



REVIEW

Antimicrobial Resistance in Ventilator-Associated Pneumonia: Predictive Microbiology and Evidence-Based Therapy

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ABSTRACT

Ventilator-associated pneumonia (VAP) is a serious intensive care unit (ICU)-related infection in mechanically ventilated patients that is frequent, as more than half of antibiotics prescriptions in ICU are due to VAP. Various risk factors and diagnostic criteria for VAP have been referred to in different settings. The estimated attributable mortality of VAP can go up to 50%, which is higher in cases of antimicrobial-resistant VAP. When the diagnosis of pneumonia in a mechanically ventilated patient is made, initiation of effective antimicrobial therapy must be prompt. Microbiological diagnosis of VAP is required to optimize timely therapy since effective early treatment is fundamental for better outcomes, with controversy continuing regarding optimal sampling and testing. Understanding the role of antimicrobial resistance in the context of VAP is crucial in the era of continuously evolving antimicrobial-resistant clones that represent an

urgent threat to global health. This review is focused on the risk factors for antimicrobial resistance in adult VAP and its novel microbiological tools. It aims to summarize the current evidence-based knowledge about the mechanisms of resistance in VAP caused by multidrug-resistant bacteria in clinical settings with focus on Gram-negative pathogens. It highlights the evidence-based antimicrobial management and prevention of drug-resistant VAP. It also addresses emerging concepts related to predictive microbiology in VAP and sheds lights on VAP in the context of coronavirus disease 2019 (COVID-19).

Keywords: Early effective therapy; Window; Drug-resistant organism; Novel diagnostics

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Key Summary Points

A literature review was conducted to critically evaluate the evidence on antimicrobial resistance in ventilator-associated pneumonia (VAP) in adults due to the continuous evolution of resistance mechanisms and availability of newer antimicrobials.

Rapid testing for VAP can potentially provide results in real time to tailor therapy appropriately with rapid identification of pathogens and detection of their multidrug resistance (MDR) determinants. Supporting clinical data are still limited as a result of potential confounders with an inflated estimation of the diagnostic performance.

The local ICU ecology remains a significant risk factor for acquiring MDR infections regardless of the time of intubation, and may be linked to the global increase in MDR pathogens.

Mathematical models and scoring systems are still not sufficiently developed for operational application given their limitations in predicting MDR-VAP.

Areas for priority research studies in VAP caused by resistant pathogens include the clinical utility of rapid diagnostics and validation of prediction scores in making clinical decisions to accelerate the developments in this emerging field.

INTRODUCTION

Ventilator-associated pneumonia (VAP) continues to be a major cause of morbidity and mortality despite advancements in prevention, antimicrobial therapy, and supportive care. VAP imposes a significant economic burden on healthcare systems, and more than half of antibiotics prescriptions in intensive care units

(ICU) are found to be administered for VAP cases [1–3]. The attributable cost of VAP was estimated by a Monte Carlo simulation model in a meta-analysis to be around \$40,144 per case [4]. Antimicrobial resistance in the ICU environment is highly dynamic and the rates of VAP caused by resistant pathogens can be additionally costly. Around 12% of the implicated pathogens in a retrospective study of adult patients with hospital-associated pneumonia (HAP) and VAP ($N = 8969$) between 2009 and 2016 in the USA were carbapenem-resistant. The median VAP hospital length of stay in that study was 26 days with an additional cost of \$30,000 (median \$105,947 vs \$72,810) [5]. ICU infections caused by Gram-negative bacteria account for the majority of cases worldwide [6]. Of these, 37% are estimated to be multidrug-resistant (MDR) pathogens, demonstrating acquired nonsusceptibility to at least one agent in three different antimicrobial classes. An extensively drug-resistant (XDR) status is defined as nonsusceptibility to at least one agent in all but two or fewer antimicrobial categories (isolates remain susceptible to only one or two therapeutic categories) [7]. ICU infection is an independent predictor for poor prognosis, and VAP caused by MDR and XDR strains is very challenging to cure [8]. The frequency of MDR pathogens varies between healthcare centers and within centers among different patient populations, as some patients with complex comorbidities are likely to have higher rates of antimicrobial resistance [9].

In this review, the evidence for antimicrobial therapy in cases of adult VAP in the era of antimicrobial resistance (AMR) is summarized. In particular, the review provides a brief description of risk factors for antimicrobial-resistant VAP, followed by a comprehensive overview of AMR mechanisms in the commonly implicated pathogens and their detection tools. Since pneumonia in mechanically ventilated patients represents a consortium of diverse pathological events and is not restricted to VAP, the current review highlights other forms of lower respiratory tract infections in the ICU and describes studies underlying the evidence for coronavirus disease 2019 (COVID-19)-associated VAP. Finally, challenges and key areas for

future research are presented. The review was conducted on the basis of a comprehensive search using electronic databases and reference checks. The Cochrane Library, MEDLINE, EMBASE, and Web of Science were searched from 1990 until March 2023. Various common terms related to VAP diagnostics in ICU were used to conduct the search. A checklist was adopted from the critical appraisal skills program checklist for diagnostic studies to assess the quality of the included studies prior to citing them.

This review article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by the author.

VAP DEFINITION AND RISK FACTORS

While pneumonia is identified by using a combination of imaging, clinical, and laboratory criteria, establishing a definitive diagnosis of VAP can be challenging. A recently adopted definition of VAP is pneumonia in which the patient is on mechanical ventilation for at least two consecutive days, and the ventilator was in place on the date of the event or the day before [10]. On the other hand, ventilated hospital-acquired pneumonia (vHAP) refers to severe HAP in patients requiring mechanical ventilation, and non-ventilated intensive care unit-acquired pneumonia (NV-ICUAP) stands for pneumonia that occurs at least 48 h after ICU admission [11, 12]. Hospital-acquired pneumonia is designated for other cases of pneumonia occurring at least 48 h after hospital admission, not incubating at the time of admission, and not associated with mechanical ventilation [10]. This new classification endorsed by the National Healthcare Safety Network (NHSN) categorizes all adverse ventilator-associated events (VAE) into a tier-based system on the basis of the rapidly evolving data in order to consider all potential conditions affecting morbidity in ventilated patients other than VAP as the only significant pathology. The updated surveillance definition also minimizes subjectivity and enables automated data collection

which streamlines the analysis and benchmarking, and comparison of VAP rates across institutions. vHAP is associated with higher mortality rates than VAP, and nonventilator hospital-acquired pneumonia (nvHAP) is an equally frequent subvariant of HAP that tends to occur after a longer admission and results in higher costs [13, 14]. Notably, these conditions are not independent entities and, in many cases, they may represent a continuum of the disease in hospitalized patients (Fig. 1) [12, 15].

Risk Factors for VAP

Critically ill patients tend to have more comorbidities and severe acute physiologic disturbance [16]. The frequent use of catheters and other supportive devices among ICU patients can bypass natural host defense mechanisms and provide a portal of entry for organisms into various sites. In addition, medical equipment can be a reservoir for MDR organisms, facilitating horizontal transmission across ICU patients. Frequent contact with healthcare workers is another risk for infection with nosocomial, drug-resistant pathogens. Furthermore, patients in the ICU are more likely to be under antimicrobial selective pressure in comparison with other patient populations. All these factors lead to the emergence of MDR bacterial clones and increased colonization pressure among ICU patients [17].

