were only eight investigations that were either RCTs or prospective comparative trials (five RCTs and three nonrandomized prospective comparative trials).[14,33–39] These studies combined nebulization with intratracheal instillation. Aerosolized gentamicin was used in three trials, polymyxin in two, tobramycin in one, and ceftazidime in one. There were 1,877 patients included in the meta-analysis. Primary outcomes were incidence of VAP and

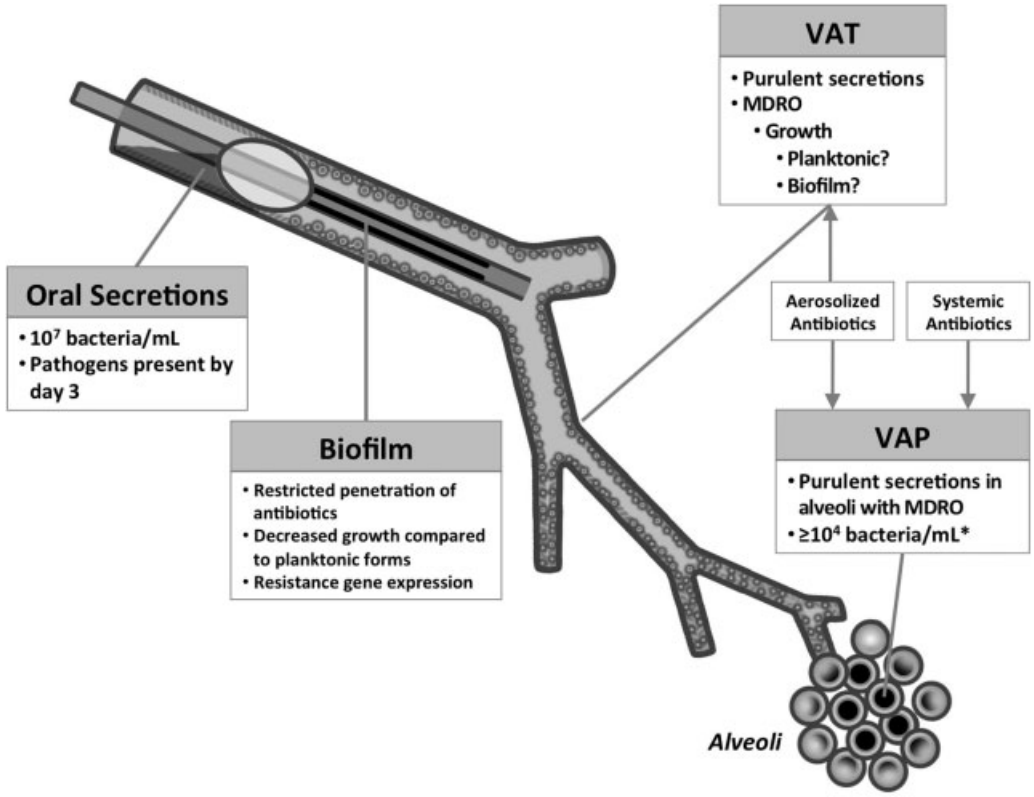

Fig. 1 This figure depicts the multifactorial process that leads to VAT and VAP. Subglottic secretions, disturbed mucociliary clearance, damaged mucosa, and bacterial biofilm may all play a role in the pathogenesis of proximal and distal infection. Within a few days of ICU admission, the bacteria are frequently MDRO. *The 10^4 cfu/mL cutoff for the microbiologic diagnosis of VAP may not pertain to patients with prolonged mechanical ventilation. ICU, intensive care unit; MDRO, multidrug-resistant organisms; VAP, ventilator-associated pneumonia; VAT, ventilator-associated tracheobronchitis. (Modified from Palmer.[58])

mortality. Secondary outcome was colonization with *P. aeruginosa*. Analysis of the five RCTs demonstrated a reduction in VAP in the treated patients with an odds ratio (OR) of 0.49 (95% CI, 0.32–0.76).[14,33,35,36,39] However, there was no effect on mortality, and there were insufficient data to assess the effect on bacterial colonization. Addition of the three nonrandomized trials to their meta-analysis yielded similar results for VAP; however, in this analysis, there was a reduction in VAP in patients colonized with *P. aeruginosa* in the group that received prophylaxis (OR, 0.51; 95% CI, 0.30–0.86). Although these data are of interest, there are no recent trials examining the role of inhaled prophylactic therapy or any guidelines that recommend this therapy. It should be noted these older prophylactic studies used a variety of delivery devices, often had no data on concentrations of the antibiotic in the lung, and represented pathogens that have currently evolved to be more resistant. RCTs with standardized delivery methods; appropriate new end points, such as ventilator-free days; reduction in the use of systemic antibiotics; and effects on bacterial resistance are needed.

Evidence for Treating Ventilator-Associated Tracheobronchitis and/or Ventilator-Associated Pneumonia

The early evidence supporting the use of inhaled antimicrobials was analyzed by Ioannidou et al in a meta-analysis of small RCTs done from 1950 to 2007.[40] The clinical efficacy of topical administration (aerosolization or instillation) with or without concurrent usage of systemic antibiotics for treatment of VAP was examined. Of 685 potential relevant articles, there were only five RCTs[12,13,41–43] with a combined total of 176 patients suitable for analysis. Antibiotics used included tobramycin, sisomicin, and gentamicin. In four of the five trials, the aerosolized antibiotic was adjunctive to IV therapy.[12,41–43] This meta-analysis demonstrated that patients receiving aerosolized or instilled antibiotics had higher rates of resolution of signs and symptoms of VAP (clinical diagnosis), intention-to-treat fixed effect model: OR, 2.39; 95% CI, 1.29–4.44; random effect model: OR = 2.75; 95% CI, 1.06–7.17 and when analyzed for clinically evaluable patients had an OR = 3.14; 95% CI, 1.48–6.70; and in random effects model, OR = 3.07; 95% CI, 1.15–8.19. There were no statistically significant differences between therapeutic regimens for mortality or toxicity.

Since Ioannidou et al's analysis, there have been multiple studies including prospective observational comparator trials, retrospective investigation, and RCTs. These are shown in ►**Table 1** which describes devices, and drugs used and microbiologic and clinical responses.[17,18,30,44–46]

Many of these are included in the four more meta-analyses and/or systematic reviews of inhaled antibiotics used to treat respiratory infections in ventilated patients

Table 1 Delivery device and microbiological and clinical response to inhaled antibiotics in the ICU 2008 to 2016[a]

Authors (year) Setting	Design	Drug and method of aerosolization Number of patients on IA or IV or placebo	Number of patients with eradication of causative organism	Number of patients with newly resistant organisms	Clinical response
Palmer et al[30] (2008) ICU, United States	Randomized double-blind, placebo controlled	Vancomycin and/or gentamicin, jet nebulizer; placebo-24; 19/24 (79%) also on IV IA-19; 17/19 (89%) also received IV	IA 6/8 (75%) at day 14 Placebo; 3/14 (21%)	Placebo 8/24 (33%) IA 0/19 (0%)	IA vs. placebo Resolution of VAP (adjusted odds ratio, − 0.29; 95% CI, 0.13–0.66, $p = 0.006$). Reduced use of systemic antibiotic $p = 0.042$ Increased weaning $p = 0.046$
Niederman et al[31] (2008) Multicite phase 2 trial in United States, Spain, and France	VAP-clinical diagnosis Proprietary amikacin BAY41–6551 vibrating mesh nebulizer 67 patients divided into three groups	All received IV antibiotics according to ATS Guidelines 2005 Inhaled amikacin[b] at 400 mg Q 12H and 400 mg Q 24H Placebo-normal saline Q 12H	Inhaled amikacin[b] 22/33 (68.8%) Placebo 10/16 (62.5%)	Not described	Inhaled amikacin[b] Q 12, 93.8% (15/16) Inhaled amikacin[b] Q 24H 75.0% (12/16), and placebo 87.5% (14/16) ($p = 0.467$) mean number of antibiotics per patient per day Inhaled amikacin[b] Q12 0.9/d in the q12h, inhaled amikacin[b] q24h 1.3/d in the q24h, and placebo 1.9/d in the placebo groups, $p = 0.02$ between groups
Kofteridis et al[17] (2010) ICU, Greece	Retrospective review, matched case–control	Colistin Aerosolization not described IV and aerosolized colistin-43 IV colistin-43	IV = 17/34 (50%) IV + IA, 19/42 (45%) $p = 0.679$	No resistance in IA group Resistance in IV group not described	IA + IV vs. IV Clinical cure $p = 0.679$ Mortality $p = 0.289$
Korbila et al[18] (2010) ICU, Greece	Retrospective review, matched case–control	Colistin Aerosolized via Siemens Servo ventilator, aerosolized colistin + IV-78 IV colistin-43	Not described	Not described	Cure IV + IA 62/78 (79%) vs. IV = 26/43 (60%) $p = 0.025$ ICU mortality 28/78 (36%) vs. 17/43 (40%) $p = 0.92$
Rattanaumpawan et al[44] (2010) ICU, Thailand	Open label RCT	Colistin Aerosolization not described IA + IV-51 Placebo + IV-49	IA + IV 31/51 (61%) Placebo + IV 19/49 (39%), $p = 0.03$	Not described	IA + IV 26/51 (51%) Placebo + IV 25/49 (51%), $p = 0.84$ AA group, shorter days of IV antibiotic
Lu et al[45] (2011)ICU France	Randomized trial comparing IA to IV antibiotics	Vibrating plate nebulizer Nebulized amikacin and ceftazidime $N = 20$ Amikacin and ceftazidime IV $N = 20$	IA-16/16 (100%) on day 5 IV-7/15 (47%) on day 5	IA day 9, 0/12 (0%) IV day 9, 5/11 (45%)	IA 14/20 (70%) IV 11/20 (55%) $p = NS$
Arnold et al[60] (2012) MICU SICU United States	Retrospective chart review with cohort study	Colistin Vibrating plate Inhaled antibiotics Colistin $N = 9$, tobramycin $N = 10$. All patients also on IV IV only $n = 74$	Not described	Not described	Increased survival by Kaplan–Meier for IA + IV $p = 0.030$

Table 1 (*Continued*)

Authors (year) Setting	Design	Drug and method of aerosolization Number of patients on IA or IV or placebo	Number of patients with eradication of causative organism	Number of patients with newly resistant organisms	Clinical response
Lu et al[46] (2012) ICU France	Prospective, observational comparator	Colistin Vibrating plate nebulizer 3 arms (1) Cohort group with organisms susceptible to β − lactams Tx = IV only $N = 122$ (2) Group with organisms resistant toβ-lactams Tx = IV plus AA $N = 15$ (3) Group with organisms resistant to β-lactams Tx = AA alone $N = 28$	Not reported	Reported for patients with recurrent infection AA 4/16 (25%) converted from β-lactam resistant to susceptible after inhaled therapy IV 24/32 = 75% of isolates developed new resistance 6/32 became resistant to all β-lactams	Clinical cure β-lactam susceptible group on IV = 81/122 [66%] β-lactam resistant group 29/43 (67%) p = NS Mortality β-lactam susceptible group on IV 28/122(7%) β-lactam resistant group on AA 7/43 (16%) $p = 0.357$
Doshi et al[59] (2013) Medical Surgical ICUs United States	Retrospective multicenter cohort study	Colistin Aerosolized with jet nebulizers or vibrating mesh nebulizer IV only = 51 patients IV plus AA colistin = 44	IV 27/51 (53%) IV + IA 18/44 (41%) $p = 0.805$	Not described	In patients diagnosed with BAL IV-9/32 (31.3%) IV + AA 19/35 (57%) $p = 0.033$
Tumbarello et al[61] (2013) ICU Italy	Retrospective cohort study	Colistin Jet or ultrasonic nebulizers IV = 104 IV + AA-104	IV 52/84 (62%) IV + AA 42/82 (51%) $p = 0.08$	Not reported	IV 57/104 (55%) IV + AA 72/104 (69%) $p = 0.03$
Palmer and Smaldone[53] (2014) MICU SICU United States	Randomized double blind, placebo controlled	Jet nebulizer Placebo plus IV $N = 18$ Inhaled antibiotic plus IV $N = 24$ Inhaled antibiotics included vancomycin and/or aminoglycoside determined by Gram stain IV antibiotics were all chosen by the responsible physician	IA + IV 26/27 (96%) isolates Placebo + IV 2/23 (9%) isolates	IA + IV 0/16 (0%) of new resistance to aerosolized drug, 2/16 (13%) new MDRO Placebo + IV 6/11 (56%) new resistance	IA + IV vs. placebo + IV CPIS deceased significantly only in AA, $p = 0.0008$
Kollef et al[25] (2016) ICUs in Europe, Middle East, and United States	Randomized double blind, placebo controlled	Vibrating mesh plate-AFIS [a]Placebo plus IV carbapenem vs. amikacin fosfomycin and IV carbapenem	IA and IV = 1/12, placebo plus IV 8/29	Among patients without microbiologic eradication the MICs showed a fourfold increase in AFIS IA plus IVvs. placebo 8 in ($p = 0.02$)	No difference in CPIS between groups

Abbreviations: AFIS, amikacin and fosfomycin inhalation system; BAL, bronchoalveolar lavage; CPIS, clinical pulmonary infection score; HAP, hospital-acquired pneumonia; IA, aerosolized antibiotic; ICU, intensive care unit; IV, intravenous; MDR, multidrug resistance; MDRO, multidrug resistant organisms; MICU, medical intensive care unit; RCT, randomized controlled trial; SICU, surgical intensive care unit; VAP, ventilator-associated pneumonia; VAT, ventilator-associated tracheobronchitis.

[a]A proprietary amikacin BAY41–6551(NCT01004445).

[b]COS, colistin only susceptible or susceptible only to colistin.

