Earn CE/CME

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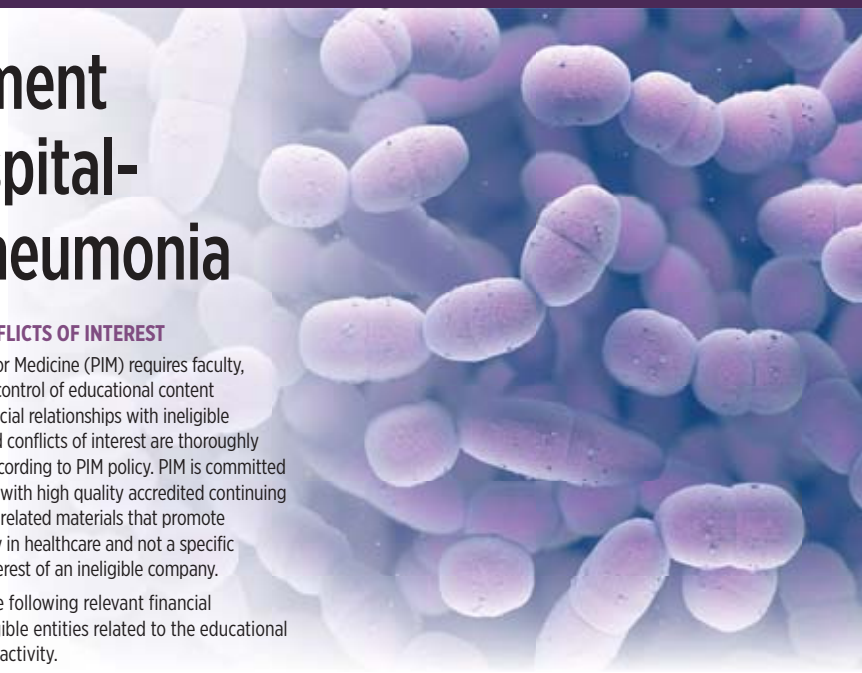
Clinical **UPDATE**

Ensuring Optimal Management of Antibiotic-Resistant Hospital- and Ventilator-Acquired Pneumonia



ESTIMATED TIME TO COMPLETE ACTIVITY

1 hour

TARGET AUDIENCE

Infectious disease physicians, infectious disease pharmacists, critical care specialists, pharmacy/formulary directors, and other providers who treat and/or monitor patients with hospital- or ventilator-acquired pneumonias (eg, clinical pharmacists, clinical microbiologists, hospitalists)

EDUCATIONAL OBJECTIVES

After completing this activity, participants should be better able to:

1. Review the diagnostic approach and pathophysiology of hospital- and ventilator-acquired bacterial pneumonia.
2. Describe the health and economic burden of hospital- and ventilator-acquired pneumonia.
3. Explain the major mechanisms of resistance seen in nosocomial pneumonias.
4. Develop an optimal treatment plan incorporating novel therapies for patients with hospital- or ventilator-acquired bacterial pneumonia including those with antibiotic resistance.

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Introduction

Pneumonia is an acute infection of the lung parenchyma.[1] Responsible for an estimated 50% of all episodes of sepsis and septic shock, pneumonia is the third most common cause of death globally.[2] An estimated 1 million US adults seek hospital care for pneumonia and 50,000 die of the disease every year.[3]

Pneumonia is caused by a wide variety of microorganisms including bacteria, viruses, and fungi.[1,4] It is often categorized based on the site of acquisition. For example, hospital-acquired pneumonia (HAP) is pneumonia that occurs 48 hours or more after hospital admission and did not appear to be incubating at the time of admission.[1,5] Ventilator-acquired pneumonia (VAP) is a device-related infection that develops 48 hours or more after endotracheal intubation.[4,5] A subclassification, ventilated HAP (vHAP), describes cases of HAP requiring mechanical ventilation (MV). Individuals with vHAP have the highest mortality rate of the 3 groups described here.[6,7] Despite an improved understanding of their causes, disease mechanisms, prophylaxis, and treatment, HAP and VAP continue to be familiar complications of hospital-based treatment. Together, they are among the most common hospital-acquired infections (HAIs), accounting for 21.6% of all HAIs in a survey of 11,282 patients across 10 geographically diverse areas.[8]