Risk Factors for Drug-Resistant VAP in Adult Patients

VAP caused by an MDR pathogen acquired in the ICU depends on both host comorbidities as well as factors related to the healthcare system. Several patients factors were found to be linked to resistant infections reported from the ICU including older age, limited mobility (e.g., bedridden status), underlying comorbid conditions such as diabetes mellitus, end-stage renal disease, immunosuppression, and malignancies, recent surgery or other invasive procedures, antimicrobial therapy in the 90 days prior to the ICU admission (odds ratio, OR 13.5), prior use of broad-spectrum antibiotic (OR 4.1), previous colonization, and increased

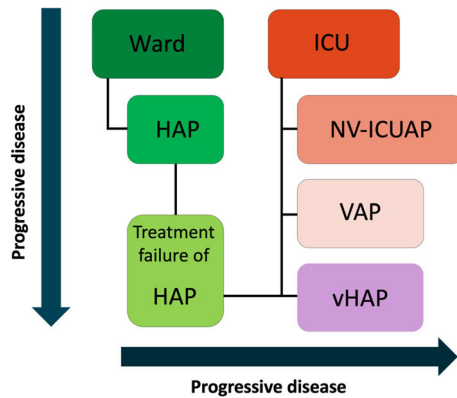


Fig. 1 Progression of nosocomial pneumonia in hospitalized patients [15]. HAP hospital-acquired pneumonia, ICU intensive care unit, NV-ICUAP non-ventilated intensive care unit acquired pneumonia, VAP ventilator-associated pneumonia, vHAP ventilated hospital-acquired pneumonia

severity of acute illness (mortality risk > 15%) (Table 1). The length of stay in the ICU and the long duration of hospitalization (> 5 days) prior to the ICU admission, including being in long-term care facilities, increase the risks of VAP and other ICU infections, particularly with a pathogen that is MDR [10, 18–21]. Additionally, prolonged mechanical ventilation for more than 7 days is an independent risk factor for MDR-VAP (OR 6.0) [22]. Regardless of onset, the initial VAP severity is another risk factor for MDR infections [22]. Other potential factors include history of MDR infection, recurrent hospitalization, and the presence of structural pulmonary disease [23]. The MDR epidemiology in an ICU environment plays an additional role where more than 25% local prevalence of MDR pathogens in a unit's antibiogram is considered a risk factor that predisposes patients to MDR-VAP [22]. Although most data on VAP infections originate from developed countries, the available evidence suggests the rates of infection can be higher in the developing world. A prospective, multicenter surveillance cohort of 55 hospital ICUs in 46 countries including India, Turkey, Morocco, and Central and South American states reported an overall rate of 22.5 infections/1000 ICU days, with a high rate of VAP equivalent to 24.1 episodes/1000 ventilator days (10.0 to 52.7) [24]. Antimicrobial

Table 1 Risk factors for antimicrobial-resistant ventilator-associated pneumonia [10, 22]

Risk factors for VAP caused by an MDR pathogen	Local epidemiology: MDR resistance rate > 25%
	Long duration of hospitalization prior to VAP
	Parenteral antibiotics in the preceding 90 days
	Hospital stay prior to VAP > 5 days
	Previous MDR colonization
	Severity of illness:
	ARDS prior to VAP
	Concurrent septic shock
	Acute renal replacement therapy prior to VAP
	Chance of mortality ≈ 15%
Specific risk factors for VAP caused by MRSA	Local MRSA rate > 20% or unknown
	MRSA colonization
Specific risk factors for VAP caused by MDR Gram-negative bacilli, e.g., <i>P. aeruginosa</i>	Local resistance rates to first-line agents > 10% or unknown
	Colonization with MDR <i>Pseudomonas</i> or other MDR Gram-negative bacilli

ARDS acute respiratory distress syndrome, MDR multidrug resistant, MRSA methicillin-resistant *S. aureus*, VAP ventilator-associated pneumonia

resistance was alarmingly high in the study (84% methicillin resistance among *Staphylococcus aureus* infections, and more than 50% resistance to third-generation cephalosporin in Enterobacterales and fluoroquinolones among *Pseudomonas aeruginosa* isolates), with a VAP mortality rate of 44.9%. The Infectious Diseases Society of America (IDSA) guidelines for adult

hospital-acquired and ventilator-associated pneumonia suggest a target threshold of at least 95% for empiric coverage of MDR pathogens when treating a high-risk patient population based on the listed risk factors, while a 90% threshold is endorsed by the European Respiratory Society (ERS), European Society of Intensive Care Medicine (ESICM), European Society of Clinical Microbiology and Infectious Diseases (ESCMID), and Asociación Latinoamericana del Tórax (ALAT) [10, 22]. Nevertheless, these risk factors have been criticized for not accurately forecasting for VAP caused by MDR while the local unit ecology and prior antimicrobial usage were shown to be the main significant predictive variables [25].

VAP Surveillance Cultures and Local Epidemiology

The role of surveillance cultures for VAP remains debatable. Nosocomial infections, including VAP, are significantly influenced by prior colonization with potential pathogens [12, 26, 27]. For instance, ICU patients with *S. aureus* colonization have a 15-fold increased chance of developing VAP in contrast to patients who are not colonized [28]. A meta-analysis by Brusselaers et al. ($N = 791$) implies that the likelihood of developing VAP can be predicted by the colonization of the respiratory tract shown in sequential surveillance cultures with a high negative predictive value ($> 90\%$), particularly in the case of Enterobacterales [29]. The area under the curve (AUC) of the hierarchical summary receiver operating characteristic (ROC) curve showed a moderate level of accuracy (AUC 0.90) in predicting multidrug resistance with improved accuracy when recent cultures are used, although heterogeneity was evident in the analysis. On the other hand, a few studies revealed that upper airway samples positive for Enterobacterales are more predictive for VAP than gastric samples, while selective oral decontamination still reduced the colonization and the rate of VAP without influencing the gastric colonization with Gram-negative rods [30, 31]. Therefore, a proactive approach to VAP employs surveillance cultures to identify colonizing bacteria including those MDR strains. Collecting endotracheal aspirates is a

relatively noninvasive procedure that can be performed on intubated patients. The prediction of these surveillance microbiological cultures was shown to be most accurate when they were routinely conducted at least twice a week [29, 32]. These samples are frequently utilized to guide empirical treatment when patients develop signs of VAP. Yet, there is inconclusive evidence that this approach improves clinical outcomes or reduces costs, even when lower respiratory tract surveillance cultures can help to predict the involvement of MDR bacteria in patients with VAP [30, 33]. Furthermore, approximately 30% of antimicrobial prescriptions in ICU are estimated to target colonization leading to inappropriate usage of antibiotics since surveillance cultures alone cannot distinguish colonization from infection even in the presence of high bacterial loads (positive predictive value of 75%) [29, 34]. In addition, the frequent use of broad-spectrum agents to treat susceptible community-acquired pathogens is frequent in the ICU environment owing to the acuity of illness [29]. Since many patients in ICU are admitted directly from the community such as trauma cases, the prevalence of resistant bacterial colonization can be initially low at the time of admission in geographical areas with low backgrounds of MDR organisms. This highlights the significance of incorporating the local epidemiology when selecting an empirical regimen along with the surveillance cultures. The complex interaction of naturally occurring changes in the prevalence of MDR colonization is created in ICU patient populations on the basis of individualized factors which is further complicated by rapid turnover of cases and different transmission routes [26].