Source: Modification of Table from Palmer LB. Aerosolized antibiotics for ventilator-associated infections. Chapter 10.4. In: Dhand R, ed. Textbook of Aerosol Medicine. Knoxville (TN): International Society of Aerosols in Medicine; 2015:e1–e28. Available at: www.isam.org.

described in ►**Table 2**. Zampieri et al analyzed the results of RCTs or matched observational studies that compared nebulized antibiotics with or without IV antibiotics with IV antibiotics alone for VAP treatment.[47] A total of 812 patients were included. The primary outcome was clinical cure and secondary outcomes were microbiological cure, ICU and hospital mortality, duration of mechanical ventilation, and ICU length of stay. Inhaled antibiotics had higher rates of clinical cure risk ratio = 1.23; 95% CI, 1.05–1.43; no differences were seen in microbiological cure, mortality, duration of mechanical ventilation, length of ICU stay, or renal toxicity. The authors also pointed out that the primary outcome of clinical cure, when evaluated by the more rigorous method of trial sequential analysis, and the number of patients included were below the information size required for a definitive conclusion.

A second meta-analysis was conducted by Valachis et al, comparing the use of inhaled colistin with IV colistin.[48] The mechanism of colistin's bactericidal activity is destabilization of the lipopolysaccharide (LPS) of the outer membrane, and in addition, it neutralizes the LPS thereby decreasing antiendotoxin activity.[49] Its IV use was discontinued for ~40 years because of its neurological and renal toxicity when used parenterally and the advent of less toxic antibiotics.[50] Highly resistant *P. aeruginosa* and *Acinetobacter* have led to the reintroduction of colistin (polymyxin E) in an aerosolized form as well as a prodrug, colistimethate (CMS). This meta-analysis found 16 studies fulfilled the inclusion criteria. Eight were comparing adjunctive aerosolized versus IV colistin (seven observational cohort or case–control studies and one randomized trial) and these were included in the meta-analysis. Another eight were single arm and were only systematically reviewed. The Grading of Recommendations Assessment, Development, and Evaluation approach showed limitations of the study designs and presence of inconsistency in most of the outcomes, but no obvious indirectness or imprecision of results reporting. Based on the earlier assessments, the quality of evidence presented for each outcome ranged from "very low" to "low." A significant improvement in clinical response (OR, 1.57; 95% CI, 1.14–2.15; $p = 0.006$; $I^2 = 37\%$), microbiological eradication (OR, 1.61; 95% CI, 1.11–2.35; $p = 0.01$; $I^2 = 0\%$), and infection-related mortality (OR, 0.58; 95% CI, 0.34–0.96; $p = 0.04$; $I^2 = 46\%$) was observed with the addition of aerosolized colistin to IV treatment, whereas the addition of aerosolized colistin did not affect overall mortality (OR, 0.74; 95% CI, 0.54–1.01; $p = 0.06$; $I^2 = 25\%$) or nephrotoxicity (OR, 1.18; 95% CI, 0.76–1.83; $p = 0.45$; $I^2 = 0\%$).

They concluded that aerosolized colistin is associated with improved outcome in the treatment of VAP although the level of evidence was low.

The third review was a systematic analysis conducted by Russell et al, examining the efficacy of aerosolized antibiotics in the treatment of VAP and ventilator-associated tracheobronchitis (VAT), using the Cochrane Collaboration guidelines.[51] Only randomized, controlled trials studying the use of nebulized antibiotics in VAP and VAT that measured clinical cure (e.g., change in clinical pulmonary infection

Table 2 Systematic review and meta-analyses 2015 to 2017

Authors	Data reviewed	Types of analysis	Clinical improvement	Microbiologic eradication	Infection-related mortality	Nephrotoxicity
Valachi et al[48] (2015)	Inhaled colistin in the treatment of VAP	Meta-analysis: 8 adjunctive trials 7 were observational or case–control studies and 1 RCT systematic review: 8 single-armed studies	OR, 1.57; 95% CI = 1.14–2.15 $p = 0.006$ Clinical response 67–100%	OR, 1.61; 95% CI = 1.11–2.35 $p = 0.01$ NA	OR, 0.58; 95% CI = 0.34–96 $p = 0.04$ 0–22%	OR, 1.18; 95% CI = 0.76–1.83 $p = 0.45$ 0–17%
Zampieri et al[47] (2015)	Inhaled antibiotics for VAP	Meta-analysis 12 studies of which 6 were RCT	RR = 1.23; 95% CI = 1.05–1.43 $p = 0.009$	RR = 1.24; 95% CI = 0.95–1.62 $p = 0.116$	Hospital mortality RR = 0.90; 95% CI = 0.76–1.08 $p = 0.252$	RR, 1.05; 95% CI = 0.07–1.57 NS
Russell et al[51] (2016)	Inhaled antibiotic for VAP or VAT	Systematic review 6 RCTs	3 RCTs inhaled antibiotics associated with significant improvement 3 studies no difference	NA	NA	NA
Solé-Lleonart[56] et al (2017)	Inhaled antibiotics in ventilated patients	Meta-analysis and systematic review 11 investigations including 6 RCTs	Clinical improvement in patients with resistant pathogens OR = 0.53; 95% CI = 0.36–0.80	NA	Observational adjunctive studies = 2 OR = 0.50 95% CI = 0.26–0.96 All-cause mortality did not differ	Risk difference in adjunctive studies − 0.02 (− 0.07, 0.03), $p = 0.48$

Abbreviations: CI, confidence interval; NA, not available; OR, odds ratio; RCT, randomized controlled trial; RR, risk ratio; VAP, ventilator-associated pneumonia; VAT, ventilator-associated tracheobronchitis.

score [CPIS]) as an outcome were included. All studies were examined for risk of bias. Six studies met full inclusion criteria.[30,43–45,52,53] For the systematic review's primary outcome (clinical cure), two studies found clinically and statistically significant improvements in measures of VAP cure, while four found no statistically significant difference in measurements of cure. No studies found inferiority of aerosolized antibiotics. The included studies had various degrees of biases, particularly in the performance and detection bias domains. Given that outcome measures of clinical cure were not uniform, the authors did not conduct a meta-analysis. Their conclusion was that there is insufficient evidence for the use of inhaled antibiotic therapy as primary or adjuvant treatment of VAP or VAT.

The fourth meta-analysis and systematic review by Solé-Lleonart et al of inhaled anti-infective agents differed from the prior ones as it divided the analysis into studies that included treatment for susceptible versus resistant organisms.[56] Moreover, they split studies in two categories: those using an adjunctive administration strategy and other studies using a substitution administration strategy. Some of their data are shown in ►**Table 2**. The clinical response for inhaled therapy arm was better regardless of susceptibility of organisms treated. However, this was not translated to benefits in terms of mortality reduction or reductions in duration of mechanical ventilation or length of hospitalization. Nephrotoxicity was reduced in a substitution administration strategy (colistin or aminoglycosides nebulized instead of systemic plus nebulized). The authors also included a meta-analysis of the four RCTs which monitored cardiorespiratory adverse events. There were 12 events in the 4 studies and 2 types were described, worsening oxygenation and obstruction of the expiratory filter. All these but one were in patients where antibiotic was delivered with a vibrating mesh nebulizer. Overall respiratory adverse events increased by 9% (95%CI, − 1 to 18%), being particularly exposed those subjects with a PaO_2/FiO_2 under 200.

Randomized Controlled Trials of Aerosolized Antibiotics for VAT or VAP

There have only been six randomized placebo-controlled studies of inhaled adjunctive antibiotics for VAT and VAP since 2005, and they are worth describing in more detail. Some of the data are shown in ►**Table 1**. A double-blind, placebo-controlled Phase 2 study of aerosolized amikacin delivered via vibrating mesh technology was given to 67 patients as adjunctive therapy in ventilated patients with gram-negative pneumonia.[31] Systemic antibiotic therapy was given by the responsible clinician following ATS guidelines.[57] Randomization was to aerosolized amikacin 400 mg daily with placebo (normal saline) 12 hours later, or 400 mg twice daily or placebo twice daily. The mean number of IV antibiotics at the end of the study (mean 7 days) was two times greater with placebo than with twice-daily amikacin ($p < 0.02$).

Palmer et al in a double-blind, placebo-controlled trial, randomized 43 critically ill intubated patients with VAT (defined as the production of purulent secretions $\geq$ 2.0 mL over 4 hours) to aerosolized (AeroTech II nebulizer, Biodex Medical Systems, Shirley, NY) gentamicin (80 mg every 8 hours) and/or vancomycin treatment (120 mg every 8 hours) dictated by Gram stain at the time of randomization. The clinician responsible for the patient administered the systemic antibiotics. Both placebo and active treatment groups received similar amounts of appropriate systemic antibiotics at randomization. Treatment with aerosolized antibiotics resulted in decreased signs and symptoms of VAP, decreased CPIS, and facilitated weaning and reduction in the use of systemic antibiotics compared with the placebo patients. Patients treated with aerosolized antibiotics had marked reduction in bacterial growth. Gram stains of cultures with zero growth revealed that in the aerosolized antibiotic group, 7 of 12 (58%) during week 1 and 6 of 8 (75%) during week 2 had no organisms on Gram stain. In placebo, only 3 of 14 cultures (21%) during week 1 and 4 of 18 (22%) during week 2 had Gram stains with no organisms.

A recent randomized controlled study compared the effects of placebo (normal saline) plus IV antibiotics to aerosolized CMS and IV antibiotics.[44] CMS is a prodrug, which must be converted in the lung to active colistin. All patients were on systemic antibiotics chosen by the responsible physicians. The baseline characteristics of the patients were similar and mean APACHE II (acute physiology and chronic health evaluation - II) score of both groups was 18.5 and 19.1, placebo and CMS, respectively. Conventional systemic antibiotic therapy of VAP in both groups was comparable. Most of the cases of VAP were caused by MDR, *A. baumannii* and/or *P. aeruginosa*. All isolates of gram-negative bacteria were susceptible to colistin. Favorable clinical outcome was 51.0% in the aerosol CMS plus systemic antibiotic group and 53.1% in the placebo plus systemic antibiotic group ($p = 0.84$). Patients in the CMS group had significantly more favorable microbiological outcome (defined as eradication or presumed eradication) when compared with patients in the control group (60.9 vs. 38.2%, $p = 0.03$). This investigation differs from all others described as CMS was used, which is thought to be less potent than colistin. The concentration of active drug in the lung is not as predictable as in those studies using colistin and may explain the less favorable clinical outcome compared with the other RCTs. Also, jet nebulizers and ultrasonic nebulizers were used; therefore, the equivalence of deposition site and concentration is unknown.

Lu et al compared treated VAP with inhaled ceftazidime and amikacin to IV delivery of the same drugs for VAP caused by *P. aeruginosa*.[45] Forty patients were included in the study. Twenty patients receiving inhaled drugs had intermediate or susceptible strain of *P. aeruginosa*. Seventeen patients receiving IV therapy all had susceptible strains. The two methods of delivery had similar efficacy, 70 versus 55. The inhaled therapy successfully treated four patients with *P. aeruginosa* that was intermediate in susceptibility. Only the IV group had acquisition of resistance to the drug delivered.

Recently, in a double-blind, placebo-controlled study, critically ill intubated patients with prolonged mechanical ventilation were randomized if they exhibited signs of respiratory infection (purulent secretions and CPIS > 6).[53] Using a well-characterized aerosol delivery system, inhaled

Table 3 Clinical response

	Randomization			EOT		
	AA [$n = 24$]	Placebo [$n = 18$]	*P* value	AA [$n = 24$]	Placebo [$n = 18$]	*P* value
CPIS*	9.3 ± 2.7	8.0 ± 2.1	0.5000†	5.3 ± 2.6	8.6 ± 2.6	0.0008†
CPIS w/o Culture data‡	7.5 ± 2.1	7.1 ± 2.6	0.9152†	4.9 ± 2.2	6.3 ± 2.0	0.0546†
Volume/4 Hours§	6.9 ± 4.7	8.9 ± 0.69	0.12	1.1 ± 1.3	6.3 ± 4.3	<0.001
Systemic WBC‖	17.1 ± 1.9	12.6 ± 1.2	0.18	13.3 ± 1.3	13.9 ± 1.5	0.726

†Mann-Whitney
Wilcoxon Analyses:
AA Randomization *vs.* AA EOT
*$P < 0.0001$
‡$P < 0.0001$
§$P < 0.0500$
‖$P < 0.0280$
Placebo Randomization vs. Placebo EOT
Not significant for any parameters in table

antibiotic or saline placebo was given for 14 days or until extubation. The responsible clinician determined administration of systemic antibiotics for VAP and any other infection. The clinical results are shown in ►**Table 3**. Compared with placebo, inhaled antibiotic significantly reduced CPIS (mean ± standard error of mean, 9.3 ± 2.7–5.3 ± 2.6 vs. 8.0 ± 23–8.6 ± 2.10; $p = 0.0008$). The effects on bacterial growth are shown in ►**Fig. 2**.

The most recent RCT by Kollef et al administered a combination of amikacin and fosfomycin with a proprietary device (AFIS) to ventilated patients with gram-negative VAP.[25] All patients received IV meropenem or imipenem (dose for gram-negative coverage) for 7 days, and longer if clinically indicated. The total number of randomized patients was 143 patients, 71 to AFIS and 72 to placebo. CPIS was the primary outcome. They found no significant change from baseline between treatment groups ($p = 0.70$). Mortality and clinical cure at day 14 were also not significant ($p = 0.68$) nor the hierarchical end points of no mortality and ventilator free days ($p = 0.06$). Mortality was 17 (24%) in AFIS and 12 (17%) in placebo, $p = 0.32$. The AFIS group had significantly fewer positive tracheal cultures on days 3 and 7 compared with placebo. This trial of adjunctive aerosol therapy compared with standard of care had no significant clinical impact. Potential weaknesses of the study included, using the same vibrating nebulizer throughout the study, which may have been associated with deceased delivery, and starting treatment late in the course of the infection.

How Do Aerosolized Antibiotics Affect Emergence of Bacterial Resistance Compared with Systemic Antibiotics?