HAP and VAP are associated with many potentially serious complications, including respiratory and/or renal failure, septic shock, pleural effusion, and empyema,[9-11] and are deadlier than other pneumonias, such as community-acquired pneumonia (CAP) and health care-associated pneumonia (HCAP). In a recent retrospective analysis of hospital discharge data, HAP and VAP accounted for approximately 15% of all pneumonia-associated hospitalizations but 42% of deaths (**Figure 1A**).[12]

HAP and VAP also are associated with significant health care costs. A retrospective cohort study assessing patients from more than 500 US hospitals found that individuals with VAP had the highest median hospital costs, followed by HAP, HCAP, and CAP (**Figure 1B**).[13] Patients with VAP and HAP also had the highest use of hospital resources vs those with other types of pneumonia, regardless of age and disease severity.[13] Some of these costs are related to hospital length of stay (LOS), which may be prolonged from 4.4 to 15.9 days in cases of HAP[14] and by 11.5 days in VAP.[10] Time on MV also is prolonged in VAP by 7.6 days.[10]

Finally, HAP and VAP often are caused by organisms that are resistant to multiple antibiotics, complicating decision making and hampering treatment.[15,16]

Rising rates of antimicrobial resistance are of grave concern around the world. Antibiotic-resistant strains of common infectious bacteria or fungi infect at least 2.8 million individuals in the United States, with at least 35,000 individuals dying as a direct result of complications associated with these infections, every year.[16] Globally, antibiotic-resistant infections cause an estimated 700,000 deaths in that timeframe.[17]

In a 2017 observational study assessing the prevalence of infections and mortality rates in intensive care units (ICUs) in 88 countries, infection with the following resistant organisms was independently associated with greater mortality risk vs other organisms: vancomycin-resistant *Enterococcus*, β-lactam antibiotic-resistant *Klebsiella*, and carbapenem-resistant *Acinetobacter* spp (**Figure 2**).[18] In this study, ICU-acquired infections were independently associated with greater mortality risk than community-acquired infections (odds ratio [OR], 1.32; *P*=0.003). The overall in-hospital mortality rate was 30% in individuals with suspected or proven infection.[18]

Pathophysiology of HAP and VAP

The pathogenesis of HAP and VAP is related to the number and virulence of microorganisms entering the lower respiratory tract and the response of the host (eg, humoral, mechanical, and/or cellular defenses). The primary route of infection of the lungs is via microaspiration of organisms that have colonized the oropharyngeal tract (or, to a lesser extent, the gastrointestinal [GI] tract).[19] Approximately 45% of healthy individuals aspirate during sleep and an even higher proportion of severely ill patients do so routinely.[20]

Colonization with microorganisms acquired from the hospital environment is extremely common; as many as 75% of severely ill patients become colonized within 48 hours of entering the hospital.[20] This can arise from direct contact with the environment, including respiratory devices and water reservoirs; disposable tubing used in respiratory circuits, tracheostomy tubes, and endotracheal tubes (ETTs) may become contaminated in the process of routine nursing care or from the hands of hospital staff, despite rigorous cleaning.[21]

Intubated patients develop VAP as a direct consequence of an ETT acting as a foreign body that bypasses key barriers to infection and facilitating aspiration of oropharyngeal secretions and bacteria into the lungs.[22,23] VAP ultimately results