MICROBIOLOGY IN VAP

Multiple variables, such as the length of mechanical ventilation, the length of hospital and ICU stay prior to VAP, the timing and cumulative antimicrobial exposure, the local ecology, and the occurrence of any potential epidemic in a particular ICU, all affect the type of organisms isolated in VAP cases. *P. aeruginosa*, *Escherichia coli*, *Klebsiella pneumoniae*, and

Acinetobacter baumannii are commonly involved Gram-negative species while *S. aureus* is the main Gram-positive pathogen [34–36]. In previously healthy patients who are not receiving antibiotics, early-onset VAP, defined as VAP onset of less than 5 days of hospitalization without MDR risk factors, typically involves normal upper airway flora, whereas late-onset VAP, occurring after at least 5 days of hospitalization, or VAP in patients with a high index for MDR pathogens (Table 1) are more likely to be caused by nosocomial organisms [10, 22, 23]. These include methicillin-resistant *S. aureus* (MRSA), Gram-negative enteric pathogens that produce extended-spectrum β -lactamases and/or carbapenemases (ESBL and CRE, respectively), and the carbapenem-resistant non-fermentative pathogens *P. aeruginosa* and *A. baumannii*. Infections caused by these resistant pathogens are difficult to treat and are associated with increased morbidity, mortality, and costs [37].

The leading VAP pathogens may change over time and from unit to unit, with variable local epidemiology of drug-resistant cases, although there has been an increasing global trend of VAP caused by MDR pathogens over time [5]. In an observational 24-h point prevalence study of 1150 centers across 88 countries that included 44% mechanically ventilated patients, 37% of Gram-negative infections causing VAP were MDR with a predominance of *Klebsiella* spp. (38%), followed by *Acinetobacter* spp. (33%), *E. coli* (18%) and *Pseudomonas* spp. (10%) [6]. Another multicenter study of more than 200 ICU in 56 countries found *P. aeruginosa* as the leading Gram-negative respiratory pathogen isolated (25%) among 7171 isolates. Multi-resistance was frequently encountered as 38% of *P. aeruginosa* isolates were nonsusceptible to piperacillin–tazobactam or meropenem. Around 68% of the strains were reported as susceptible to ceftolozane–tazobactam in the cohort [38]. Surveillance data from the USA demonstrated more than 100% increased rates of ESBL production and 800% rise in carbapenem resistance in Enterobacterales, resulting in limited therapeutic options [39]. High resistance rates were also reported in VAP cases in other geographical areas. For example, up to

89% of VAP isolates were MDR, XDR, or pan-drug resistant in Greece, and 89% of *A. baumannii* isolated from VAP cases from Saudi Arabia were XDR [40, 41]. In a recently published cohort from a tertiary care hospital in Northern Saudi Arabia, XDR *A. baumannii*, XDR *P. aeruginosa*, and *K. pneumoniae* with an ESBL profile were predominant etiologies of VAP [42]. Around 87.5% of Gram-negative VAP pathogens were described as XDR over a 4-year observational study in a tertiary care cancer center in India [9]. Colistin/polymyxin resistance in Gram-negative pathogens is being increasingly reported following increased consumption of the drug to treat VAP caused by XDR organisms, which is further complicated by non-availability of susceptibility testing to the drug in many routine laboratories as it requires special laborious assays [42]. The IDSA guidelines recommend against the routine use of colistin in treating VAP while European guidelines similarly state the empiric therapy to be guided by the mortality risk, local ecology, and other MDR selection risk factors [10, 22]. Yet, colistin-based combination therapy is still used in some critical care centers to empirically treat XDR pathogens [43]. Less common VAP bacterial pathogens include *Stenotrophomonas maltophilia*, *Burkholderia cepacia*, *Legionella*, and anaerobes which are known for their intrinsic resistance to multiple antimicrobial classes [44, 45]. VAP can be polymicrobial in origin which further complicates the therapeutic approach.

Key Mechanisms of Antimicrobial Resistance in VAP

Bacterial resistance to antibiotics may result from alteration of the antibacterial target, decreasing intracellular concentrations as a result of reduced permeability or efflux pumps, or enzymatic inactivation of the drug [46]. In some instances, intrinsic antimicrobial resistance can exist where every strain of a species exhibits reduced susceptibility to a particular agent as in the case of *S. maltophilia* expressing a metallo- β -lactamase that is chromosomally encoded, rendering the organism resistant to

carbapenems [45]. Alternately, formerly sensitive species might acquire resistance genes from foreign DNA or undergo genetic mutation to become resistant.

Antibacterial use can lead to the selection and expansion of drug-resistant bacterial clones through disturbing the individual's microbiome. Following the increased usage of carbapenems, Gram-negative bacteria with chromosomally encoded β -lactamases, such as *A. baumannii* and *S. maltophilia*, have become more frequent, especially in patients receiving mechanical ventilation [44–46]. Chromosomal and plasmid DNA replicate as bacteria propagate through a mechanism that is highly prone to errors during nucleic base incorporation, with the potential of producing functional gene products in favor of bacterial survival in the presence of antibiotics such as SHV-2, an ESBL which imparted resistance to expanded-spectrum cephalosporins that was created when serine replaced glycine at position 238 in the SHV-1 β -lactamase [47]. The importation of insertion sequences (IS) can also inactivate several genes affecting their functions. For instance, the *ccrA* gene in *Bacteroides fragilis* expresses a metallo- β -lactamase that is only produced if an IS has been placed upstream of this structural gene [48]. Subsequent antibiotic exposure favors growth of strains with mutations that enable the bacteria to survive in the presence of high concentrations of the drug.

A variety of mechanisms of antimicrobial resistance in VAP pathogens have been described that explain the genetic basis of acquired reduced susceptibility to antimicrobials (Table 2). The molecular basis of resistance listed in Table 1 can co-exist in one bacterium, rendering therapy challenging. It is important to note that resistance to one β -lactam in cases of *P. aeruginosa* may not predict resistance to others since a wide variety of genetic mechanisms are frequently encountered in this organism [49, 50]. In addition to these genetic determinants, there has been debatable evidence for the relationship between the ability of the organism to form a biofilm and a significant reduction in its antimicrobial susceptibility. Biofilm formation and distribution of virulence genes did not appear to differ between VAP and

non-VAP pseudomonal isolates in an in vitro study, although the VAP isolates were less virulent in an in vivo model [51, 52]. Difficult-to-treat resistance (DTR) in *P. aeruginosa* is a new terminology that was introduced to describe strains exhibiting nonsusceptibility to all of piperacillin–tazobactam, ceftazidime, cefepime, aztreonam, meropenem, imipenem, and fluoroquinolones [50]. Therapeutic agents that may retain activity on VAP caused by DTR *P. aeruginosa* are limited and mainly based on ceftolozane–tazobactam, ceftazidime–avibactam, imipenem–relebactam, or cefiderocol, although the evidence supporting the use of these agents is still being collected.