Increased bacterial resistance in the ICU has been shown to have a direct relationship to the amount of systemic antibiotics prescribed. There have been very little data in the literature, however, analyzing the impact of aerosolized antibiotics on the emergence of resistance. The meta-analysis of Ioannidou et al mentioned previously described a 6.5% (3/46) incidence of new resistance at the end of treatment in the five RCTs included.[40] ►**Table 1** shows recent data on the eradication of pathogens and the emergence of resistance for studies published between 2008 and 2016 mentioned previously. Seven trials report data on the emergence of resistance. In these trials, no new resistance to drug administered was detected. Included are five RCTs with resistance data. Kofteridis et al described no new resistance in the group that received aerosol, but there were no data provided for the patients that reviewed only systemic antibiotics.[17] Palmer et al demonstrated that 8 of 24 participants receiving placebo inhaled antibiotic and systemic antibiotics acquired resistant organisms during treatment compared with 0 of 19 aerosolized antibiotic patients, $p = 0.0056$.[30] In the placebo group receiving only systemic antibiotics, four participants with sensitive bacteria (three *P. aeruginosa* and one *Klebsiella pneumoniae*) developed resistance on treatment. Two participants acquired a resistant *Acinetobacter* and two acquired methicillin-resistant *S. aureus*. One of 19 aerosolized antibiotic participants transiently acquired a resistant organism, a resistant *Acinetobacter* that resolved during therapy. All patients who acquired resistant organisms received systemic antibiotics. Lu et al's randomized trial of IV versus inhaled antibiotics (as exclusive treatment) again showed the emergence of resistance only in the comparator group that received systemic antibiotics.[45] In another investigation with more chronically ventilated patients, aerosolized antibiotics eradicated 26 of 27 organisms present at randomization compared with 2 of 23 organisms in the placebo group ($p = 0.0001$) despite both groups being on similar amounts of appropriate systemic antibiotics.[53] Inhaled antibiotics eradicated the original resistant organism on culture and Gram stain at the end of treatment in 14 out of 16 patients compared with 1 of 11 for placebo ($p = 0.001$). Resistance to

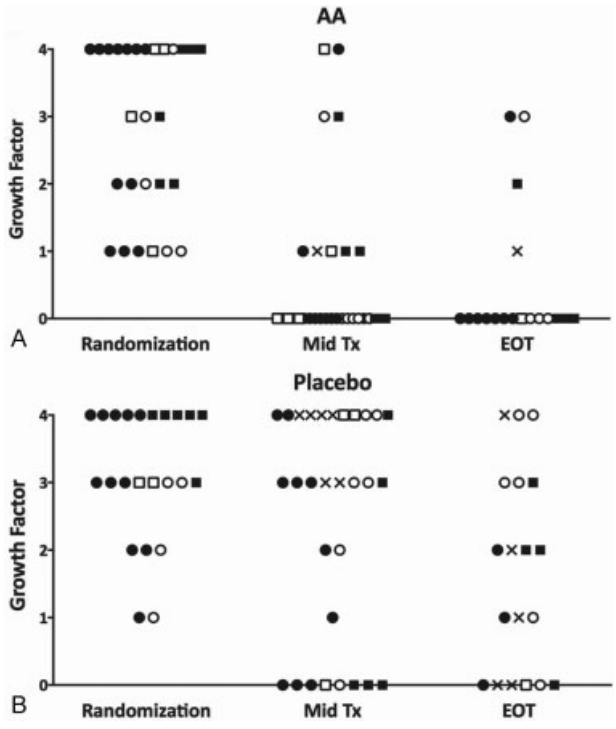

Fig. 2 Bacterial growth from tracheal aspirates obtained at the time of randomization, Mid Tx, and at the EOT for (**A**) AA and (**B**) placebo. Growth is quantified using a graded scale from 0 to 4 from semiquantitative cultures: multidrug-resistant gram-negative organisms (filled circles), nonresistant gram-negative organisms (open circles), resistant gram-positive organisms (filled squares), nonresistant gram-positive organisms (open squares), and newly resistant organisms on treatment (X). Some patients had multiple isolates. At Mid Tx all the isolates with zero growth represent organisms detected at randomization that did not grow in isolates sampled at Mid Tx. At EOT the isolates with zero growth represent organisms detected at randomization and Mid Tx that did not grow in samples obtained at EOT. There was a clear difference in pattern of bacterial growth between AA and placebo. Two AA isolates demonstrated persistent growth at EOT: one methicillin-resistant Staphylococcus aureus (filled square) that was not eradicated by AA but had no gram-positive cocci on Gram stain, and one persistent *Acinetobacter* (filled circle) with organisms present on Gram stain. More newly resistant organisms were seen in the placebo group. AA, aerosolized antibiotics; EOT, end of treatment; Mid Tx, mid-treatment. (Reprinted with permission of the American Thoracic Society. Copyright © 2014 American Thoracic Society. Palmer and Smaldone.[53])

systemic antibiotics significantly increased in placebo patients receiving only systemic antibiotics ($p = 0.03$). In chronically intubated critically ill patients, inhaled antibiotics successfully eradicated existing MDRO and reduced the pressure from systemic agents for new microbial resistance. It is important to note that most the data described earlier are examining the effects of centrally deposited drugs on pathogens in the large airways. Data on drug concentrations in the parenchyma and resistance in the alveolar space were not studied.

In the most recent investigation by Kollef et al of adjunctive therapy for VAP with MDR gram-negative organisms, there were no clinical differences in CPIS at the end of treatment between the placebos versus the active drug groups; however, there were differences in effects of treatment on the MIC of the randomization organisms.[25] In those patients who did not have eradication of the randomization organisms, patient out of 12 of the AFIS patients, compared with 8 out of 29 in the placebo group ($p = 0.02$) showed a $\geq$ fourfold increase in MICs exceeding the parenteral breakpoint for an IV antibiotic with gram-negative activity.

If the emergence of resistance in the ICU continues to escalate, as the prescribers of systemic antibiotics, we are responsible for the evolution of MDRO. Future investigations are needed to determine the role of inhaled antibiotics in mechanically ventilated patients and their overall effect on MDRO. Contrary to the data on topical therapy from the 1970s, it is now worth exploring how targeted therapy may become one of the new tools combating antimicrobial resistance.

Concerns

Regulatory standards are set with the objectives to protect safety of the patients and to prevent use of agents that are not proven. The use of aerosolized antibiotics in mechanically ventilated patients has been advocated for treating patients with pneumonia or at risk of pneumonia and colonization by carbapenem-resistant Enterobacteriaceae, *A. baumannii* and carbapenem-resistant *P. aeruginosa*, which represent a serious threat. As a consequence, widespread use has been implemented[56] in countries with high prevalence of MDRO, such as China, India, Turkey, or Greece. Unfortunately, the safety and efficacy, particularly in patients with serious hypoxemia due to pneumonia or acute lung injury, data are sparse.[52,53,56]

Although higher rates of clinical resolution have been associated with the administration of nebulized antibiotics, no significant differences were found for the rest of the efficacy outcomes analyzed, such as duration of mechanical ventilation (MV) support and ICU hospitalization period.[54] The overall quality of the evidence was very low due to the serious indirectness and very serious imprecision of the results for all the outcomes. In addition, the evaluation of their safety was associated with a higher incidence of respiratory complications in patients with hypoxemia and potential nephrotoxicity associated to their use as adjunctive administration strategy.[54]

A major caveat is that there are insufficient data available to ascertain the appropriate dose and formulation. Aerosol toxicology is limited on aztreonam lysine and tobramycin, with systemic formulations discouraged because they can induce respiratory adverse events. An example is the amikacin dose. Whereas standard practice is 30 mg/kg/d parenteral which is why most experts (J. Roberts, PhD, personal written communication) advocate this dose for nebulization as well. However, peak epithelial lining fluid concentrations from a 30 mg/kg dose are in the thousands with these doses and while there is an effect of mucin binding which reduces the effective concentration by 90%, the resultant pharmacological concentration is still 300 to 900.

In summary, the evidence in support of the routine use of aerosolized antibiotics as standard therapy for VAP or VAT is still very poor. Aerosolized colistin has been associated with respiratory failure and serious adverse events have been

reported in well-designed randomized trials. Thus, until well-designed randomized trials with homogeneous populations, standardized drug delivery, predetermined clinical efficacy, and safety outcomes[54] are available, its use should be restricted as salvage rescue therapy in patients without other therapeutic options, under close monitoring of the administration technique by an expert physician.[54,55]

The Future

There are significant challenges in demonstrating superiority in clinical registration trials for aerosolized antibiotics whose main advantage is likely to be activity against MDRO. These include the choice of the comparator, the dose (and duration) of administration, the patient population under study, and the end points to be studied.

There is an ethical requirement to select a comparator which has activity against the likely causative pathogens. Bacterial resistance patterns vary considerably by geography, resulting in a scenario where a suitable comparator in one geography may not be a suitable comparator in other. Based on recent data,[54] the use of a substitution administration strategy (rather than adjunctive to systemic administration) should be preferred.

The duration of treatment is unknown, with no data on the effects on respiratory microbiome. It has been assumed that the duration recommended for systemic administration is recommended for aerosolization. However, the high concentrations of drug achieved in the respiratory airways are not comparable to systemic administration suggesting that shorter duration is suitable. Moreover, dose used in indications for nonventilated patients has been extrapolated to ventilated patients. However, flora and inspiratory flows in chronic obstructive pulmonary disease (COPD) or cystic fibrosis patients are not representative of mechanically ventilated patients. Deposition of the drug in the upper airways is around 40% and subsequent increases of dose have been recommended. Moreover, small particles such as aminoglycosides (in contrast with colistin) can penetrate the alveolar–blood barrier, requiring plasma levels to avoid potential nephrotoxicity. This is of most concern in patients with decreased renal function. Thus, further research is required to identify recommended doses.

The complex nature of ICU patients with serious pulmonary infections presents a significant challenge to demonstrate superiority in terms of outcomes. Treatment in heterogeneous populations such as head trauma patients, patients in a respiratory ICU (many COPD), or involving surgical or oncologic patients may have different treatment requirements. Thus, further research should identify the target population, avoiding heterogeneity. In addition, there may be diagnostic uncertainty about the causative pathogen or difficulties in obtaining samples. Approvable indications in registration trials are usually based on infection site, rather than pathogen, and not all investigational sites yield sufficient number of patients with resistant pathogens to support a meaningful statistical analysis. However, consensus exists[52] that the area of greatest unmet need, and therefore the developmental focus for aerosolized antibiotics, is the population with pneumonia caused by MDRO.

The most widely accepted outcome measure in antibiotic trials is resolution of infection, usually expressed as test of cure. This may be a clinical evaluation of patients' improvement. As this is a late end point, it has been proposed[55] to use "time to clinical resolution" as a preferred end point. Microbiological eradication has been demonstrated in the proximal airway with devices targeted at this location.[30,53] However, eradication in the alveolar space is more difficult to achieve; therefore, microbiologic efficacy end points may differ by location. Composite end points or scores should be discouraged, unless composed by meaningful variables with sound clinical significance. Improvement of daily organ failure or oxygenation, improvement in inflammatory biomarkers, 30-day mortality, duration of mechanical ventilation, and ICU stay should be the preferred end points to be used in future clinical trials. Patients should be balanced by degree of hypoxemia and the population with PaO_2/FiO_2 under 200 is an unmet clinical need. Alternative end points such as reduction in days of systemic antibiotics should also be considered.

In contrast with trials with systemic antibiotics, most investigations of aerosolized therapy have been thwarted by not following the axioms of antimicrobial therapy, knowing the proper dose and having well characterized reliable delivery devices that will achieve the concentration necessary at the site of infection.[60] Delivery needs to be carefully standardized and monitored with safety outcomes predetermined. In addition, the strategy of humidification in the ventilator circuit needs to be controlled. Most nebulizers are designed to deliver drugs to the proximal airways and not the lung parenchyma. Thus, choice of nebulization devices should be guided by the desired deposition site. Jet nebulizers will provide optimal treatment to the proximal airway, but different devices which deliver smaller particles (under 5 μm) will be needed for more distal airways. Large comparative studies of various aerosol antibiotic delivery devices are currently lacking.

Finally, at the reimbursement approval stage, some degree of cost/benefit, or cost-effectiveness assessment is considered by national or local authorities. To be approved for inclusion on the hospital formulary, some degree of economic justification is requested. Thus, cost–benefit studies, taking in account severity of the patient and outcome such as length of stay are urgently needed.

Summary

- There is a growing body of data that suggest aerosolized antibiotics may have a role in the treatment of respiratory infection in the ICU.
- The current studies are very heterogeneous in design, dosing, and end points. Future multisite studies must define the appropriate dose, the optimal devices, and the duration of therapy.

- A decrease in the MDRO after inhaled treatment has been seen in single-site RCTs in patients treated with inhaled antibiotics compared with IV therapy alone.[30,53]

Future studies should describe the effects of inhaled therapy on both respiratory and nonrespiratory sites.

- Clinical trials must be designed to assess not only clinical end points such as resolution of signs and symptoms of respiratory infection, but data should be acquired for new primary outcomes, such as effects on the amounts and duration of systemic antibiotic use while also documenting antimicrobial resistance in the ICU.

Disclosure
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Body Position and Ventilator-Associated Pneumonia Prevention

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Abstract

Seminal studies have demonstrated that tracheally intubated, mechanically ventilated patients, positioned in supine horizontal position, are at a high risk of developing ventilator-associated pneumonia, through aspiration of gastric pathogens. In the 1990s, innovative clinical findings promoted a radical change in practice, through the use of the semirecumbent position in all mechanically ventilated patients. Here, we critically review the main indications, pulmonary effects, and controversies on the use of the semirecumbent position. Also, we will depict potential roles of prone and lateral positions in the prevention of ventilator-associated pneumonia. Our review will span from preclinical experimental insights to clinical evidence, and we will discuss potential controversies on the use of the semirecumbent position as the standard of care. We will also detail potential alternatives to ultimately improve outcomes of tracheally intubated and mechanically ventilated patients.

Keywords
- ventilator-associated pneumonia
- semirecumbent position
- prone position
- continuous lateral position
- tracheal intubation
- critical care

Ventilator-associated pneumonia (VAP) is an iatrogenic pulmonary infection caused by pathogens highly prevalent in hospital settings. VAP develops in patients on invasive mechanical ventilation for more than 48 hours.[1] Incidence of VAP ranges between 9 and 13 cases per 1,000 ventilator days,[2] but it varies considerably among patient populations, types of intensive care units (ICUs), and level of applied preventive measures. Theoretically, VAP is an avoidable disease and prevention is highly recommended to decrease the overall burden and health care costs.[3,4] Nevertheless, a comprehensive understanding of VAP pathogenesis is essential to implement the most promising and clinically valuable preventive interventions.