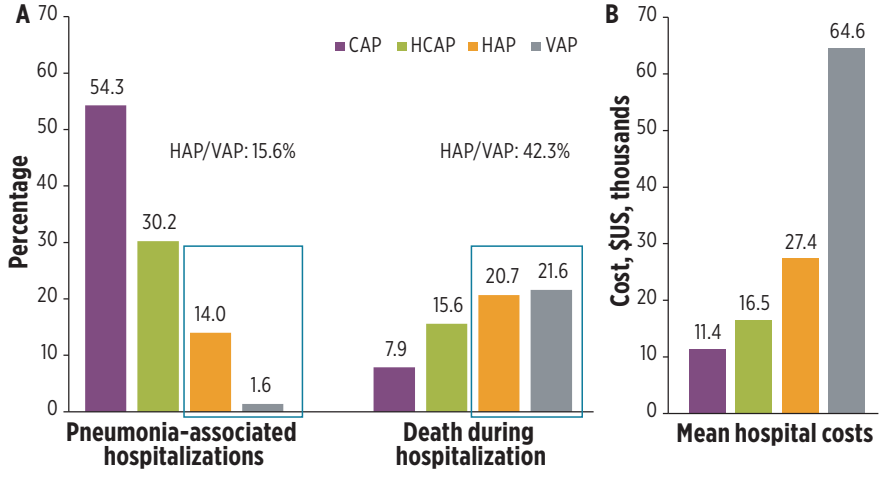

Figure 1. (A) Hospitalizations and deaths and (B) costs associated with HAP and VAP vs other pneumonias.[12,13]

CAP, community-acquired pneumonia; **HAP,** hospital-acquired pneumonia; **HCAP,** health care-acquired pneumonia; **VAP,** ventilator-associated pneumonia.

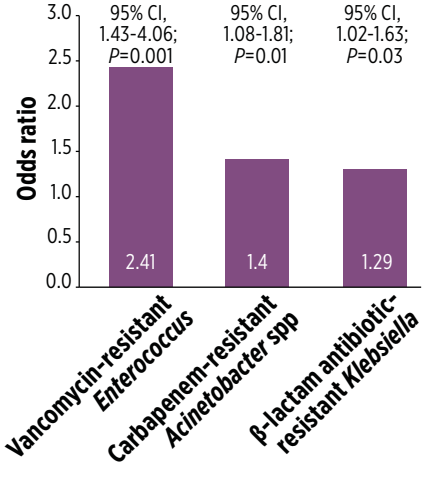

Figure 2. Organisms associated with greatest mortality risk.[18]

[a] β-lactam antibiotics included third-generation cephalosporins and carbapenems.

from varying degrees of aspiration of secretions pooled above the ETT cuff and direct inoculation from the biofilm that forms on the ETT surface.[21,22]

Finally, disruption of the normally near-sterile stomach and upper GI tract and alterations in gastric pH due to illness, medication, or enteric feeding have been shown to increase risk for nosocomial pneumonia.[24] Because of this, much attention has been given to the potentially risky use, in critically ill patients, of ulcer prophylaxis regimens that raise the gastric pH.[24]

Microbiology of HAP and VAP

HAP and VAP may be caused by a wide variety of pathogens and can be polymicrobial.[25,26] Common pathogens include aerobic gram-negative bacilli (eg, *Klebsiella* spp *Enterobacter* spp, *Pseudomonas aeruginosa, Acinetobacter* spp, and *Escherichia coli)* and gram-positive cocci (eg, *Staphylococcus aureus,* including methicillin-resistant *S. aureus* [MRSA] and *Streptococcus* spp).[25,26] There is increasing recognition that a substantial fraction of nosocomial pneumonias may be due to viruses in general medical and surgical patients.[27,28]

The bacteria associated with HAP are stratified into those causing early- and late-onset disease. Early-onset HAP occurs on hospital days 3 to 7 and usually involves community-acquired organisms such as *Streptococcus pneumoniae* and *Haemophilus influenzae*. Late-onset HAP arises after hospital day 7 and is more often caused by hospital-acquired gram-negative bacilli and *S. aureus* (including MRSA).[29] The distribution of organisms implicated in HAP and VAP evolves over time and varies by hospital, patient cohort, and previous antimicrobial exposure.[29]

Mechanisms of Resistance

HAP and VAP may be caused by gram-positive bacteria but are more likely to involve gram-negative bacilli such as *P. aeruginosa, K. pneumoniae, E. coli, and Enterobacter* spp.[1] The most common resistance mechanism among gram-negative bacilli is the disruption of β-lactam rings of antibiotics by enzymatic hydrolysis.[30] Several other mechanisms have been described (**Figure 3**).[31]