Carbapenem-resistant *A. baumannii* (CRAB) is a critical-priority pathogen that is linked to persistent outbreaks in critical care settings [53]. It requires combination therapy of two active agents even if a single drug demonstrates in vitro activity, where ampicillin/sulbactam in high dose is a preferred agent in combination with either polymyxin, colistin, a tetracycline, or meropenem in extended infusion [50]. These recommendations are based on two meta-analyses which evaluated different therapeutic regimens, and in 23 studies ($N > 2100$ patients) ampicillin–sulbactam-based combination therapy reduced mortality relative to polymyxin- or tigecycline-based treatment [54]. A more recent meta-analysis of 18 studies ($N > 1800$ patients) has also concurred that ampicillin–sulbactam-containing regimens reduced mortality and nephrotoxicity in critically ill patients in comparison to colistin-based protocols [55]. Cefiderocol may constitute a base for the combination regimen for CRAB with very limited evidence currently to support its use [56]. Interventional trials are still underway to evaluate its potential role in the treatment of MDR-VAP. Table 2 summarizes the most commonly reported mechanisms of resistance in *A. baumannii*.

There are few therapeutic choices for VAP caused by CRE, and no antibiotic regimen has been firmly established as being superior to another [57]. The isolate's genotype and phenotypic susceptibility profile both affect the therapeutic choice. Meropenem may remain a viable second agent in a combined regimen if the CRE isolate has a minimal inhibitory

Table 2 Mechanisms of acquired antimicrobial resistance in common Gram-negative pathogens causing ventilator-associated pneumonia [46, 49, 50]

Organism	Mechanism of resistance	Features
<i>P. aeruginosa</i>	AmpC β -lactamase	Most common β -lactamase observed in <i>P. aeruginosa</i> Resistance to penicillins, cephalosporins other than cefepime
	Extended-spectrum β -lactamase	Confer resistance to penicillin, all cephalosporins, aztreonam e.g., OXA-11, 14,16, 19, 28, PER-1, VEB
	Metallo- β -lactamases	Resistance to penicillin, all cephalosporins, carbapenems Can not hydrolyze aztreonam e.g., NDM, VIM, IMP, SPM-1
	OprD downregulation (porin loss)	Major cause of carbapenem nonsusceptibility, e.g., imipenem resistance and reduced susceptibility to meropenem Susceptibility maintained to cephalosporins
	MexAB-OprM upregulation (efflux)	Reduced susceptibility to meropenem but not imipenem Reduced susceptibility/or resistance to penicillin Resistance to cephalosporins and fluoroquinolones
	Topoisomerase II/IV mutations	Fluoroquinolone resistance
<i>A. baumannii</i>	AmpC β -lactamase	Chromosomally encoded cephalosporinases intrinsic to all strains Low level of expression does not cause clinical failure unless co-existing with a promoter insertion sequence ISAbal
	Serine-carbapenemase	Resistance to penicillin, all cephalosporins, carbapenems OXA-23 and OXA-24/40-like and OXA-23-like
	Metallo- β -lactamases	Very rare
	Extended-spectrum β -lactamase	Not widely spread among the species
	Porin downregulation	Poorly characterized mechanism Reduced susceptibility to β -lactams
	Efflux overexpression	Reduced susceptibility to β -lactams, fluoroquinolones, chloramphenicol, tetracyclines, and tigecycline Usually in association with AmpC or carbapenemases overexpression

Table 2 continued

Organism	Mechanism of resistance	Features
Enterobacterales	Carbapenemase	High level resistance to carbapenems e.g., KPC, NDM, VIM, OXA-48, SME Isolates may also co-produce other β -lactamases, e.g., ESBL, AmpC
	Extended-spectrum β -lactamase	Low level resistance to β -lactams
	AmpC β -lactamase	Low level resistance to β -lactams
	Porin downregulation or Efflux overexpression	Low level resistance to β -lactams
<i>S. maltophilia</i>	Zinc-containing penicillinase (L1), cephalosporinase (L2)	Resistance to β -lactams including carbapenems, and aztreonam
	Acetyl-transferase and temperature-dependent changes in the outer membrane LPS	Aminoglycoside resistance
	Efflux pumps	Resistance to multiple antimicrobial classes
	Biofilm formation	Resistance to multiple antimicrobial classes

concentration (MIC) for meropenem of 8 $\mu\text{g}/\text{mL}$ or lower [58]. For the treatment of infections by organisms that produce a serine carbapenemase, such as *K. pneumoniae* carbapenemase (KPC) or oxacillinase 48 (OXA-48), ceftazidime–avibactam is among novel β -lactam– β -lactamase inhibitor combination drugs that can be used with an overall good clinical experience [50]. Of note, ceftazidime–avibactam resistance can develop within 10–19 days during treatment, necessitating retesting the isolate in the laboratory on clinical demand and the addition of a second agent, usually a carbapenem, for possible synergistic effects based on a few in vitro and in vivo reports [59–61]. Further studies are required to examine the clinical significance of higher MIC values for serine-CRE on ceftazidime–avibactam therapy since MIC to β -lactam agents could be altered, leading to restored susceptibility in variant isolates [59]. A polymyxin-based (colistin or polymyxin B) combination regimen is used when the strain is susceptible in vitro based on broth microdilution assays and no other medication is available

for use [50]. The rationale for this combination is based on reducing mortality associated with invasive CRE infections and the possibility of emergence of colistin resistance during monotherapy as seen in observational studies in which meropenem use with colistin favored better clinical outcomes whenever its MIC was below 16 $\mu\text{g}/\text{mL}$ [58]. In comparison to polymyxins, the β -lactam– β -lactamase inhibitor combinations offer better safety profiles, more consistent dosage, and higher in vitro susceptibility rates based on little but encouraging data which support their superior effectiveness [62, 63]. Randomized controlled trials (RCT) are yet to corroborate these observational studies which are prone to selection bias. Alternative effective options for treating serine-CRE include meropenem–vaborbactam and imipenem–cilastatin–relebactam, and the siderophore cefiderocol; the last of these agents has been approved for clinical use in VAP [10]. Tigecycline can also be used for CRE infections particularly for respiratory infections with its ability to penetrate tissues [64]. A polymyxin in combination with

tigecycline had a mortality rate of 30% ($N = 23$) in comparison with 12.5% mortality ($N = 16$) seen with a combined regimen of colistin, tigecycline, and extended-infusion meropenem [58, 65]. Because resistance to polymyxins is an increasingly reported problem, laboratory testing is crucial to optimize its use with a possibility of retesting as development of polymyxin resistance during therapy has been described in Enterobacterales [66, 67]. Polymyxin-resistant CRE infections have been shown to be an independent risk factor for mortality [66].