Critically ill and intubated patients are at a high risk for developing nosocomial infections, because of the underlying illness, comorbidities, and invasive devices/procedures. Aspiration of colonized oropharyngeal secretions across the endotracheal tube (ETT) cuff is the main mechanism for the development of VAP. This is related to the design of ETT cuffs, which were developed for ICU patients on long-term mechanical ventilation. Indeed, these cuffs present a large external diameter to exert low pressure to the tracheal wall and prevent injury. Nonetheless, upon inflation, folds form along the cuff surface, causing consistent aspiration of oropharyngeal secretions.[5] Pathogens may also adhere to the ETT internal surface and form a biofilm, which facilitates colonization of the lower airways, due to breakage and dislodgement of bacteria and biofilm particles.[6] As for the etiology of the disease, it is well established that during mechanical ventilation the oral flora progressively shifts to a predominance of aerobic gram-negative pathogens,[7] *Pseudomonas aeruginosa*, and methicillin-resistant

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Staphylococcus aureus. There is still controversy on the exact sequence of colonization and sources of pathogens. In particular, some investigators assume that the oropharynx is the primary site to become colonized by pathogens,[8] due to potential comorbidities, that is, alcohol abuse,[9,10] diabetes,[11] the vast use of antibiotics, and impairment of oropharyngeal defense mechanisms.[12,13] Whereas, according to the gastropulmonary hypothesis of colonization, some investigators believe that the stomach is the primary source of colonization, due to the gastric alkalization, enteral nutrition, and stress ulcer prophylaxis.[14] Then, gastroesophageal reflux facilitates translocation of microbes into the oropharynx,[15] which are aspirated across the ETT cuff into the airways, ultimately causing VAP.

Given aforementioned pathogenic mechanisms, it is clear that several factors, implicated in the development of VAP, can be modified. In particular, in the past decades, extensive efforts have been devoted to reducing, through body positioning, the risks for oropharyngeal colonization, and aspiration of pathogens. There is strong evidence from preclinical and clinical experimentation that gastroesophageal reflux,[16,17] pulmonary aspiration of oropharyngeal contents, and clearance of colonized airways secretions[18,19] can be altered through body positioning. Thus, specific interventions have been recommended to appropriately position and mobilize the critically ill patient and modulate risks of VAP.

The purpose of this review is to critically discuss laboratory and clinical studies assessing effects of positioning in the prevention of VAP. In particular, we will focus on the supine semirecumbent and prone positions. Moreover, we will provide details regarding a recently implemented position, namely, the lateral-Trendelenburg position, and we will also consider potential feasibility challenges.

The Semirecumbent Position

As mentioned in the previous paragraphs, tracheally intubated patients frequently present gastroesophageal reflux and pulmonary aspiration of gastric pathogens. As a result, pulmonary infections may ensue.[14,16,20,21] In critically ill patients, the stomach becomes colonized by pathogens because of alkalization of gastric contents[22]; administration of enteral nutrition,[23] and reflux of bilirubin.[20,21] Also, pathogens may cause overgrowth in the duodenum, because of the broad use of antibiotics and paralytic ileus.[24] Following gastric colonization, pathogens may eventually translocate into the respiratory system, specifically when patients are enterally fed. Pivotal studies,[16,17] using radiolabeled markers instilled into the stomach, have clearly shown that tracheally intubated patients may aspirate gastric contents, particularly when they are positioned supine and on enteral nutrition. Conversely, in patients positioned supine, with the head of the bed elevated 30 to 45 degrees above horizontal, namely, the semirecumbent position, gastroesophageal reflux is reduced. Therefore, since the late 1990s, the semirecumbent position has become the standard of care to compartmentalize gastric colonization, prevent pulmonary aspiration, and VAP. During positioning, the patient is first placed supine, then the head of the bed is elevated between 30 and 45 degrees (►**Fig. 1A**) to achieve semirecumbency.

Interestingly, great controversy remains on the rationale supporting the use of the semirecumbent position for all intubated patients. In particular, investigators who are skeptical on its broad use have primarily questioned the role of the stomach in the pathogenesis of VAP. A substantial number of studies[25–31] have not found a temporal and causal association between bacteria colonizing the stomach and development of VAP. Hence, assuming a marginal association between oropharyngeal and gastric colonization, the rational of keeping colonized patients in the semirecumbent position is questionable. Such position could increase the hydrostatic pressure exerted by bacteria-laden subglottic secretions above the ETT cuff; therefore, facilitating pulmonary aspiration across the cuff. Also, several preclinical studies[18,19,32] have shown that in the semirecumbent position, mucus clearance is severely

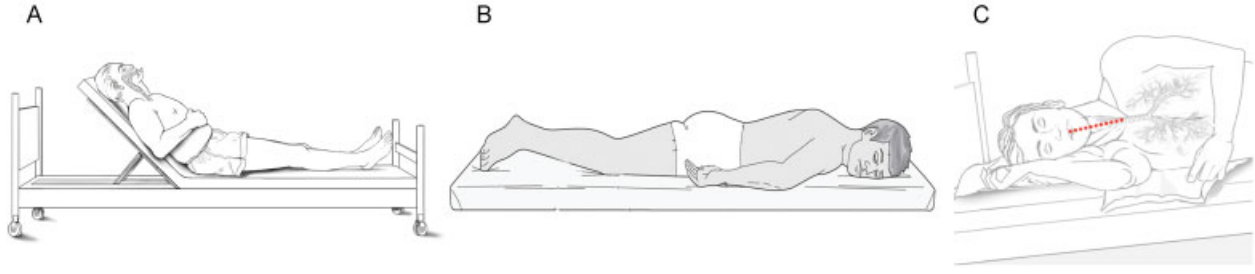

Fig. 1 Potential body position to prevent ventilator-associated pneumonia in critically ill, invasively ventilated patients. (**A**) The semirecumbent position. The patient is kept supine, with the head of the bed elevated between 30 and 45 degrees above horizontal. The semirecumbent position is aimed at achieving an esophageal orientation above horizontal to hinder the reflux of colonized gastric contents and resulting oropharyngeal colonization. (**B**) The prone position. The prone position is indicated in patients with severe acute respiratory distress syndrome, and it is primarily aimed at improving gas exchanges. It is speculated that prone position could reduce risks of ventilator-associated pneumonia, through enhanced clearance of respiratory secretions. (**C**) The lateral-Trendelenburg position. Patients are positioned in a semilateral position, similar to the recovery position; with the bed tilted 5–10 degrees in Trendelenburg position. An imaginary line (dotted red line) from the sternal notch to the mouth, passing through the middle of the trachea is used as a surface landmark. The patient is positioned to maintain this line slightly below horizontal to ensure an orientation of the trachea and endotracheal tube 2 to 5 degrees below horizontal. Every 6 hours, the patient is turned from one side to the other.

impaired, and mucus is transported up to the ETT cuff to be retained, colonized, and eventually driven, through gravity, toward, and into the lungs. This could further promote translocation of oropharyngeal pathogens into the lungs.

Irrespective of these thought-provoking arguments, several studies have been conducted to test the efficacy of the semirecumbent position in the prevention of VAP. To the best of our knowledge, one important observational study[33] and three prospective randomized clinical trials, published in English, have assessed the efficacy of the semirecumbent position on VAP prevention.[34–36] In a first report, Kollef et al[33] conducted a multivariate analysis to identify relevant risk factors for VAP. The authors found that maintaining the supine position, during the first 24 hours of mechanical ventilation, was associated with the development of VAP (adjusted odds ratio = 2.9; 95% confidence interval [CI], 1.3–6.8; $p = 0.013$). To date, only one randomized monocenter clinical trial has clearly demonstrated the efficacy of the semirecumbent position in preventing VAP.[35] Drakulovic et al randomized 86 patients to be positioned either in the semirecumbent (head of the bed elevated 45 degrees) or fully supine horizontal (0 degrees) position. Of note, the study was conducted in a medical ICU, and severely obese patients or undergoing abdominal and neurological surgery were excluded from the study. The study was discontinued at the first interim analysis, because microbiologically confirmed VAP developed in 2/39 (5%) and 11/47 (23%) of the patients positioned in the semirecumbent and horizontal positions, respectively ($p = 0.018$). Multivariate analyses showed that supine body position (odds ratio, 6.8 [95% confidence interval (CI) 1.7–26.7], $p = 0.006$) and enteral nutrition (odds ratio, 5.7 [95% CI 1.5–22.8], $p = 0.013$) were independent risk factors for VAP, further highlighting the gastropulmonary route of colonization in the acquisition of VAP.

In a later study by van Nieuwenhoven et al,[36] 221 patients were randomized to be placed either in the semirecumbent (head of the bed elevated 45 degrees) or a standard position (head of the bed elevated 10 degrees). A comprehensive description of dissimilarities between van Nieuwenhoven and Drakulovic studies is reported in ►**Table 1**. Microbiologically confirmed VAP developed in 8 of 109 patients (7.3%) in the supine group (incidence rate, 7.8/1,000 days) and 13 of 112 patients (11.6%) in the semirecumbent group (incidence rate, 10.2/1,000 ventilator days), without differences between groups. Also, no statistically significant differences were reported in secondary outcomes. One of the main strengths of this study was the inclusive evaluation of the feasibility of the semirecumbent position to prevent VAP, through the continuous digital recording of patient position. Of note, in the treatment group, patients should have been maintained with an orientation of the head of the bed of 45 degrees; yet, such orientation was seldom achieved, only during 15% of the study time. The adherence to the intervention decreased throughout the study, resulting in an average orientation of 28.1 and 22.6 degrees at days 1 and 7, respectively. A great variability in the supine position was also reported, in fact, patients were maintained at 9.8 ± 3.9 degrees on day 1 to 14.8 ± 7.1 degrees on day 7, questioning the level of diversity among groups. Similarly, Keeley et al[34] conducted a study in 56 patients, who were randomized to be positioned with the head of the bed oriented either 25 or 45 degrees. Clinically diagnosed VAP developed in 54% of the patients positioned at 25 degrees, in comparison to 29% of patients positioned at 45 degrees ($p = 0.176$). The study presented several methodological limitations, and it was likely underpowered to detect any difference in the incidence of VAP between treatment groups. Finally, a recent meta-analysis,[37] pooling data from 10 randomized clinical trials involving 878 participants compared the semirecumbent position (30–60 degrees) versus supine position (0–10 degrees). In line with findings above by Drakulovic et al, the higher head of the bed orientation (45 degrees), reduced the risk of clinically suspected VAP compared with 0 to 10 degrees supine position (14.3 vs. 40.2%, risk ratio [RR]: 0.36; 95% CI: 0.25–0.50; with moderate quality evidence). Microbiologically confirmed VAP was not different. Whereas, as confirmed by van Nieuwenhoven et al,[36] 45 versus 25 to 30 degrees semirecumbent positions did not have any effect on the clinically or microbiologically confirmed VAP.

In conclusion, there is still a lack of clinical evidence and an important debate on the preventive value of the semirecumbent position. From the available clinical evidence, it could be extrapolated that the semirecumbent position prevents VAP, in comparison to the full horizontal supine position, particularly in enterally fed patients. Nevertheless, it is still unclear (1) whether the 45-degree elevation of the head of the bed, as originally reported by Drakulovic is feasible; (2) which is the lowest inclination of the head of the bed that could still provide preventive benefits; (3) which are the ICU subpopulations who could benefit the most of the intervention; (4) whether the semirecumbent position is safe in all ICU subpopulations, particularly in patients who develop oropharyngeal colonization during the course of mechanical ventilation.

The Prone Position

Patients with acute respiratory distress syndrome (ARDS) are often characterized by a severe mismatch between alveolar ventilation and perfusion, which causes life-threatening hypoxemia, often unresponsive to standard therapies. This is mainly related to the increased weight of ARDS lungs, due to the severe parenchymal inflammation. Thus, under such abnormal weight, the lungs behave as a wet sponge, and the dependent pulmonary regions become atelectatic,[38] causing severe hypoxemia. In this context, for more than 40 years, the prone position (►**Fig. 1B**) has been applied to homogenize lung perfusion,[39] improve ventilation/perfusion mismatch, and reduce risk of ventilator-induced lung injury.[40,41]

Some investigators have also suggested that prone position could reduce risks of VAP. The underlying mechanisms for the prevention of VAP are not fully elucidated, but investigators often implied that prone position could improve drainage of retained noxious biofluids, and prevents pulmonary translocation of oropharyngeal pathogens. Indeed, when patients are positioned prone, outward drainage

Table 1 Randomized clinical trials, published in English, on the semirecumbent position for the prevention of ventilator-associated pneumonia

First author	Drakulovic	van Nieuwenhoven	Keeley
Year	**1999**	**2006**	**2007**
Study population	**86**	**221**	**30**
Center	Single-center One medical and one respiratory ICUs	Multicenter (three hospitals) Four mixed medical/surgical ICUs	Single-center One mixed medical/surgical ICU
Exclusion criteria	Recent abdominal surgery Recent neurological surgery Shock refractory to vasoactive drugs Previous tracheal intubation	SDD Extensive abdominal surgery Recent neurological surgery	Severely obese Recent abdominal surgery Previous tracheal intubation
Interventions	Semirecumbent (45 degrees) vs. supine horizontal (0 degrees)	Semirecumbent (45 degrees) vs. supine slightly inclined (10 degrees)	Semirecumbent (45 degrees) vs. supine slightly inclined (25 degrees)
Position monitoring	Checked daily	Checked every 60 s through a transducer with a pendulum, placed on the bed frame. Data digitally recorded	NA
Diagnosis of microbiologically confirmed VAP	Tracheal aspirate BAL PSB	BAL	Tracheal aspirate BAL PSB
Incidence of clinical suspected VAP	Semirecumbent position 3/39 (8%) Supine position 16/47 (34%) $p = 0.003$	Semirecumbent position 16/112 (18%) Supine position 20/109 (14%) NS	Semirecumbent position 5/17 (29%) Supine position 7/13 (54%) NS
Incidence of microbiologically confirmed VAP	Semirecumbent position 2/39 (5%) Supine position 11/47 (23%) $p = 0.018$	Semirecumbent position 13/112 (12%) Supine position 8/109 (7%) NS	Semirecumbent position 4/17 (24%) Supine position 5/13 (38%) NS
Important limitations	Small sample size—Stopped at first interim Single-center study	Small difference in bed angulation Mixed and nonprotocolized use of large and small nasogastric feeding tubes VAP incidence lower than expected	Very small sample size Diagnostic accuracy Single-center study