Extended-Spectrum β-Lactamases

The extended-spectrum β-lactamases (ESBLs) developed from amino acid substitutions in β-lactamases. Their appearance coincided with the introduction of third-generation cephalosporins the 1980s, and their prevalence increased through the ensuing decade.[30] Today, ESBLs are pervasive around the world, with more than 300 individual enzymes described. The most common ESBLs belong to the TEM, SHV, and CTX-M families, the latter of which is believed to have been acquired from a nonpathogenic Enterobacteriaceae. All ESBLs are plasmid encoded and most are expressed by Enterobacteriaceae. They hydrolyze penicillins, aztreonam, and most cephalosporins but are inactive against the cephamycins (eg, cefotetan, cefoxitin) and carbapenems.[30]

Rates of ESBLs have been increasing in the United States. One study documented an increase in the incidence of ESBL-producing infections in Southeastern US hospitals from 11.1 to 22.1 infections per 100,000 patient-days between 2009 and 2014.[32] ESBL prevalence is even higher in Asia, Latin America, and the Middle East, reaching 60% in *K. pneumoniae* isolates from Argentina and 48% in *E. coli* isolates from Mexico.[33] Human gut carriage likely represents the largest reservoir of ESBLs; other common sources include rivers, undomesticated animals, and food products.[30]

Carbapenemases

The first carbapenemase-producing Enterobacteriaceae was reported in a Japanese patient in 1991, and carbapenem-resistant Enterobacteriaceae (CRE) have since become widespread.[30] The significance of the CRE resistance mechanism is that it eliminates a class of antibiotics that was previously highly active against gram-negative organisms (eg, those producing ESBLs). CRE also often have mechanisms that confer resistance to other antibiotics.[34]

The most common carbapenemase in the United States is *K. pneumonia* carbapenemase (KPC), a class A serine β-lactamase that was first isolated from a *K. pneumoniae* isolate in North Carolina in 1996 and has since proliferated.[35] The *KPC* gene is plasmid-borne and has been reported from multiple Enterobacteriaceae spp and *Pseudomonas* spp.[30] The KPC resistance mechanism is strongly associated with hospital outbreaks.

Another essential carbapenemase enzyme, NDM-1, is a metallo-β-lactamase that was first isolated in 2008 in a *K. pneumoniae* isolate.[36,37] NDM-1 was described in several European and African countries and the United States in 2010, and is now found worldwide.[30] This enzyme has the potential for rapid dissemination among bacteria species by plasmid-mediated horizontal transfer. A clinically significant association exists between the incidence of NDM-1 and hospitalization in India and Pakistan.[38]

Acinetobacter spp

Acinetobacter spp are an important cause of HAIs globally. They can survive for prolonged periods in health care settings, potentiating outbreaks that spread horizontally in health care centers.[39] Dramatic multihospital outbreaks have been described in the United States, Europe, South America, Africa, Asia, and the Middle East.[26,40-43]

The development of antimicrobial resistance in *Acinetobacter* spp likely results from an ability to respond to challenges raised by antimicrobials. For example, the low permeability of their outer cell membranes confers resistance to many antibiotics, as does constitutive expression of certain efflux pumps.[39] *Acinetobacter* spp also can accumulate components of resistance mechanisms encoded on plasmids, transposons, and integrons from settings associated with heavy antibiotic use.[39]

P. aeruginosa

P. aeruginosa is among the most common causes of VAP and has the highest mortality rate among HAIs.[44] A variety of mechanisms of antibiotic resistance in *P. aeruginosa* have been described, including:

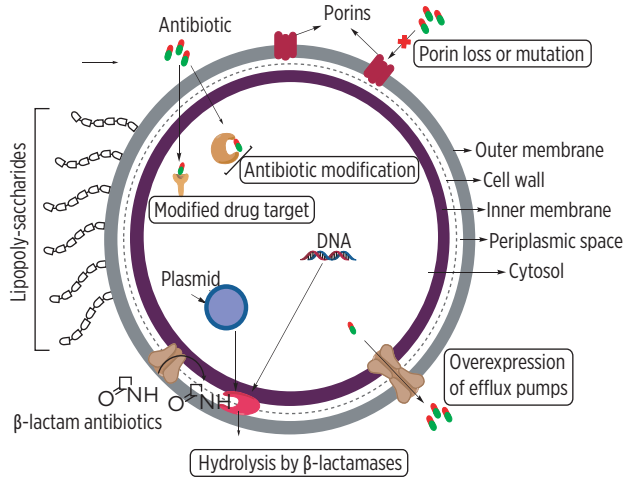

Figure 3. Mechanisms of resistance among gram-negative bacteria against antimicrobial agents.[31]