For the metallo- β -lactamase (MBL)-CRE infections, an aztreonam-based regimen with either ceftazidime–avibactam or cefiderocol is proposed while, as in the case of serine-CRE, a polymyxin-based regimen offers an alternative option when the novel β -lactams cannot be used for MBL-producing Enterobacterales [50]. No β -lactams other than these two agents, cefiderocol and aztreonam, possess powerful antibacterial activity against MBL-harboring CRE isolates [68]. The combination of ceftazidime–avibactam and aztreonam may potentially exhibit a synergistic effect because the avibactam inactivates the enzymes, increasing aztreonam activity. Despite the fact that MBL-producing isolates frequently produce other β -lactamases conferring resistance to aztreonam, this combination maintained its therapeutic effectiveness in a small number of reports of cases with highly resistant MBL-producing CRE infections [69, 70]. On the other hand, there is very limited clinical experience with cefiderocol treatment of MBL-producing pathogens [71]. Figure 2 summarizes the currently available options for treating VAP caused by CRAB, DTR *P. aeruginosa*, and CRE.

MICROBIOLOGICAL DIAGNOSTICS FOR VAP AND DETECTION OF RESISTANCE

The diagnosis of VAP is suspected in patients with a new or progressive pulmonary infiltrate on imaging and supportive clinical signs of infection like fever and leukocytosis. The microbiological diagnosis is established when a pathogen is identified from a lower respiratory

tract sample in a clinically compatible case. Sampling is preferably performed prior to the empiric initiation or changing of antimicrobial therapy to optimize the diagnostic yields of the respiratory microscopy and culture, and blood cultures should be also routinely collected [72]. As a result of the lack of a gold standard for the diagnosis of VAP, clinical practice may largely vary among institutions, practitioners, and also from case to case.

Invasive, Quantitative Versus Noninvasive, Semiquantitative Lower Respiratory Tract Testing

The recommendations from the ERS, ESICM, ESCMID, and ALAT endorse quantitative cultures conducted on invasive samples such as mini-bronchoalveolar lavage (BAL) or equivalents [22]. The justification for this strategy is the significant impact on diagnostic accuracy and reduction of unnecessary antimicrobial use. Given the lack of definitive evidence that either methodology has an influence on mortality or duration of stay, the IDSA and the American Thoracic Society (ATS) still advocate noninvasive sampling techniques with semiquantitative VAP cultures instead [10]. Yet, as demonstrated in numerous studies, bronchoscope-based sampling and quantitative cultures are more helpful in optimizing the use of antibiotics and de-escalating therapy without adverse effects on prognosis or length of ICU stay [73, 74]. When quantitative cultures are performed, cutoff thresholds should be carefully assessed to avoid missing VAP events or false positives leading to unjustified therapy. Thresholds of 10^6 or more colony forming units (cfu)/mL, 10^4 cfu/mL, and 10^3 cfu/mL have been proposed for endotracheal aspirates, mini-BAL or bronchoscopic BAL, and protected brushing to minimize overdiagnosis of VAP [22, 75]. Quantitative cultures are more labor-intensive, time-consuming, and expensive than semiquantitative cultures from a laboratory perspective.

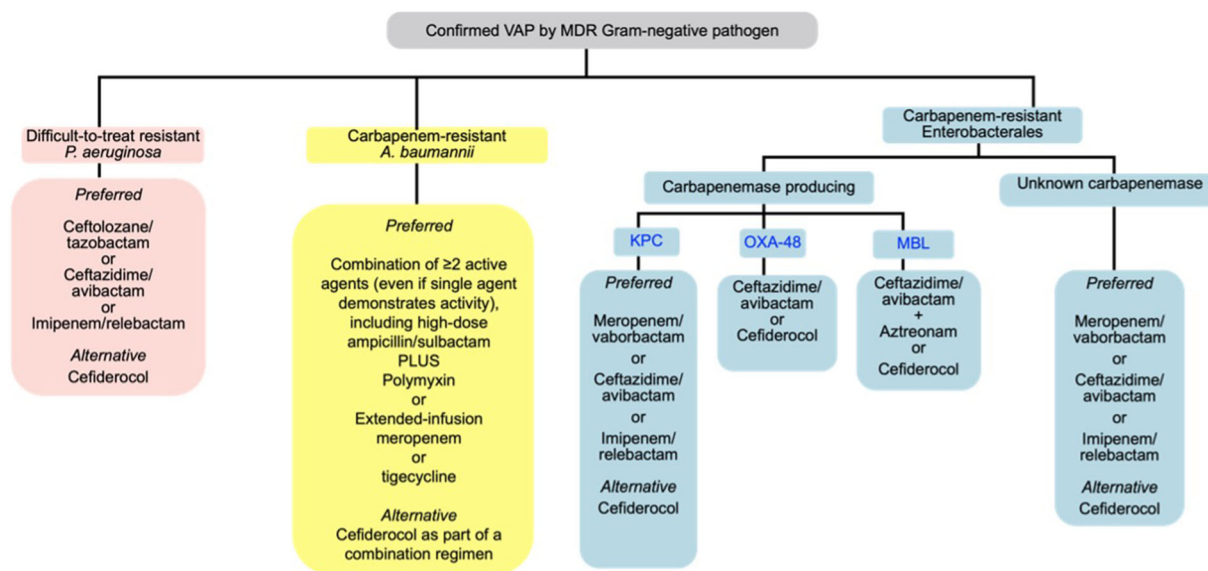


Fig. 2 Recommendations for management of ventilator-associated pneumonia caused by MDR Gram-negative pathogens [50]

Molecular Diagnostics and Novel Assays

In VAP care, rapid diagnostic testing is occasionally employed to shorten the time to appropriate therapy. Antimicrobial escalation is not thought to be beneficial for Gram-negative infection in adults who remained critically ill after appropriate empirical therapy which may support the use of rapid diagnostics such as molecular tests that can be helpful tools for the rapid identification of pathogens and the detection of antibiotic resistance markers [76]. Multiplex syndromic testing platforms are commercially available for VAP using lower respiratory and blood specimens [77]. Table 3 outlines the currently available instruments for rapid detection of pathogens from blood and lower respiratory samples. These assays, however, in their current setup are considered an adjunct testing option that cannot replace standard microbiological tests, with the main advantage of the short turnaround time (TAT). While several rapid diagnostic platforms are available to detect common Gram-negative and Gram-positive respiratory pathogens which are widely acceptable by intensivists, validation of a systematic methodology is still required in

order to make the comparison of various studies possible [78]. Additionally, the evidence for clinical utility of those rapid tools is still evolving with debatable impact on clinical outcomes [79, 80]. A multiplex respiratory panel was shown to be helpful to reduce unnecessary antimicrobial escalation between 72 h and 7 days (7.8% versus 14.2%; $p = 0.007$) and marginally lower overall hospital costs ($\$1413.5 \pm 1438.0$ vs $\$1759.4 \pm 1929.2$; $p = 0.008$) according to a retrospective case-control study ($N = 692$) evaluating the clinical utility of molecular point-of-care diagnostics in respiratory infections in China [80]. In contrast, a systematic review by the Cochrane collaboration that assessed the effects of rapid antimicrobial susceptibility testing (AST), defined by $TAT \leq 8$ h, versus conventional assays for detecting resistance determinants in pathogens isolated from bacteremic infections found little or no difference in time-to-discharge (relative risk (RR) 1.0, 95% CI 0.7–1.5; low-certainty evidence), time-to-appropriate therapy (RR – 17.3, CI – 45.1 to 10.5; low-certainty evidence), and mortality (RR 1.1, 95% CI 0.8–1.5; low-certainty evidence) in the qualitative and subgroup analysis of six RCTs