Abbreviations: BAL, bronchoalveolar lavage; ICU, intensive care unit; NA, not applicable; NS, nonsignificant; PSB, protected-specimen brush; SDD, selective digestive decontamination; VAP, ventilator-associated pneumonia.

of respiratory secretions is favored. One early study[42] has originally assessed this hypothesis and reported negative results. Gillart et al evaluated the effects of proning on mucus production in 15 ARDS patients, and they found that the weight of secretions retrieved before and after pronation was not significantly different, from 3.0 ± 7.5 to 4.4 ± 6.1 g; also, the improvement in oxygenation associated with prone position, was not related to a number of retrieved secretions. It is important to point out that quantitative measurement of aspirated mucus is a surrogate endpoint that poorly predicts mucus clearance function. Among the randomized clinical studies that evaluated the effects of prone position on VAP, controversial findings have been reported. Two studies[43,44] have shown a significant decrease in the incidence of VAP using the prone position. Conversely, other studies[45–47] consistently failed to find any statistically significant results. Sud et al[48] pooled data from seven studies on 1,066 ARDS patients enrolled in prone-supine studies, and they found that prone position significantly reduced VAP (RR, 0.81%; 95% CI, 0.67–1.00; $p = 0.05$). Finally, in the latest study by Guerin et al[49] prone position was highly beneficial in ARDS patients and resulted in decreased mortality. A subsequent study by Ayzac[50] et al, retrospectively evaluated whether prone position also had an impact on VAP. Unfortunately, they found that the cumulative probability of VAP was higher in the prone than in the supine position group (46.5% at 90 days in the prone position group [27–66%] and 33.5% in the supine position group (23–44%) ($p = 0.11$). Importantly, to correctly interpret the results of these important studies, it should be highlighted that incidence of VAP was only a secondary outcome in all these reports, and likely methodological limitations were present. Other potential limitations were that VAP adjudication was not blind, diagnostic methods were highly heterogeneous; cofactors, knowingly associated

with increased risk for VAP were not controlled; finally, most of the studies were likely underpowered to detect any significant reduction of VAP. In conclusion, there is not enough evidence to support the use of prone position as a VAP preventive measure in patients with ARDS. Future studies, not biased by diagnostic limitations, should be promoted to interpret the potentials of the intervention correctly; yet, the design and development of a large trial on prone position for VAP prevention would encounter several ethical and procedural challenges, and the feasibility of the intervention is debatable.

The Lateral-Trendelenburg Position

For more than a decade, comprehensive findings on the pathogenesis of VAP, initially explored at the National Institutes of Health, Bethesda, MD and successively reaffirmed at our division of animal experimentation, Hospital Clinic, Barcelona, Spain have challenged the underlying rationale of the semirecumbent position.[18,19,51–53] These studies imply that gravity plays a key role in the pathogenesis of VAP, and keeping the ETT, trachea, and thorax obliquely oriented, as in the semirecumbent position, allow leakage across the ETT cuff and translocation of oropharyngeal pathogens into the lungs. An animal model of long-term mechanical ventilation was developed at the laboratories of the National Institutes of Health.[52] The investigators used healthy sheep, which characteristically present oropharyngeal pathogens at the time of intubation, and frequently develop VAP, through translocation of these pathogens into the lungs. Whereas, in our settings, we developed a novel porcine model of VAP, in animals obliquely positioned, as in the semirecumbent position.[32] Of note, in this later model the main pathogenic human mechanism, through pulmonary aspiration of oropharyngeal secretions colonized by *P. aeruginosa* was reproduced. Indeed, *P. aeruginosa*, instilled into the oropharynx of the animals, rapidly translocated, through gravity, into the airways and colonized tracheal secretions. VAP primarily developed in the right medium and lower lobes, which strongly suggested a gravity-driven dissemination of the infection.

Panigada et al[52] first assessed how the orientation of the ETT/tracheal axis could affect airways colonization and development of VAP. Sheep were mechanically ventilated up to 72 hours and randomized to be positioned in a model of the semirecumbent position or the lateral position (►**Fig. 2**). An additional group in the latter position received nasogastric enteral feeding. When the animals were in semirecumbent, significant decrease in lung function and heavy bacterial colonization of the lungs was found. In particular, following 72 hours of mechanical ventilation, lungs, bronchi, and trachea of all sheep in this group were heavily colonized (10^3–10^9 colony-forming units [CFU]/g). Two of seven sheep were killed after 36 hours because of severe clinical deterioration and lung bacterial colonization ranging between 10^6 and 10^7 CFU/g. Conversely, all sheep in lateral position completed the 72-hour study, and excellent lung function was retained. Upon autopsy, no evidence of bacterial lung colonization and VAP was found even when continuous nasogastric feeding was administered.

In a later report,[18] we addressed the effects of ETT/trachea orientation on mucus clearance in 16 intubated sheep. Interestingly, we found that tracheal mucus was transported by cilia at a mean rate of 2.0 ± 1.9 mm/min and 2.1 ± 1.1 mm/min in sheep with ETT/trachea oriented above and below horizontal, respectively; confirming that gravity did not affect mucociliary transport. However, in semirecumbent animals, mucus was first transported by cilia toward the inflated ETT cuff, accumulated at the proximal trachea, and eventually moved by gravitational force backward toward and into the lungs (►**Fig. 3**). Importantly, in all groups, the tracheal region around the cuff was found colonized (10^3–10^9 CFU/g), because of the bacterial seepage around the cuff. Therefore, when retained mucus at the proximal trachea became colonized, the gravity-driven backward flow of mucus led to an intratracheal route of lung colonization.

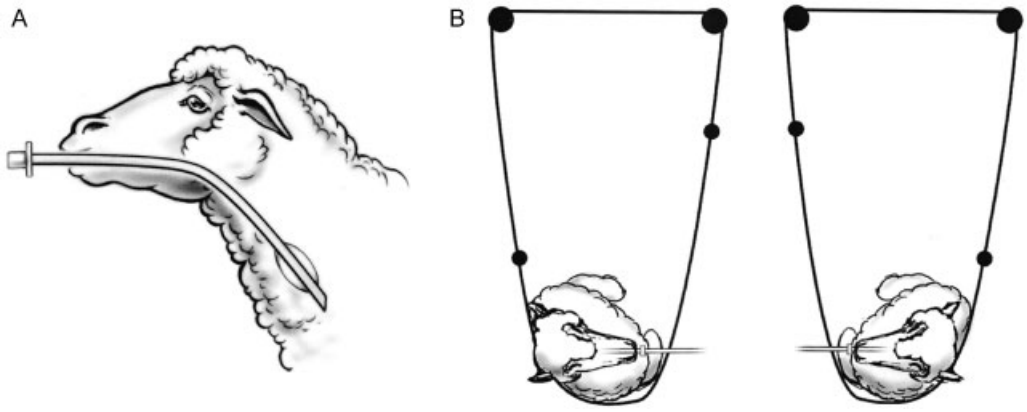

Fig. 2 (**A**) Model of the semirecumbent position, as originally reported by Panigada et al. Sheep were kept prone with the neck, endotracheal tube, and trachea elevated 30 degrees from horizontal. (**B**) To maintain the trachea and the endotracheal tube horizontal or just below and to avoid pulmonary aspiration of oropharyngeal contents, the authors placed the sheep on a lateral body rotation device, and body rotation was accomplished to achieve a 45 degrees semilateral position, alternating from one side to the other. (Reproduced with permission from Panigada et al.[52])

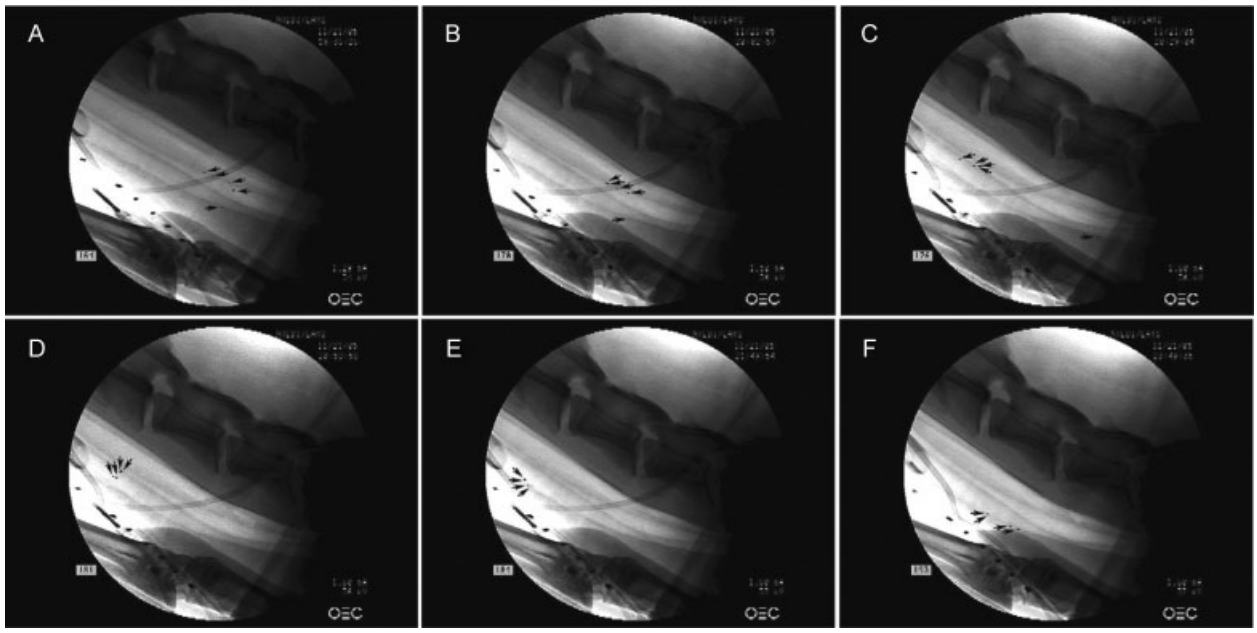

Fig. 3 Tracheal mucus velocity studies in sheep after 12 hours of tracheal intubation and positioned with a tracheal orientation above horizontal. Black/white arrows indicate each tantalum disk, tracked to evaluate mucus transport. (**A**) Following disk insufflation, five tantalum disks were deposited in the trachea; four disks were on the dorsal (nondependent) part of the trachea, and one disk was on the ventral (dependent) part of the trachea (black dots). Fluoroscopic images were taken (**B**) 24 minutes and (**C**) 59 minutes following insufflation showed mucus transport toward the glottis on the nondependent part; while mucus on the dependent part of the trachea moves toward the lungs. (**D–E**) After 80 minutes, mucus almost reached the tip of the endotracheal tube, gravitated to the dependent part of the trachea, and (**F**) reversed flow back toward the lungs. (Reproduced with permission from Li Bassi et al.[18])

Indeed, the same pathogens were isolated from both the proximal trachea and the lungs. Conversely, with the tracheal and pulmonary-axis oriented below horizontal, mucus consistently cleared outward, colonization of the proximal airways was compartmentalized, and lungs infection avoided. In a more recent study,[19] using the porcine animal model of VAP detailed above, we confirmed these thought-provoking assumptions. Indeed, we found that following oropharyngeal colonization by *P. aeruginosa*, the only preventive intervention that avoided development of VAP was the Trendelenburg position. This position fully preserved mucus clearance, which, as expected was strongly associated with lung colonization (►**Fig. 4**). Finally, we also studied the preventive potentials of the Trendelenburg position against ETT-biofilm-related infections.[54] We studied 18 pigs, intubated with ETTs fully colonized by *P. aeruginosa* biofilm. Animals were randomized to be mechanically ventilated up to 24, 48, or 72 hours. In an additional group, we developed ARDS with an infusion of oleic acid and then animals were ventilated for 48 hours. We found that animals of the 24-hour group never developed *P. aeruginosa* respiratory infections, whereas 20, 60, and 25% of the animals ventilated for 48 hours, 48 hours with ARDS, and 72 hours developed *P. aeruginosa* tracheobronchitis, respectively ($p = 0.327$). Interestingly, VAP never developed, even in the group with lung injury. Therefore, these findings confirm that the lateral-Trendelenburg position may also have potentials to compartmentalize ETT biofilm-related colonization and VAP.

These experimental studies provide outstanding evidence against the semirecumbent position and raise awareness on

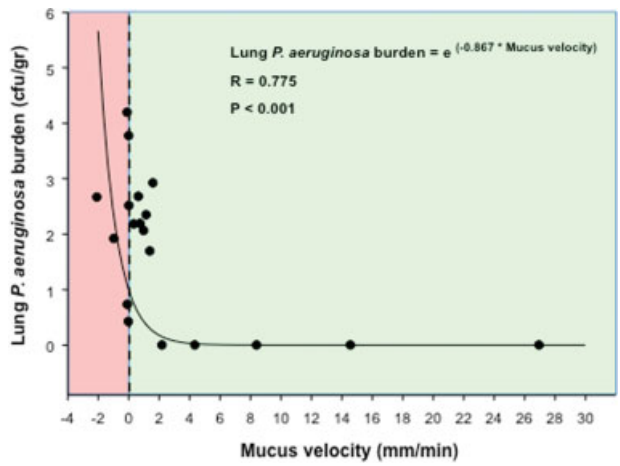

Fig. 4 Lung *Pseudomonas aeruginosa* colonization as a function of mucus clearance rate in pigs challenged in the oropharynx with *P. aeruginosa*. The exponential decay equation was fitted to predict lung *P. aeruginosa* burden by the decrease in mucus clearance rate. The dark and light grey sections of the graph emphasize mucus velocity rates toward the lungs or glottis, respectively. As predicted by the regression, mucus moving toward the lungs at a velocity of −1.27 mm/min was associated with a lung *P. aeruginosa burden* of 3 log CFU/g. (Reproduced with permission from Li Bassi et al.[19])

the significant role of gravity in pulmonary aspiration, mucus retention, and pathogenesis of VAP. Overall, these studies suggest that in intubated semirecumbent patients, with pathological oropharyngeal colonization, there could be a potential risk for gravity-driven translocation of pathogens

into the lungs and VAP. Nevertheless, these preclinical studies present several limitations that need to be taken into account. First, these animals presented oropharyngeal colonization with pathogens, either at the time of intubation or shortly after that; while, in ventilated humans the oropharyngeal flora commonly shift to a predominance of pathogens after days of mechanical ventilation. Second, these studies were conducted in deeply sedated animals; while, latest recommendations[55] underline lighter sedation for ventilated patients. Finally, it should also be highlighted that pigs and sheep, in comparison to humans, have different gastrointestinal pathogens and the dynamics of gastropulmonary aspiration could be different, particularly in ruminants. Therefore, although these studies offer interesting new insights into VAP pathogenesis and prevention, clinical trials are mandatory to corroborate these theories.