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- AmpC β-lactamase[45]
- ESBLs[46,47]
- Downregulation of the outer membrane protein OprD, a carbapenem-specific porin[48,49]
- Multidrug efflux pumps[50-54]
- Ability of the organism to form a biofilm[55,56]
- Possible transfer of a 16S rRNA methylase gene from Actinomycetes[57]

Diagnosis of HAP/VAP

The diagnosis of HAP or VAP is difficult because the clinical findings can be nonspecific. The 2016 Infectious Diseases Society of America (IDSA)/American Thoracic Society (ATS) guidelines for the management of HAP and VAP recommend a clinical diagnosis based on a new lung infiltrate plus clinical evidence that the infiltrate is of infectious origin, which includes new onset of purulent sputum, leukocytosis, fever, and decline in oxygenation.[5]

Although these clinical findings support the diagnosis of HAP or VAP, no individual sign or symptom nor any combination of signs and symptoms has been found to be highly sensitive or specific for diagnosis.[58,59] For example, the presence of a new or progressive radiographic infiltrate plus at least 2 of 3 clinical characteristics (purulent secretions, leukocytosis or leukopenia, fever >38°C) had 69% sensitivity and 75% specificity for a diagnosis of VAP.[58]

Molecular diagnostic tests for the detection of respiratory pathogens are being developed and offer hope for more rapid identification of the causes of HAP or VAP.[60-62] Although their sensitivity and specificity may be limited (eg, determining colonization or a true pathogen), these tests offer the potential for more rapid identification of pathogens and resistance patterns (eg, methicillin-resistance for *S. aureus*, carbapenemase production for Enterobacteriaceae), which may result in improved selection of active empiric regimens and more rapid tailoring of directed antibiotic regimens.[62-64] For example, the BioFire FilmArray Blood Culture Identification (BCID) panel tests for 43 targets, including gram-negative bacteria, resistance genes, and MRSA, in about an hour.[65] In an analysis of samples from 165 patients with suspected VAP, BCID identified the main causative microorganisms as *P. aeruginosa*, *Acinetobacter baumannii*, and *K. pneumoniae*. For this group as a whole, sensitivity and specificity were 79% and 98%, respectively; and positive and negative predictive values were 87%, and 97%.[66]

Approaches to Therapy for HAP/VAP

Once HAP or VAP is suspected, diagnostic specimens should be obtained and antimicrobial therapy started as soon as possible, particularly in individuals with signs of septic shock or rapidly progressive organ dysfunction.[5] Treatment delay or failure to give a regimen with activity against the causative pathogen(s) can lead to high mortality rates.[5] Empiric treatment choices for HAP and VAP should be informed by the prevailing local distribution of pathogens and antimicrobial susceptibility patterns within the health care setting.[5,67] All hospitals are encouraged to create and disseminate a hospital antibiogram (ideally unit-specific) on a regular basis.[5] Therapy for HAP and VAP typically includes agents with activity against *S. aureus*, *P. aeruginosa*, and other gram-negative bacilli.[5]

In addition to awareness of local pathogen distribution, antimicrobial selection should be based on patient risk factors for susceptibility to multidrug-resistant (MDR) pathogens (**Table 1**), including recent antibiotic use, underlying diseases, and culture data.[5,68] Individuals at risk for MDR infections should receive empiric broad-spectrum multidrug therapy.[5]

Of note, a recent study of 507 adult patients who were treated for nosocomial pneumonia at 6 ICUs in Spain found that the most prevalent risk factors for MDR infection were admission to hospital settings with high rates of MDR pathogens and prior antibiotic use, with sensitivities of 92% and 85%, respectively.[69]

Empiric Treatment Regimens for HAP/VAP

Several therapies are available for the empiric treatment of HAP and VAP, as laid out in the IDSA/ATS guidelines (**Tables 2 and 3**).[5]