Table 3 Commercially available diagnostic platforms useful for detection of ventilator-associated pneumonia and multidrug-resistant pathogens

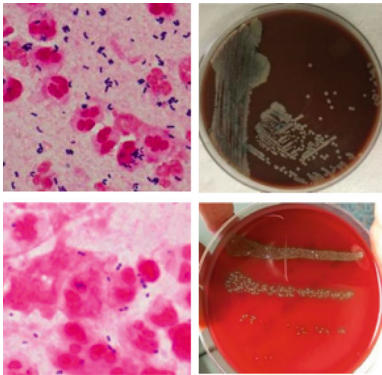


Platform	TAT	Testing panel	Cost
Routine microbiology tests 	48–72 h Can be longer in polymicrobial VAP	Potentially any culturable organism Provides susceptibility testing for most organisms	\$
Routine cultures + MALDI-TOF 	24–48 h Can be longer in polymicrobial VAP	Potentially any culturable organism Subtyping and antibiotic susceptibility testing requires additional processing and access to other databases	\$\$
BioFire FilmArray Respiratory and pneumonia panels 	1 h	9 viruses, 18 bacteria (pneumonia panel) Resistance markers for CRE/ESBL/MRSA: mecA/mecC, MREJ/MREJb KPCc, NDMc, OXA-48-like VIMc, IMPc, CTX-Mc	\$\$\$

Table 3 continued



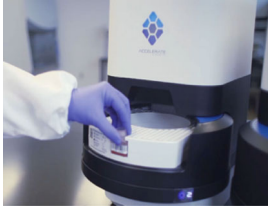
Platform	TAT	Testing panel	Cost
Curetis Unyvero Respiratory (P50, P55) and pneumonia panels	5 h	Pneumonia panel: No viral targets, 19 bacteria, 1 fungus (<i>Pneumocystis jirovecii</i>) 22 Resistance markers mecA, blaTEM, CTX-Mc OXA-48-like, OXA-23, OXA-24, OXA-58, KPCc, NDMc, VIMc	\$\$\$
			
Nanosphere Verigene	2.5 h	6 viruses, <i>Bordetella</i> , no common bacteria No resistance markers	\$\$\$
			
Hologic Gen-Probe Prodesse assay	5 h	ProFluþ, ProFASTþ, ProAdenoþ, ProParafluþ, Pro hMPVþ 4 viruses, no bacteria	\$\$\$
Verigene	2.5 h	6 viruses, <i>Bordetella</i>	
ePlex respiratory panel	1.5 h	Pneumonia panel 2: 9 viruses, atypical bacteria (<i>Mycoplasma, Chlamydia</i>)	\$\$\$
eSensor respiratory panel	6 h	6 viruses, no bacteria	\$\$\$
NxTAG	5 h	8 viruses, atypical bacteria (<i>Mycoplasma, Chlamydia, Legionella</i>)	\$\$\$
Seegene Respiratory panel	2.5 h	9 viruses, 7 bacteria No resistance markers	\$\$\$
Carba-R cartridge-based PCR	50 min after growth of culture colonies	No organism identification 5 resistance markers KPC, OXA-48, NDM, IMP, VIM in Gram-negative bacteria: Enterobacterales, <i>P. aeruginosa</i> , and <i>A. baumannii</i>	\$\$\$

Table 3 continued

Platform	TAT	Testing panel	Cost
accelerate Pheno® 	1.5 h after flagging of blood cultures and 7 h for AST	16 bacteria MIC for 25 antibiotics 2 Resistance genes (<i>mecA</i> , <i>MLSb</i>)	\$\$\$

TAT turnaround time, *AST* antimicrobial susceptibility testing

($N = 1638$) [81]. It endorsed the urgent need for future large prospective studies designed to focus on clinically relevant outcomes rather than the assay characteristics. Furthermore, false negative molecular testing results can lead to delayed effective therapy and may not justify additional costs [82]. Nevertheless, molecular testing methods can be useful in selected cases as they have the potential to identify respiratory pathogens that are not evident in routine culture growth as a result of their fastidious nature or prior antimicrobial therapy. The integration of those novel tools into clinical practice remains a challenge for several institutions, and their implementation strategies should reinforce indication while assuaging the potential limitations [78]. Ongoing research is under development in the rapid diagnostics field which can not only solve some VAP diagnostic challenges but also elucidate new concepts in its pathogenesis such as the detection of pathogens in the human lung parenchyma through an optical fiber-based endoscope [83, 84]. Metagenomic signatures have been recently introduced and employed to accurately identify VAP-associated pathogens and their resistance markers with an overall accuracy of 98.1% in less than 5 h [85].

Role of Biomarkers

Several biomarkers, like procalcitonin (PCT), C-reactive protein (CRP), mid-region fragment of pro-adrenomedullin (MR-proADM), interleukin-1 beta (IL-1 β), and soluble triggering receptor sTREM-1, have been assessed as potential aids in the diagnosis of VAP. None of these proved to be reliable for confirming or ruling out the diagnosis in a suspected case, nor can they differentiate drug-resistant VAP. Currently, the IDSA/ATS guidelines endorse incorporating PCT as well as clinical criteria in antibiotic de-escalation decisions while the European guidelines recommend against PCT routine use in determining VAP cases who can undergo de-escalation and advocate for utilizing the Clinical Pulmonary Infection Score (CPIS) to determine low-risk patients in whom antimicrobials can be ceased in 72 h [10, 22].