We recently completed a large randomized clinical trial (Gravity-VAP trial, available from ClinicalTrials.gov, NLM Identifier: NCT01138540) in tracheally intubated adult patients to confirm whether the lateral-Trendelenburg position could safely reduce the incidence of VAP. The Gravity-VAP trial was designed to translate aforementioned experimental findings and assess feasibility/safety of the intervention. During the design of the trial, we encountered a few challenges, primarily because the orientation of human trachea presents an oblique course, running from superoanterior to inferoposterior.[56] Given such orientation, a full tracheal orientation below horizontal could be achieved only through a steep Trendelenburg position. Thus, we decided to keep the patients in a semi-lateral, slight-Trendelenburg position to offset the oblique tracheal course. In particular, according to a midtrachea placement of the ETT cuff, we attempted to keep the axis from the sternal notch to the mouth horizontal or slightly below, to avoid leakage across the ETT cuff (►**Fig. 1C**). Also, we aimed at orienting the proximal segment of the ETT and respiratory circuit below horizontal to promote outward clearance of respiratory secretions and circumvent any aspiration of fluids from the artificial airways. Of note, based on the experience with the prone position, we were expecting a few possible complications, that is, edema of the face, tongue, and neck; ocular compression; increased gastroesophageal reflux; difficulties in providing enteral feeding; compression of the common peroneal nerve of the dependent leg and of the neurovascular axillary structures of the dependent arm. In addition, given that patients were manually rotated from one side to the other every 6 hours, we expected some challenges, due to additional nursing workload.

The results of the Gravity-VAP trial are much awaited. In the meanwhile, to the best of our knowledge, only one report[57] has attempted to translate theories above in critically ill adults. Investigators tested feasibility and prevention of gastro-pulmonary aspiration through lateral body position, with no Trendelenburg. Ten patients were placed in the lateral position (►**Fig. 5**), in comparison to 10 patients in the semirecumbent position. In the lateral position, patients were turned from one side to the other every 2 to 4 hours for up to 24 hours. The study showed that the lateral horizontal position was feasible and did not cause serious adverse events. Presence of pepsin in tracheal aspirates, an index of gastropulmonary aspiration, did not increase in the lateral position and was found in seven patients in the semirecumbent group (33% of all tracheal aspirate samples), and five (38% of all tracheal aspirate samples) in the lateral horizontal group ($p = 0.32$). Interestingly, the authors found more ventilator-free days and a trend of lower incidence of VAP when the lateral position was applied, but the study was underpowered due to the small sample size.

Additionally, Aly et al[58] randomized 60 intubated infants, to be positioned either supine horizontal, with the ETT held upright in the vertical position or on their side, with the ETT maintained horizontal (►**Fig. 6**). Colonization of the airways was assessed. After 5 days of mechanical ventilation tracheal cultures were positive in 26/30 (87%) and 9/30 (30%) of the patients positioned in the supine and lateral position, respectively ($p < 0.01$).

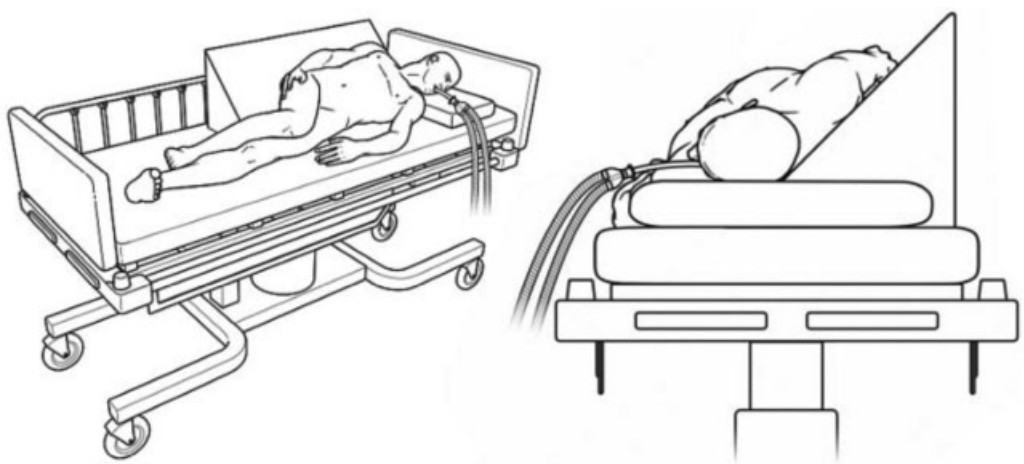

Fig. 5 The 45 degrees semilateral horizontal position of the intubated patient, as originally reported in the study by Mauri et al. A padded wedge behind the torso is placed to obtain the semilateral position. The bed is horizontal, and the patient's head and the endotracheal tube rest laterally to improve secretions drainage. (Reproduced with permission from Mauri et al.[57])

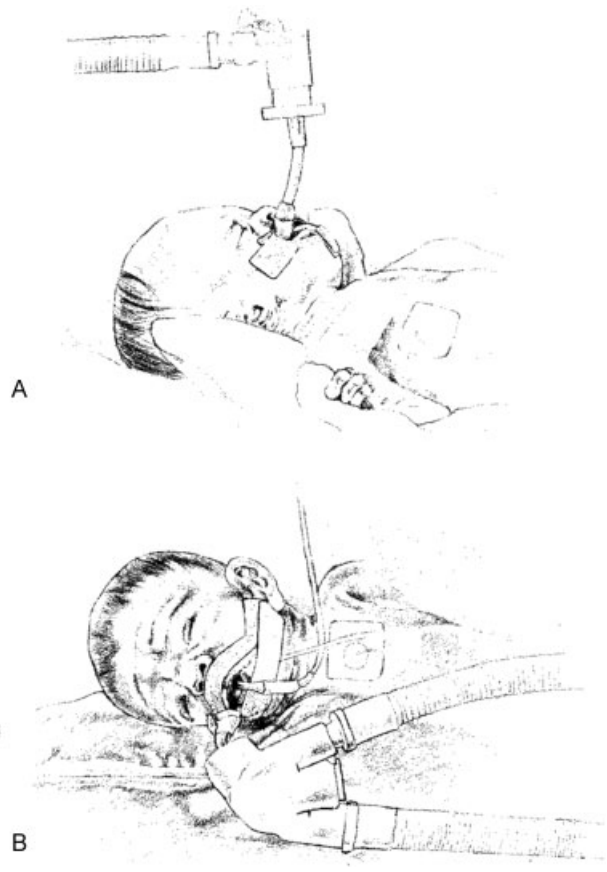

Fig. 6 Study positions as originally reported by Aly et al. (**A**) The infant is maintained supine horizontal with the endotracheal tube held upright in the vertical position. (**B**) The infant is positioned on his/her side with the endotracheal tube and respiratory circuit maintained horizontal to reduce gravity-driven pulmonary aspiration of pathogens. (Reproduced with permission from Aly et al.[58])

Conclusions

In conclusion, critically ill tracheally intubated patients are often placed in the semirecumbent and prone positions. The semirecumbent position was originally indicated to prevent gastropulmonary aspiration of pathogens and VAP. Nevertheless, only one study has demonstrated that the semirecumbent position reduces VAP in comparison with supine, fully horizontal, position. Consistent results from laboratory experimentation are implying that gravity-driven translocation of pathogens from the oropharynx into the lungs could be a primary mechanism in the pathogenesis of VAP and, in patients with oropharyngeal colonization, the semirecumbent position could be deleterious. Nevertheless, translation and clinical application of these new concepts may be challenging. A large randomized clinical trial on the lateral-Trendelenburg position has recently concluded and will shed light on these controversial arguments. Prone position is primarily indicated in patients with ARDS to improve hypoxemia and, theoretically, could also improve drainage of respiratory secretions. At this moment, the prone position cannot be recommended as an effective intervention to prevent VAP.

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Oropharyngeal Decontamination with Antiseptics to Prevent Ventilator-Associated Pneumonia: Rethinking the Benefits of Chlorhexidine

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Abstract

Daily oral care with chlorhexidine for mechanically ventilated patients is ubiquitous in contemporary intensive care practice. The practice is predicated upon meta-analyses suggesting that adding chlorhexidine to daily oral care regimens can reduce ventilator-associated pneumonia (VAP) rates by up to 40%. Close analysis, however, raises three concerns: (1) the meta-analyses are dominated by studies in cardiac surgery patients in whom average duration of mechanical ventilation is $<$ 1 day and thus their risk of VAP is very different from other populations, (2) diagnosing VAP is subjective and nonspecific yet the meta-analyses gave equal weight to blinded and nonblinded studies, potentially biasing them in favor of chlorhexidine, and (3) there is circularity between diagnostic criteria for VAP and chlorhexidine; as an antiseptic, chlorhexidine may decrease the frequency of positive respiratory cultures but fewer cultures does not necessarily mean fewer pneumonias. It is therefore important to look at other outcomes for corollary evidence on whether or not oral chlorhexidine benefits patients. An updated meta-analysis restricted to double-blinded studies in noncardiac surgery patients showed no impact on VAP rates, duration of mechanical ventilation, or intensive care unit length of stay. Instead, there was a possible signal that oral chlorhexidine may increase mortality rates. Observational data have raised similar concerns. This article will review the theoretical basis for adding chlorhexidine to oral care regimens, delineate potential biases in randomized controlled trials comparing oral care regimens with and without chlorhexidine, explore the unexpected mortality signal associated with oral chlorhexidine, and provide practical recommendations.

Keywords

- ventilator-associated pneumonia
- oral care
- chlorhexidine
- quality improvement
- ventilator bundles

Ventilator-associated pneumonia (VAP) remains a common and morbid complication of mechanical ventilation. The U.S. Centers for Disease Control and Prevention estimate that VAP currently affects ~6.6% of patients on mechanical ventilation, corresponding to ~50,000 cases per year in the United States alone.[1] Notwithstanding prior reports that VAP rates have been decreasing, recent analyses suggest that the incidence of VAP has changed little over the past decade.[2] Professional societies, quality improvement organizations, and regulators have identified VAP as a priority target for prevention and have encouraged hospitals to adopt ventilator bundles to prevent VAP and other complications of

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mechanical ventilation. The components of different hospitals' ventilator bundles vary widely but ~80% of hospitals' bundles include an antiseptic mouth rinse, most often chlorhexidine gluconate.[3,4] For many years, practice guidelines have recommended routine oral care with chlorhexidine in all patients on mechanical ventilation.[5–7] This article will review the theoretical basis for routine oral care with chlorhexidine to prevent VAP, summarize randomized controlled trials evaluating the impact of chlorhexidine on VAP, explore the unexpected signal that chlorhexidine may increase mortality risk in some patients, and suggest practical guidance for the oral care of ventilated patients while we await more evidence.

Rationale for Oral Chlorhexidine to Prevent VAP

Researchers have hypothesized for years that most cases of VAP are attributable to macroaspiration of oral and/or gastric fluids at the time of intubation, or microaspiration of fluids around the cuff of the endotracheal tube following intubation. Concurrent cultures from stomach, oropharynx, and lungs have yielded the same organism in some patients.[8] Radiolabeling studies have confirmed the passage of radiolabeled gastric contents from the stomach to the pharynx to endobronchial secretions, particularly in supine patients.[9] These studies affirmed the importance of the mouth and stomach in the pathogenesis of VAP but left open to debate the question of which of these reservoirs is most important. Is pneumonia typically due to direct aspiration of gastric contents into the lungs, gastric contamination of the oropharynx alone followed by aspiration of contaminated oral secretions, or endogenous colonization and proliferation of oral organisms independent of the stomach followed by aspiration of oral secretions? Serial surveillance cultures and pulsed-field gel electrophoresis analyses of gastric, oral, and tracheal secretions suggest that all three routes are possible but most pneumonias appear to be caused primarily by endogenous organisms from the oropharynx.[10–12]

Researchers reasoned that if most pneumonias are caused by aspiration of oral microorganisms, then decolonizing the oropharynx using antibiotics or antiseptics might help prevent pneumonia. Early studies demonstrated that daily application of topical oral antibiotics to the oropharynx (and in some studies, the stomach and nasopharynx as well) decreased the incidence of respiratory infections but raised concerns that daily antibiotic use might select for antibiotic-resistant organisms.[13–15] DeRiso et al consequently hypothesized that an antiseptic might confer similar reductions in pneumonia without the risk of cultivating antimicrobial resistance.[16] They selected chlorhexidine as their antiseptic of choice given its extensive history of safety and efficacy treating gingivitis and other oral infections.[17,18]

DeRiso et al randomized 353 cardiac surgery patients to twice daily oral rinses with 0.12% chlorhexidine versus placebo. They reported a 69% reduction in the incidence of upper and lower respiratory tract infections in the chlorhexidine group without any evidence of bacterial resistance. In addition, they reported a striking difference in mortality rates: 1.2% of patients randomized to oral care with chlorhexidine died versus 5.6% of patients randomized to placebo.[16]