HAP

Patients with HAP should receive an antibiotic with activity against *S. aureus*, and those with risk factors for MRSA infection or mortality should receive an antimicrobial with activity against MRSA. In this situation, either vancomycin or linezolid is recommended.[5]

At least one antimicrobial with activity against *P. aeruginosa* is recommended as well.[5] Those with risk factors increasing the likelihood of *Pseudomonas* or other gram-negative infection or at high risk for mortality should receive antibiotics from 2 different classes with activity against *P. aeruginosa*. When making this recommendation, the guideline panel considered indirect evidence from studies in patients with VAP. However, because most of the studies excluded individuals at increased risk for resistant pathogens, it made this recommendation applicable to those at low risk for infection with resistant pathogens or in whom resistant pathogens have been excluded. The panel decided that this was an appropriate balance between improving clinical outcomes (eg, mortality) and avoiding excessive treatment that may lead to antimicrobial resistance and adverse events (AEs).

VAP

The IDSA/ATS guidelines recommend coverage for *S. aureus*, *P. aeruginosa*, and other gram-negative bacilli in all empiric regimens for the treatment of VAP (**Table 4**).[5] This includes one antibiotic against *P. aeruginosa* in individuals without risk factors for antimicrobial resistance who are being treated in ICUs where at least 10% of gram-negative isolates are resistant to the agent being considered for monotherapy. It also includes an agent active against MRSA in patients with any of the following: a risk factor for multidrug resistance, treatment in units where more than 10% to 20% of *S. aureus* isolates are methicillin-resistant, or treatment in units where the prevalence of MRSA is unknown. If empiric coverage for MRSA is indicated, either vancomycin or linezolid is recommended.[5]

The IDSA/ATS guidelines suggest prescribing 2 antipseudomonal antibiotics from different classes for the empiric treatment of suspected VAP in individuals with any of the following: a risk factor for antimicrobial resistance, treatment

Table 1. Risk Factors for MDR Pathogens[5]

Outcome	Risk factors
MDR VAP	• IV antibiotic use in previous 90 d • Septic shock at time of VAP • ARDS preceding VAP • ≥5 d of hospitalization prior to VAP onset • Acute renal replacement therapy prior to VAP onset
MDR HAP	IV antibiotic use in previous 90 d
MRSA VAP/HAP	IV antibiotic use in previous 90 d
MDR *Pseudomonas* VAP/HAP	IV antibiotic use in previous 90 d

ARDS, acute respiratory distress syndrome; **HAP,** hospital-acquired pneumonia; **IV,** intravenous; **MDR,** multidrug resistant; **MRSA,** methicillin-resistant *Staphylococcus aureus;* **VAP,** ventilator-acquired pneumonia.

in a unit where more than 10% of gram-negative isolates are resistant to an agent being considered for monotherapy, or treatment in an ICU where local antimicrobial susceptibility rates are not available.[5]

European Guidelines

Guidelines for HAP and VAP were published jointly by the European Respiratory Society (ERS), European Society of Intensive Care Medicine (ESICM), European Society of Clinical Microbiology and Infectious Diseases (ESCMID), and Latin American Thoracic Society (ALAT) in 2017.[70] Similar to the IDSA/ATS guidelines, they emphasize the importance of familiarity with local antibiograms in the selection of appropriate empiric therapy. Both also recommend initial empiric coverage for *Pseudomonas* spp and MRSA in individuals with risk factors for MDR infections and/or admitted to an ICU with a high prevalence of MDR pathogens. The European guidelines are organized around 7 clinical questions that generated a series of recommendations for HAP/VAP diagnosis, treatment, and prevention.[70]

In contrast to the IDSA/ATS recommendations, the ERS/ESICM/ESCMID/ALAT publication uses an algorithm to suggest narrow- or broad-spectrum therapies based on different levels of risk for mortality and MDR infection (**Figure 4**).[70] It also differs by making specific recommendations for early-onset VAP (the IDSA/ATS guidelines do not stratify therapy by onset) and by not providing specific recommendations for dose optimization.