Predictive Scores

Recently, logistic regression has been used in multiple studies to predict VAP caused by MDR species with a main focus on VAP caused by CRE [5]. In a study by Lodise et al. to create predictive models for the probability of VAP caused by resistant species, logistic regression models were transformed into an Excel-based user-friendly

interface to estimate the risk of resistance by launching a bedside tool that predicts the likelihood of six phenotypes of MDR pathogens among hospitalized adult patients with Gram-negative infections [86]. This initiative will require further clinical evaluation of its utility. Another simple scoring system was proposed by Richter et al. who demonstrate the utilization of clinical heuristics from existing electronic medical records to inform clinical decision-making [87]. A report from China by Gao et al. examined predictors of CRE-VAP and proposed utilizing length of hospital stay greater than 7 days and the use of β -lactamase inhibitor combination agents or carbapenems to measure the MDR index [88]. Another recent US-based study conducted by Weston et al. utilized prior resistant nonbacteremic cultures and exposure to skilled nursing facility as predictors of carbapenem resistance in one institution to guide empirical therapy [89]. Although the modeling studies have enabled understanding of the evolutionary dynamics of MDR-VAP, further research should focus on validating the usefulness of these various scores in different populations and institutions to produce operational predictions and assessing their cost-effectiveness. Once an optimal score model is identified, it needs to be thoroughly examined in an interventional trial to determine its clinical impact where a proposed model needs to be calibrated and finetuned in order to replicate its empirical observations. Of importance, the mathematical models have predictive limitations. Certain elements can influence the selection and co-selection of AMR in bacteria which may not be accounted for in existing models [90]. Furthermore, it is not yet fully understandable which antimicrobial class has the greatest influence on the emergence of AMR. It is unknown how the competition with sensitive strains impacts the occurrence of persistent counterparts after the establishment of MDR status and how their coexistence over extended periods of time affects prognosis [91–93]. Fitting the models to various types of pathogens remains computationally challenging as the structure of MDR models becomes more complex. Spillover is another significant barrier for prediction that has not been

adequately addressed where horizontal transmission of AMR between places predisposes a patient without known risk factors for infections by MDR pathogens, highlighting the impact of local ecology of a unit [94]. Additionally, reliable routine screening for MDR colonization is suboptimally performed in several ICUs with limited resources, making it challenging to predict MDR-VAP using such models. Simplified artificial intelligence-based systems may support the integration of various laboratory and clinical data and streamline the VAP diagnosis in the future.

EMPIRICAL ANTIMICROBIAL THERAPY

Early Effective Therapy

Once respiratory samples has been collected, the likely pathogens should be the focus of empiric antibiotic therapy for VAP and the choice of a specific regimen should be based on the epidemiology of circulating pathogens and their susceptibility profiles in an ICU, local antibiograms, as well as the individualized patient index for MDR, which includes previous microbiology results and initial microscopy findings, although the latter alone cannot differentiate VAP pathogens from each other and its diagnostic yield is also variable. A recent open-label, multicenter RCT of VAP ($N = 206$) demonstrated that the clinical cure in cases of microscopy-guided empiric regimen was non-inferior to the guideline-based group (77% vs 72%; 95% CI – 0.07 to 0.17) [95]. The Gram stain-based group had lower consumption of anti-MRSA and anti-pseudomonal agents (61% vs 100% and 70% vs 100%, respectively) without significantly impacting the mortality, ICU-free days, and ventilator-free days. Local unit antibiogram and epidemiologic resistance data should be taken into consideration if empiric dual coverage for VAP pathogens is being explored as in the case of *P. aeruginosa*, although this is still debatable [96].

Earlier time to appropriate therapy is associated with reduced mortality in cases of VAP [10]. Nonetheless, MDR pathogens are

frequently encountered in respiratory samples of mechanically ventilated patients and treatment decision for suspected VAP should take into account a multi-consideration approach based on the clinical presentation, the specimen type, diagnostic yield, and risk of increasing AMR.

Risk Stratification Models and Empiric Windows

The first empiric window refers to the short time between sampling and retrieving microscopic findings which is usually around an hour (Fig. 3). Appropriate empiric antibiotic selection should be maximized during the first empiric window when the patient is in severe illness using predictive microbiology and clinical heuristics, while utility of the predictive scores in later empiric windows is likely to be limited [97]. Determining empiric therapy requires an understanding of the variables that predict clinical resistance. For instance, prior cultures with antimicrobial resistance demonstrated a suboptimal sensitivity and positive predictive value (PPV) (48% and 61%) with moderate specificity and negative predictive value (NPV) (88% and 81%) as predictors of AMR in subsequent infections [98]. In a recent quasi-experimental study, Elligsen et al. evaluated the occurrence of clinically significant discordance in empiric treatment and described shorter times of discordance post-intervention for Gram-negative infections (25 h versus 55 h; $p = 0.001$; adjusted hazard ratio 1.95, 95% CI – 1.4 to 2.8). More intricate measurements combine the local microbiology with patient-specific variables [99]. More complex metrics were developed in the last decade to incorporate patient-specific factors in combination with the local epidemiology of organisms. Multivariable

logistic regression is applied in predictive models for the appropriate treatment regimen taking into account variables such as age, gender, the patient's preceding microbiology, admitting unit, concurrent bloodstream infection, the source of infection, previous hospitalization, and prior ICU admission in addition to antimicrobial exposures [100]. An example of such a decision-assisting tool is the weighted-incidence syndromic combination antibiograms (WISCA). This advanced multicomponent antibiogram has an advantage over conventional laboratory antibiograms by showing the likelihood of adequate antimicrobial coverage in a particular patient with VAP while accounting for polymicrobial etiology and combination therapy [101, 102]. The narrowest possible adequate therapy is the end goal for any predictive tool without compromising clinical outcomes.

PROGNOSIS, MORTALITY, AND PREVENTIVE TOOLS

Antimicrobial resistance may contribute to the higher mortality rates associated with VAP, although this is difficult to measure because of the multiple underlying factors [103]. The available evidence shows that VAP is associated with a variably high risk of crude all-cause mortality (13–50%) [8, 10]. Population attributable fraction of VAP is frequently used to calculate the difference between observed ICU mortality and ICU mortality that would have been observed for the same population if all VAP cases were prevented [8, 104]. A meta-analysis from 24 randomized prevention trials ($N = 6284$) estimated an overall VAP-related mortality of 13%, while a contradicting multicenter European study by Steen et al. estimated

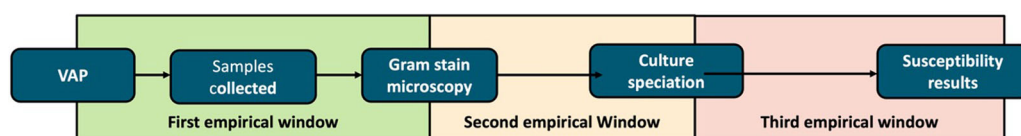


Fig. 3 Empirical therapeutic windows where earlier targeted therapy is the aim [97, 100]

3.6% VAP attributed mortality among the 60-day ICU mortality, which was linked to the effectiveness of modern preventive tools in developed countries [105, 106]. VAP caused by an MDR pathogen is associated with increased mortality, which can be related to the delayed initiation of effective antimicrobial therapy when risk stratification is not implemented [107–109]. Delays in the administration of effective treatment are independent predictors of mortality in serious illnesses and are involved in the high mortality rates linked to resistant infections [87, 110]. Further, the use of second- and third-line antimicrobial agents, indicated by the presence of an MDR pathogen, leads in certain cases to inferior antimicrobial activity and less favorable pharmacological properties as in the case of vancomycin use to treat staphylococcal VAP [111]. Mortality is also influenced by variables such as the severity of presenting illness, primary diagnosis, underlying comorbidities, and concurrent bacteremia [112].