Since the publication of DeRiso et al's trial, more than 20 additional studies have evaluated the impact of oral chlorhexidine on VAP rates.[19] Individually, only three of these studies found significant decreases in VAP rates,[20–22] but a landmark meta-analysis published in the *British Medical Journal* in 2007 reported that on collective analysis of trials completed by that time, oral antiseptics were associated with a 40% decrease in VAP rates (relative risk [RR]: 0.61, 95% confidence interval [CI]: 0.45–0.82).[23] This meta-analysis included six studies of chlorhexidine and one study of povidone-iodine but since studies of chlorhexidine predominated, the net impression was that chlorhexidine was beneficial. A subsequent meta-analysis published in *Lancet Infectious Diseases* in 2011 included 12 studies of chlorhexidine alone and reported a 33% reduction in VAP rates (RR: 0.67, 95% CI: 0.55–0.94).[24] Most recently, a Cochrane review that included 18 randomized controlled trials reported a 26% reduction in VAP rates (RR: 0.74, 95% CI: 0.61–0.89).[19]

VAP prevention guidelines published in the United States, Canada, and Europe in 2008 and 2010 embraced these findings and suggested that daily oral care with chlorhexidine should at least be considered for all patients.[5–7] At the same time, centers around the world began publishing their experience implementing daily process-of-care bundles to prevent VAP. Although bundle components varied widely between hospitals, many included oral care with chlorhexidine and most centers reported striking decreases in VAP rates following implementation of their bundle.[25] The Institute for Healthcare Improvement in the United States noted these data and became a strong advocate for bundling care to prevent nosocomial deaths.[26] Their 100,000 Lives Campaign and subsequent 5 Million Lives Campaign included a ventilator bundle that was expanded to include daily oral care with chlorhexidine in 2010.[27] More than 2,000 hospitals across the United States formally joined the Institute for Healthcare Improvements' campaigns helping make daily oral care with chlorhexidine a routine practice in most intensive care units (ICUs). Cross-sectional surveys of ICUs suggest that ~80% of the U.S. hospitals, the majority of European hospitals, and many other hospitals around the world now provide daily oral care with chlorhexidine to all intubated patients.[3,4,28–31]

Critical Appraisal of the Literature on Oral Care with Chlorhexidine and VAP

Notwithstanding the widespread penetration of daily oral care with chlorhexidine into routine practice, the evidence supporting this intervention is nuanced. The vast majority of individual randomized controlled trials failed to demonstrate lower VAP rates, although many studies put a positive spin on negative results by emphasizing lower colonization rates or more time to VAP onset. The evidence of possible

benefit for chlorhexidine thus comes almost exclusively from meta-analyses.[19,23,24,32] Combining studies for meta-analysis, however, can conceal important aspects of study design and differences between trial populations that are critical to their interpretation. Three points of caution merit consideration.

First, the meta-analyses combined studies of cardiac surgery and noncardiac surgery patients. The vast majority of cardiac surgery patients are extubated < 24 hours after surgery and discharged from the ICU < 48 hours after surgery.[20,33] These patients' duration of exposure to chlorhexidine, risk of pneumonia, and risk of adverse effects from chlorhexidine are therefore very different from other ventilated patients. The primary respiratory outcome in these trials is not VAP but a mix of ventilator-associated and nonventilator-associated pneumonias. One cannot extrapolate from lower pneumonia rates in nonventilated patients to lower pneumonia rates in ventilated patients because the pneumonia risk for intubated and nonintubated patients differs markedly. An endotracheal tube acts as a reservoir and conduit for microbes to enter patients' lungs, allows for pooling of secretions above the cuff that can leak into the lungs, impairs normal ciliary clearance, limits patients' mobility, and often compels the use of sedatives and/or neuromuscular blockers that further increase infection risk.[34,35] Studies in cardiac surgery patients account for ~50% of the total patients in many meta-analyses and therefore exert an outsized influence on their findings.

Second, most meta-analyses failed to differentiate between blinded and nonblinded studies. This is critical because the diagnosis of VAP is subjective and nonspecific.[36–38] There are no absolute diagnostic criteria for VAP. Instead, most studies define VAP as the presence of new infiltrates in patients with purulent secretions, abnormal temperature and/or white blood cell counts, and positive respiratory cultures. There is ample room for discretion in deciding what constitutes a new infiltrate or deciding whether secretions are purulent. Studies of interrater variability have found low rates of agreement between assessors.[39–42] Unblinded studies are therefore at high risk for subconscious bias if investigators' expectations of chlorhexidine's benefits colors their evaluation for VAP. Even studies that require microbiological confirmation of suspected pneumonia using quantitative cultures of invasive samples are beholden to whether clinicians and/or investigators decide to obtain samples and whether these cultures are taken before or after antibiotics are administered (most studies have not required preemptive bronchoalveolar lavage for all patients with any possibility of VAP).

Third, the lack of specificity in VAP criteria puts even double-blinded studies at risk of bias because of circularity between the intervention (oral antisepsis) and diagnostic criteria for VAP (positive cultures).[43] Positive cultures are neither sensitive nor specific for VAP.[44] Oral chlorhexidine may decrease the rate of positive cultures in the intervention arm of chlorhexidine studies, but this does not necessarily mean that VAP has been averted. The estimated sensitivity and positive predictive values of quantitative bronchoalveolar lavage cultures relative to histological analysis are only 57% (95% CI: 47–66%) and 77% (95% CI: 66–85%), respectively.[44,45] What this means is that some patients who meet study VAP criteria do not have pneumonia. They might instead have a mimicking condition such as pulmonary edema, acute respiratory distress syndrome (ARDS), or atelectasis, and their positive cultures may be due to colonization rather than infection. Conversely, some patients without positive cultures may still have VAP. Oral chlorhexidine is likely to decrease the percentage of patients with positive respiratory cultures, but it is difficult to know whether this reflects less pneumonia, less colonization, or some combination of both of these.

Given these concerns, it is essential to look beyond VAP rates alone when evaluating oral care with chlorhexidine and other VAP prevention measures.[43,46–48] Are the purported decreases in VAP rates supported by parallel improvements in patients' other outcomes such as mean duration of mechanical ventilation, ICU length-of-stay, mortality, antibiotic utilization, or ventilator-associated events? These outcomes have the virtue of being more objective than VAP and thus less susceptible to the biases that plague VAP.

Updated Meta-analyses of the Impact of Oral Care with Chlorhexidine

My colleagues and I recently published an updated meta-analysis of randomized controlled trials of oral care with chlorhexidine in ventilated patients that was specifically designed to address these three concerns.[49] Cardiac surgery and noncardiac surgery studies were considered separately. Studies were stratified by blinding status. Data on duration of mechanical ventilation, ICU length of stay, hospital length of stay, mortality, and antibiotic utilization were collated. The meta-analysis included 16 studies altogether, 3 in cardiac surgery patients and 13 in noncardiac surgery patients. The collective enrollment across all 16 studies was 3,630, including 1,868 patients from cardiac surgery studies and 1,762 patients from noncardiac surgery studies.[16,20–22,33,50–60]

On combining all studies, oral care with chlorhexidine was associated with a 27% decrease in VAP risk (RR: 0.73, 95% CI: 0.58–0.92). This result paralleled the effect estimates reported in the meta-analyses by Chan et al (7 studies, RR: 0.56, 95% CI: 0.39–0.81) and Labeau et al (12 studies, RR: 0.72, 95% CI: 0.55–0.94) that helped catalyze broad uptake of chlorhexidine.[23,24] These favorable risk ratios, however, were largely driven by the three studies in cardiac surgery patients. The risk ratio in the three cardiac surgery studies was highly significant at 0.56 (95% CI: 0.41–0.77), whereas the risk ratio in noncardiac surgery studies was not significant at 0.78 (95% CI: 0.60–1.02). The signal for possible benefit was further diminished when considering blinding status. The risk ratio in the six open-label studies in noncardiac surgery patients was 0.61 (95% CI: 0.35–1.04), whereas the risk ratio in the seven double-blinded studies was 0.88 (95% CI: 0.66–1.16). Forest plots of the effect of chlorhexidine on VAP rates stratified by cardiac surgery and blinding status are shown in ►**Fig. 1**. The marked difference in the risk ratios for the open-label versus

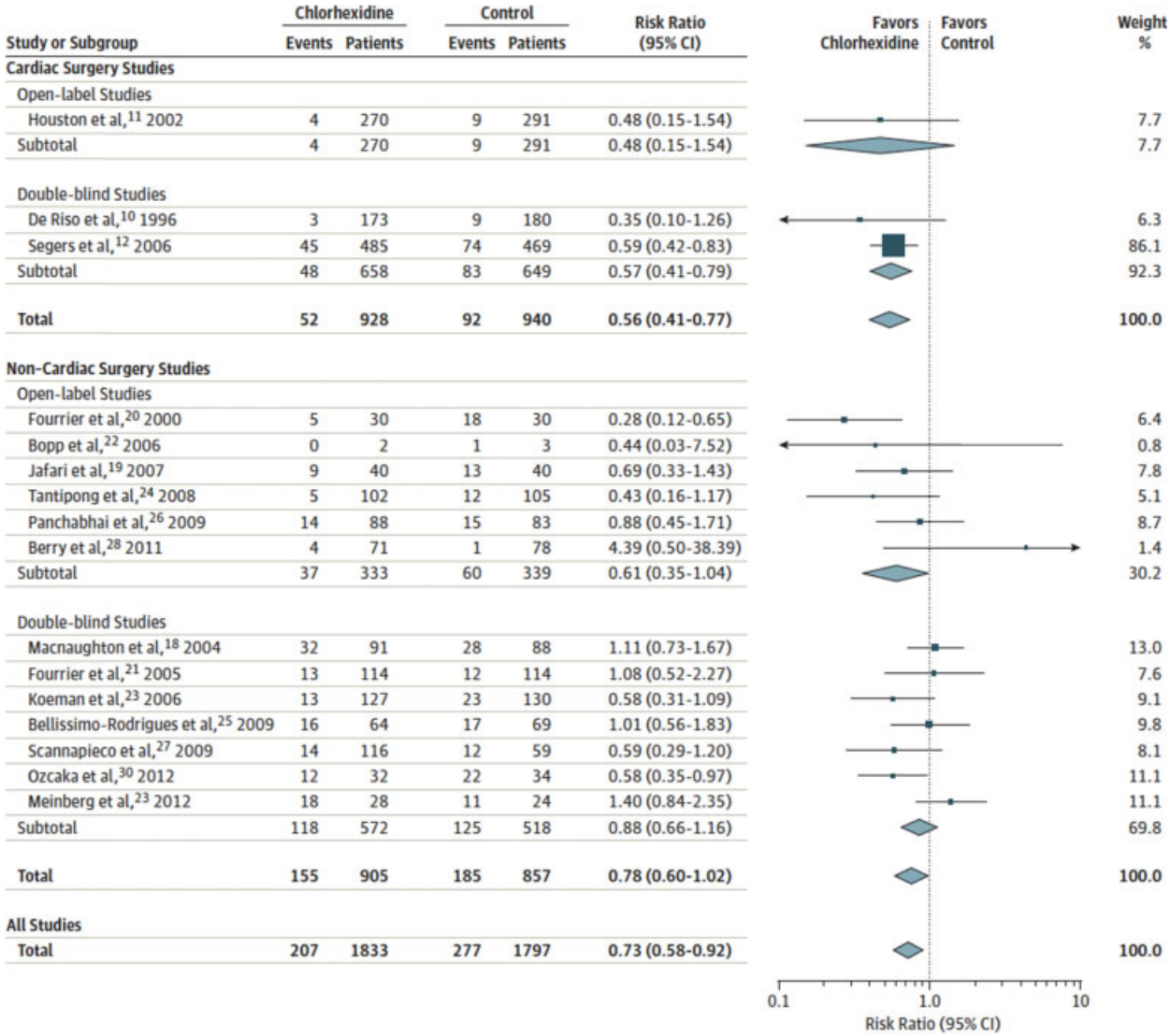

Fig. 1 Impact of chlorhexidine versus comparators on nosocomial pneumonia in cardiac surgery patients and ventilator-associated pneumonia in noncardiac surgery patients. Reproduced with permission from Klompas et al. JAMA Internal Medicine 2014;174(5):751–761. Copyright © 2014 American Medical Association. All rights reserved.[49]

double-blinded studies affirms the subjectivity of diagnosing VAP and its risk for bias.

The nonsignificant risk ratio for VAP reduction in double-blinded studies was paralleled by the absence of improvements in other outcomes. There were no differences between the chlorhexidine and placebo arms in either the cardiac surgery or noncardiac surgery studies in mean duration of mechanical ventilation, ICU length of stay, or hospital length of stay. The effect estimate in noncardiac surgery studies for change in mean duration of mechanical ventilation was − 0.15 days (95% CI: − 2.18 to 1.89 days), and the estimate for change in ICU length of stay was + 0.08 days (95% CI: − 1.41 to 1.57 days). One study in cardiac surgery patients reported a decrease in antibiotics prescribed to patients randomized to oral care with chlorhexidine but none of the four studies in noncardiac surgery patients with data on this outcome reported any significant differences in antibiotic prescribing.[16,55,57–59]

An Unexpected Mortality Signal

Surprisingly, the meta-analysis yielded a near-significant signal that mortality rates may be higher in patients randomized to chlorhexidine versus placebo (►**Fig. 2**).[49] The risk ratio for mortality among all studies was 1.13 (95% CI: 0.99–1.28). Mortality rates varied widely among the three cardiac surgery studies leading leading to a broad CI and no clear signal of increased risk (RR: 0.88, 95% CI: 0.25–3.14). The mortality signal was more consistent, however, across the noncardiac surgery studies (RR: 1.13, 95% CI: 0.99–1.29). In addition, these studies also showed a stepwise increase in the effect estimates for mortality with increasing concentrations of chlorhexidine: RR: 1.01 (95% CI: 0.46–2.20) for 0.12% preparations, RR: 1.13 (95% CI: 0.96–1.32) for 0.2% preparations, and RR: 1.16 (95% CI: 0.92–1.46) for 2.0% preparations.