Specific Antimicrobial Considerations

Data suggest that linezolid is superior to vancomycin for nosocomial pneumonia. In a recent double-blind, controlled, multicenter study of hospitalized adult patients with HAP or HCAP who were randomized to receive either intravenous (IV) linezolid or vancomycin, 57.6% of those receiving linezolid and 46.6% of those receiving vancomycin achieved clinical success at the end of the study (P=0.042).[71] All-cause 60-day mortality was similar, as was the incidence of AEs, across groups. Nephrotoxicity occurred more frequently with vancomycin vs linezolid (18.2% vs 8.4%).

An antimicrobial with activity against MRSA is telavancin.[72] This agent is FDA-approved for HAP and VAP caused by *S. aureus* (including MRSA) but not by other bacteria.[73] Data supporting its use come from 2 randomized studies comparing telavancin with vancomycin for hospitalized patients with HAP caused by gram-positive pathogens, particularly *S. aureus*.[74] Pooled results from these 2 trials revealed no differences in overall cure rates or mortality in the vancomycin vs telavancin groups.

Novel Agents

Many older antimicrobials, such as colistin, are hampered by resistance, unfavorable toxicity profiles, limited clinical trial data, and/or poor tissue penetration.[75,76] Recent years, however, have seen the emergence of novel antibiotics that are useful for the treatment of resistant gram-negative infections.

Ceftazidime-avibactam, a cephalosporin–β-lactamase inhibitor combination, was FDA-approved for the treatment of HAP or VAP in 2018.[77] Approval was based on a multicenter, international randomized study assessing 879 patients with HAP or VAP.[78] Clinical cure and mortality rates were similar for ceftazidime-avibactam and the comparator, meropenem; however, the rate of serious AEs was higher in the ceftazidime-avibactam arm (18.5% vs 13.4%).

Ceftolozane-tazobactam, another cephalosporin–β-lactamase inhibitor combination, was approved for HAP and VAP in 2019.[79] This combination is active against many resistant strains of *P. aeruginosa*. A recent comparison with meropenem in 726 VAP/vHAP patients on MV demonstrated similar rates of clinical cure (54% vs 53%), 28-day mortality (24% vs 25%), and AEs across treatment arms.[80]

Imipenem-cilastatin/relebactam, a combination containing a carbapenem antibiotic, renal dehydropeptidase inhibitor, and β-lactamase inhibitor, was approved for HAP and VAP in 2020[81] based on 2 phase 3, double-blind, multicenter trials. In RESTORE-IMI 1, rates of favorable overall response were similar for imipenem-cilastatin/relebactam and the comparator, colistin-imipenem, in 31 hospitalized adults (primary outcome, 71.4% vs 70%).[82] AEs related to the study drug occurred in 16% and 31% of each treatment arm. In RESTORE-IMI 2, imipenem-cilastatin/relebactam was noninferior to piperacillin-tazobactam in 537 hospitalized patients with HAP/VAP on the primary end point of all-cause mortality at day 28.[83] Rates of AEs related to the study drug were similar between groups.

Cefiderocol is the most recent addition to the HAP/VAP armamentarium. A siderophore cephalosporin with structural stability against a variety of β-lactamases and a novel mechanism for penetrating the outer cell membrane of gram-negative pathogens, cefiderocol was FDA-approved for HAP and VAP in September 2020.[84]

The randomized, double-blind APEKS-NP study compared cefiderocol with high-dose, extended-infusion meropenem in critically ill patients with HAP, VAP, and HCAP caused by gram-negative bacteria.[85] Both therapies were given in 2-g doses via 3-hour IV infusion every 8 hours for 7 to 14 days with linezolid 600 mg IV every 12 hours. The most common baseline organisms were *K. pneumoniae*, *P. aeruginosa*, *Acinobacter baumannii*, *E. coli*, and *Enterobacter cloacae*. The study met its primary end point of noninferiority on all-cause mortality in the intention-to treat-population at day 14, with rates of 12.4% in the cefiderocol arm and 11.6% in the

Table 2. IDSA/ATS Recommended Initial Empiric Antibiotic Therapy for HAP[5]