Efforts need to be intensified in order to reduce selective pressures, avoid unnecessary treatment in colonized patients, and prevent the emergence and spread of resistant clones in an ICU through effective antimicrobial stewardship programs (ASP) and thus reducing antimicrobial-resistant VAP [113–115]. In a study that evaluated the rates of MDR infections in two ICUs in the USA, more than fourfold reduction in MDR Gram-negative infections was achieved after implementing a comprehensive ASP over a 7-year period [116]. The longitudinal impact of introducing an effective ASP through significant rise in the rates of infections caused by carbapenem-susceptible *P. aeruginosa* was evident in another 7-year study of an Australian ICU [117]. Thus, it is increasingly being recognized that an antimicrobial team is a necessity in the modern ICU [114, 118]. The total incidence of VAP cases should also be reduced by routinely implementing high-impact interventional strategies such as the VAP prevention bundles, although accurate assessment of their impact is difficult because of the lack of specific VAP diagnostic criteria and the subjectivity of some components in these bundles [119, 120]. A meta-analysis of 13 observational studies examined

the impact of VAP bundles on mortality and reported a 10% reduction following implementation (OR 0.9, 95% CI 0.8–0.9) [121]. Thus, active VAP surveillance and prevention strategies within a unit will lead to lower mortality and reflux reduction in VAP caused by MDR pathogens, although it is challenging to assess the effectiveness of control strategies intended to lower the incidence of antibiotic-resistant bacteria in ICU because of the naturally occurring high changes in the prevalence of colonization [26].

VAP AND COVID-19

It is thought that COVID-19 is linked to a higher risk of VAP, which is not entirely accounted for by the prolonged duration of ventilation time. This is hypothesized to be connected to the secondary invaders that produce superinfection as well as the pulmonary dysbiosis brought on by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection [122]. VAP in patients with COVID-19 has been associated with shock, bacteremia, and polymicrobial infections [123, 124]. With a crude mortality rate of greater than 40%, the rate of VAP in hospitalized COVID-19 cases varies significantly, ranging from 7% to 86% [125]. The etiologies of VAP in COVID-19 cases have been variable in different studies. In a review of 171 patients with COVID-19 and VAP, the median mechanical ventilation duration before VAP onset was 9 days (95% CI – 5 to 15 days). Of those, 45% of the cases underwent microbiological sampling and grew *P. aeruginosa* (35%) and *S. aureus* (23%) as the leading two pathogens causing VAP in the cohort study [126]. A study by Pickens et al. ($N = 179$), in which BAL was routinely obtained at the point of intubation and upon clinical suspicion of superinfection, estimated the rate of VAP as 45 cases/1000 mechanical ventilation days (44%). MDR organisms were not frequently isolated (three cases) which can reflect the variation in local epidemiology [127]. Another study by Alnimr et al., in which 57.4% of 67 non-survivor COVID-19 cases were described to develop VAP, showed that most of the cases were caused

by XDR *A. baumannii*, *P. aeruginosa*, and *S. aureus* (56.4%) [124]. MDR pathogens were also reported as etiological agents in 35% of VAP cases in 774 patients with COVID-19 [128]. de Macedo et al. investigated the healthcare facility as an independent risk factor for MDR organisms in critically ill patients with COVID-19 and found a significant link between admission to a newly opened hospital and the acquisition of MDR VAP in Brazil (OR 3.24; 95% CI 1.39–7.57; $p = 0.006$). Other non-modifiable risk factors were also identified for MDR superinfections in COVID-19 cases which included male gender and hypoxemia at presentation [129]. It should be noted that noninvasive sampling was used most often in the literature documenting VAP in patients with COVID-19 to prevent the pathogen from being aerosolized. Tracheal aspirates were collected utilizing closed-circuit suctioning under airborne isolation measures. Mini-BAL and BAL were less commonly used alternatives to avoid aerosol-generating procedures that were performed only when they were likely to alter the prognosis or in emergency situations. Lower respiratory tract sampling is not required for the diagnosis of viral pneumonia including COVID-19 as nasopharyngeal samples are optimal specimens for both the molecular assays and antigen detection kits developed for SARS-CoV-2 [130, 131]. It is reserved for severely ill patients with a high suspicion of SARS-CoV-2 infection but repeatedly negative tests on upper airway specimens. Sputum induction is also not advised for safety consideration. It is important to consider that most SARS-CoV-2 laboratory kits were not validated for lower respiratory specimens during the emergency use authorization in the pandemic. Thus, a laboratory that opts to test and report results of SARS-CoV-2 from these samples needs to adequately validate specimens for various assay characteristics including the lower limit of detection (analytical sensitivity) and interference (analytical specificity). Point of care tests were evidently useful during the COVID-19 pandemic by providing rapid microbiological tools that support patient care under surge circumstances.

CONCLUSIONS AND FUTURE PERSPECTIVES

VAP caused by MDR pathogens is associated with high mortality rates, length of hospital stays, and hospital costs. It can be caused by a variety of pathogens which harbor various resistance mechanisms, making treatment challenging. Rapid testing for VAP has developed and can potentially provide results in real time to tailor therapy appropriately with rapid identification of pathogens and detection of their resistance determinants. In the era of widespread AMR, use of rapid diagnostics has the potential to reduce the use of antibiotics and improve clinical outcomes in patients with VAP. However, robust clinical data from well-designed RCTs are still evolving to assess the impact of these novel diagnostic platforms on antimicrobial usage and prognosis. Considerations remain for potential confounding bias leading to an inflated estimation of their diagnostic performance especially in studies where the outcome measures did not include clinically pertinent parameters. When used, rapid diagnostic tools should be integrated into effective antimicrobial stewardship processes. Nevertheless, the local epidemiological patterns and patient-specific risk factors for MDR pneumonia can support the clinical decision toward a broader therapy and minimize delays to appropriate empiric treatment with its prognostic impacts. Various elements are currently incorporated in predictive scores which are hot research topics for which various models are under development with a variable level of complexity and resourcing. Clinical validation of those evolving models in large, multicenter prospective studies is urgently needed to increase the utility of potentially useful tools for a serious ICU infection. As the prevalence of drug-resistant VAP continues to increase, ASP must be activated in critical care areas to reduce selective pressures in circulating clones and prevent colonization by MDR and XDR species, which is often

a source of serious MDR infections or outbreaks. ICU should invest in establishing effective antimicrobial teams, and the laboratory

needs to play an active role in liaison with the ICU to develop a facility-specific model of diagnostic stewardship that can create reflex, rapid testing and reporting of critical cases. This will facilitate timely initiation of appropriate targeted therapy with less collateral damage. Emphasis should be put on preventive tools for VAP including cases caused by MDR organisms along with audit and feedback tools to incorporate institution-specific factors based on available evidence. Areas for future research in VAP caused by MDR pathogens include the clinical efficacy and cost-effectiveness of rapid VAP diagnostics and validation of AMR clinical prediction scores as well as their actual use in making treatment decisions in various settings.

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