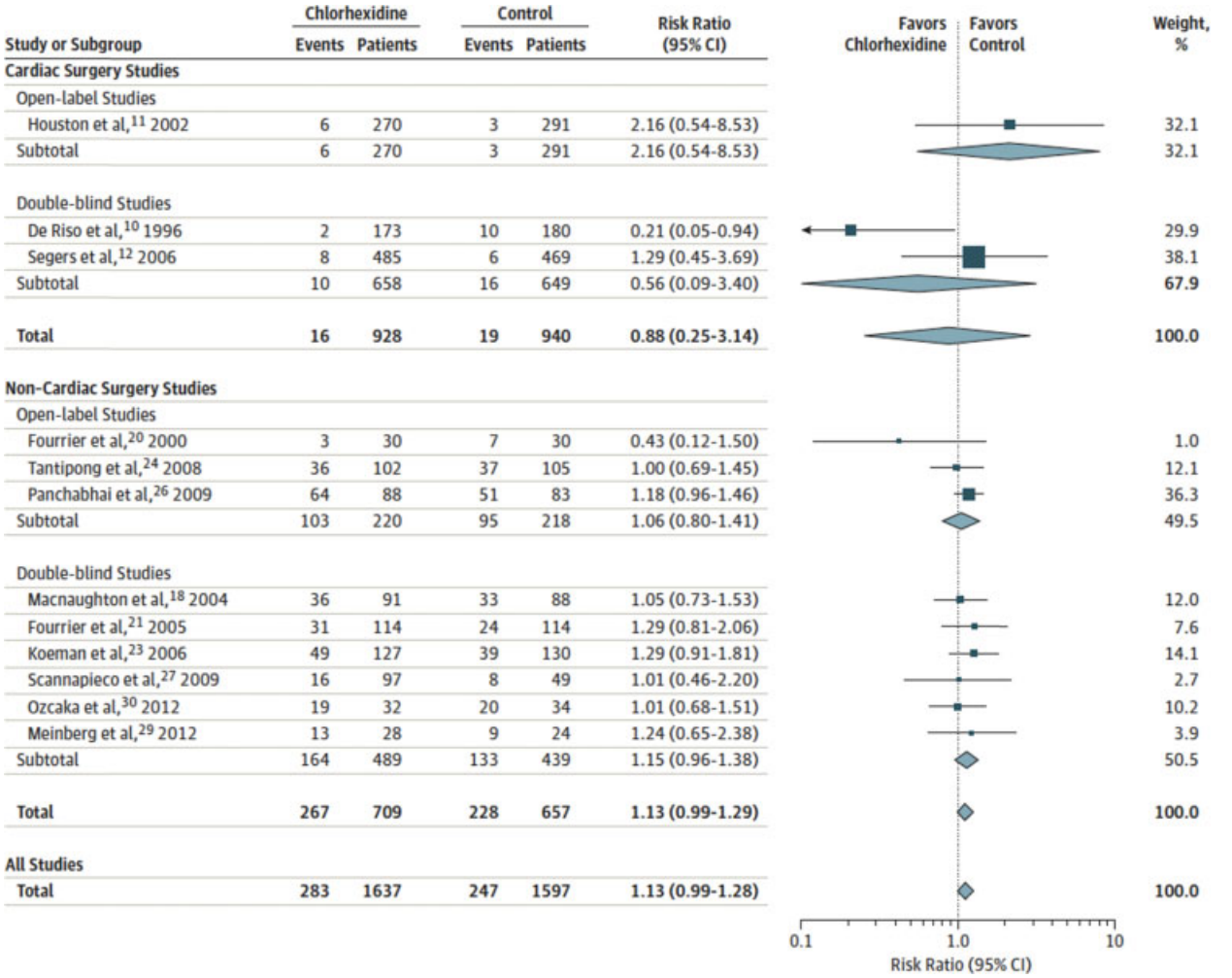

Fig. 2 Impact of chlorhexidine versus comparators on mortality. Reproduced with permission from Klompas et al. JAMA Internal Medicine 2014;174(5):751–761. Copyright © 2014 American Medical Association. All rights reserved.[49]

The possibility that oral care with chlorhexidine may increase mortality risk has also been noted in two other studies. The first was a network meta-analysis published in the same year as our meta-analysis.[61] Price et al analyzed 11 randomized controlled trials of chlorhexidine versus placebo in noncardiac surgery patients, including 8 of the 12 studies included in our mortality analysis (the other three studies included by Price et al were excluded from our meta-analysis because of incomplete data in two cases and the inclusion of large numbers of nonventilated patients in the third case).[54,62,63] They reported that oral care with chlorhexidine was associated with an odds ratio for death of 1.25 (95% CI: 1.05–1.50).

The other study to purport a possible association between oral care with chlorhexidine and increased mortality risk was a retrospective analysis of the impact of daily ventilator bundle compliance on patient outcomes.[64] This study included 5,539 consecutive episodes of mechanical ventilation from a single academic hospital in Boston. The authors assessed daily compliance with each of six processes of care for ventilated patients: head-of-bed elevation, sedative infusion interruptions, spontaneous breathing trials, thromboprophylaxis, stress ulcer prophylaxis, and oral care with chlorhexidine. The authors used competing risk models to assess the association between each process of care and ventilator-associated events, time to extubation versus ventilator death, and time to hospital discharge versus hospital death. The analysis included covariates for patients' demographic characteristics, comorbidities, unit type, severity of illness, recent procedures, calendar year, daily assessment of whether a given process was contraindicated, and day-to-day markers of patients' clinical status (use of sedative, neuroleptics, opioids, neuromuscular blockers, vasopressors, and presence of severe hypoxemia).

The findings from this study paralleled the results from our meta-analysis: oral care with chlorhexidine was associated with a lower risk for respiratory infections but higher risk for death. Specifically, oral care with chlorhexidine was associated with significantly fewer infection-related ventilator-associated complications (hazard ratio [HR]: 0.60, 95% CI: 0.36–1.00) and numerically fewer ventilator-associated pneumonias (HR: 0.55, 95% CI: 0.27–1.14) but a significantly higher risk for ventilator death (HR: 1.63, 95% CI: 1.15–2.31).[64] There was no association between oral care with chlorhexidine and

hospital death, but the hospital mortality analysis was restricted to patients who survived mechanical ventilation. As with our meta-analysis, there was no suggestion that oral care might decrease time to extubation (HR for extubation: 0.92, 95% CI: 0.80–1.04) or hospital discharge (HR for discharge alive: 0.99, 95% CI: 0.98–1.01). The associations among sedative interruptions, spontaneous breathing trials, and stress ulcer prophylaxis with duration of mechanical ventilation and other outcomes in this trial also matched prior literature from randomized controlled trials lending credence to the overall study methodology and observations.[64]

Notably, a Cochrane meta-analysis of oral care with chlorhexidine published after the release of our 2014 meta-analysis did not report a significant increase in mortality rates (RR: 1.09, 95% CI: 0.96–1.23).[19] The differences between the two meta-analyses were as follows: (1) the Cochrane review included three studies in children, whereas our study was limited to adults[65–67]; (2) the Cochrane review included a study by Cabov et al that we excluded because one-third of the study population did not receive mechanical ventilation[63]; (3) the Cochrane review included a study by Munro et al that we excluded because the authors only provided outcome data on 192/547 (35%) patients enrolled in the study[62]; and (4) we included one study that was only published in abstract form[55] and one study in which the mortality rate was obtained from a secondary publication rather than the original article.[23,57] The exclusion of studies in children appears to be responsible for the difference in mortality risk ratios between our study and the Cochrane review since the study by Cabov et al reported a mortality rate of 0% and the study by Munro et al reported numerically higher mortality rates in patients randomized to chlorhexidine.[62,63] It might be then that if in fact there is a mortality risk associated with chlorhexidine, it might be restricted to adults.

Possible Reasons Why Oral Care with Chlorhexidine May Increase Mortality Rates

There is no proven explanation of why oral care with chlorhexidine might increase mortality risk. We speculate that some fraction of patients may aspirate some chlorhexidine into the lung parenchyma triggering ARDS. Data supporting this hypothesis include a case report about a patient who developed fatal ARDS following inhalation of chlorhexidine and observations of patients aspirating during oral care.[68,69] Studies in rats have confirmed that tracheal instillation of a single dose of chlorhexidine can trigger acute lung injury including perivascular and intra-alveolar hemorrhage, pulmonary congestion, and fibrosis.[70,71] The risk of lung injury appears to be concentration dependent with no apparent risk at 0.01% but progressive injury with 0.1 and 1.0% solutions. The dose of chlorhexidine in this study was 300 µL/kg which would correspond to 18 mL of solution in a 60 kg person. In addition, chlorhexidine can be absorbed into the systemic circulation following aspiration or oral ingestion of large quantities.[68,72] Unfortunately, none of the randomized controlled trials of oral care with chlorhexidine has thus far have included ARDS as an outcome; therefore, there are no direct data to affirm or refute whether aspiration leading to ARDS is the mechanism whereby chlorhexidine might increase mortality risk for some patients. Other investigators have reported, however, that ventilated patients can aspirate oral antiseptics and that this might trigger ARDS. Seguin et al, for example, reported that 6.0% of patients randomized to oral care with povidone-iodine developed ARDS versus 0% of patients randomized to placebo.[73]

Other Possible Harms Associated with Oral Chlorhexidine

Chlorhexidine's proclivity to stain teeth has long been known but more recent reports note other oral adverse effects, particularly with higher concentrations. Plantinga et al reported erosive oral mucosal lesions in almost 10% of patients randomized to daily care with 2% chlorhexidine digluconate.[74] Median time to development of oral lesions was 8.0 days and required discontinuation of chlorhexidine in ~50% of affected patients. Oral lesions occurred in less than 1% of patients after these investigators switched to a 1% gel preparation.

A different concern associated with chlorhexidine is the time and effort required of nurses to perform this intervention. One large academic hospital estimated that nurses spend a median of 160 minutes per day (interquartile range, 104–244 minutes) providing oral care to ventilated patients, including a median of 20 minutes (interquartile range: 10–34 minutes) rinsing patients' mouths with chlorhexidine.[75] If the benefit of chlorhexidine is questionable then the time spent applying this intervention may paradoxically harm patients by decreasing nurses' time and focus on other activities that might have a greater and more consistent effect on improving patient outcomes. Examples of nursing intensive interventions that have more consistently been associated with less time to extubation, and in some studies lower mortality rates, include minimizing sedation, spontaneous awakening trials, spontaneous breathing trials, and early mobility.[64,76–81]

Finally, some clinicians anecdotally note that oral chlorhexidine ordered in the ICU as part of a ventilator prevention bundle is often continued after patients are extubated and after discharge from the ICU. This is rarely because of a deliberate decision but rather reflexive continuation of medications started in the ICU. If chlorhexidine is deleterious for some patients then this practice may magnify the potential harm associated with this medication.

Oral Care *without* Chlorhexidine

It is important to note that the analysis in this article pertains solely to the chlorhexidine component of oral care regimens. All the randomized controlled trials included in the meta-analyses in this study compared oral care with chlorhexidine to oral care without chlorhexidine. These studies only show then that chlorhexidine does not confer additional benefit relative to oral care without chlorhexidine. Although very

few studies have formally evaluated care with oral hygiene to care without oral hygiene, there are independent compelling reasons to provide oral care. These include patient comfort and prevention of tooth and gum disease. Observational studies do suggest that oral care alone may also decrease VAP rates, but there are insufficient data to know this with certainty.[53,82] A related area of interest is whether oral care with toothbrushing confers additional benefit over oral care without toothbrushing. The evidence from randomized controlled trials is mixed.[19,83,84] Meta-analyses report effect estimates that allow for the possibility that toothbrushing may lower VAP rates but the 95% CIs traverse one and many of the same biases that apply to evaluating the effect of chlorhexidine on VAP also apply to toothbrushing. Further data are needed.

Summary and Recommendations

The observed associations between oral chlorhexidine and increased mortality are suggestive but far from definitive. Importantly, no single randomized controlled trial has documented significantly higher mortality rates in patients randomized to chlorhexidine. It is entirely possible that the observed association is due to chance alone and that further studies will obviate the concern. Nonetheless, the signal has appeared in two independent lines of investigation (meta-analyses of randomized controlled trials and competing risk analysis of observational data) and a biological mechanism for increased mortality is conceivable.

If there is a possible risk associated with oral care with chlorhexidine then we need to weigh this risk against any possible benefits that oral chlorhexidine may confer, taking into account both the magnitude of the risk and our relative uncertainty about the risk. The prevailing perception is that chlorhexidine lowers VAP rates and is therefore warranted but as we have reviewed, this perception may be colored by biases introduced by mixing analyses from cardiac and noncardiac populations, lack of blinding, and difficulty distinguishing decreases in colonization from decreases in pneumonia. It is notable that meta-analysis restricted to double-blinded studies in noncardiac surgery patients have not shown significant decreases in VAP rates. Similarly, there is no indication that oral care with chlorhexidine can provide other benefits, such as decreasing time to extubation or ICU discharge, and the predominance of evidence is that oral care with chlorhexidine does not decrease antibiotic utilization. Therefore, while the question of whether oral care with chlorhexidine increases mortality risk or not is very much open to debate, there does not appear to be any compelling evidence of benefit to counterbalance the possibility of harm. If there is no evidence of benefit and even just a small risk of harm then routine oral care with chlorhexidine no longer appears to be justifiable.

Recently published guidelines have been gravitating toward this conclusion. The latest update to the Society for Healthcare Epidemiology of America's Compendium of Strategies to Prevent VAP downgraded oral care with chlorhexidine from a routinely recommended practice for all hospitals to a special practice reserved for hospitals that have persistently high VAP rates despite effective implementation of more basic practices.[85] Similarly, the United Kingdom's Intensive Care Society now recommends against the use of oral chlorhexidine for noncardiac surgery patients.[86]

There is at least one large, multicenter randomized controlled trial ongoing at present that may shed further light on the risk–benefit balance of chlorhexidine (NCT02208154). This trial includes many more patients than any of the studies that have been published to date and thus has the potential to modify our understanding of the role of chlorhexidine. In the interim, however, it would appear that hospitals and patients have more to gain by focusing their efforts on other interventions with clearer evidence of benefit. Possibilities include selective digestive decontamination, minimizing sedation, spontaneous breathing trials, and early mobilization. These interventions have all been associated with less time to extubation and in some cases lower mortality rates.[77,78,87,88] These unambiguous benefits are particularly compelling relative to the possible harm and questionable benefits of oral chlorhexidine.

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