Patient Group		Recommendations														
• **Not high mortality risk** • **No factors increasing likelihood of MRSA**	Choose 1	Piperacillin-tazobactam	*or*	Cefepime	*or*	Levofloxacin	*or*	Imipenem Meropenem								
• **Not high mortality risk** • **Factors increasing likelihood of MRSA**	Choose 1	Piperacillin-tazobactam	*or*	Cefepime Ceftazidime	*or*	Levofloxacin Ciprofloxacin	*or*	Imipenem Meropenem	*or*	Aztreonam + vancomycin	*or*	Linezolid				
• **High risk for mortality** • **Receipt of IV antibiotics in past 90 d**	Choose 2	Piperacillin-tazobactam	*or*	Cefepime Ceftazidime	*or*	Levofloxacin Ciprofloxacin	*or*	Imipenem Meropenem	*or*	Amikacin Gentamicin Tobramycin	*or*	Aztreonam + vancomycin	*or*	Linezolid		

ATS, American Thoracic Society; **HAP,** hospital-acquired pneumonia; **IDSA,** Infectious Diseases Society of America; **IV,** intravenous; **MRSA,** methicillin-resistant *Staphylococcus aureus.*
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meropenem arm. Cefiderocol was well tolerated, and its safety profile was consistent with that of other cephalosporins and/or carbapenems. The incidence of treatment-emergent AEs (TEAEs), drug-related TEAEs, serious AEs, and TEAEs leading to discontinuation was similar for both treatment arms.[85]

The randomized, open-label (descriptive) CREDIBLE-CR trial assessed outcomes with cefiderocol and with best available therapy (BAT) in a heterogeneous population with a range of serious infections including nosocomial pneumonia, bloodstream infections/sepsis, and complicated urinary tract infections.[86] The most common carbapenem-resistant pathogens were *A. baumannii*, *K. pneumoniae*, and *P. aeruginosa*. BAT was defined as no more than 3 drugs for 7 to 14 days and consisted of combination therapy in 71% of cases, with 28 different regimens represented. Cefiderocol was given as monotherapy in 83% of cases. Rates of clinical cure and microbiological eradication were generally similar between cefiderocol and BAT (**Figure 5**), except for metallo-β-lactamase infections, in which cefiderocol performed substantially better (clinical cure, 75% vs 29%; eradication, 44% vs 14%).[86]

An increase in all-cause mortality was observed for cefiderocol vs BAT at days 14 (18.8% vs 12.2%) and 28 (24.8% vs 18.4%).[86] The difference was described as "striking" in an accompanying editorial[87] but could not be explained by any cefiderocol-related toxicity. The authors hypothesized that it could be due to an imbalance of risk factors at baseline, as it occurred primarily among individuals with *Acinetobacter* spp infections, but that it is unclear whether it reflects "a chance finding in this heterogeneous population or truly reflects a deficit in the activity of cefiderocol."[86] No deaths were attributed to cefiderocol-related AEs. The complexity of interpreting this seemingly conflicting data reflets the balance that must be found between the need for advances in treatment and uncertainty that can arise from the best available evidence.

Table 3. IDSA/ATS Suggested Empiric Treatment Options for Clinically Suspected VAP in Units Where Empiric MRSA Coverage and Double Antipseudomonal/Gram-Negative Coverage Are Appropriate[5]

Choose 1 gram-positive option from row A,	**A. Gram-positive antibiotics with MRSA activity**	Vancomycin	*or*	Linezolid				
1 gram-negative option from row B, and	**B. Gram-negative antibiotics with antipseudomonal activity: β-lactam–based agents**	Piperacillin-tazobactam	*or*	Cefepime Ceftazidime	*or*	Imipenem Meropenem	*or*	Aztreonam
1 gram-negative option from row C	**C. Gram-negative antibiotics with antipseudomonal activity: non–β-lactam–based agents**	Ciprofloxacin Levofloxacin	*or*	Amikacin Gentamicin Tobramycin	*or*	Colistin Polymyxin B		

ATS, American Thoracic Society; **HAP,** hospital-acquired pneumonia; **IDSA,** Infectious Diseases Society of America; **IV,** intravenous; **MRSA,** methicillin-resistant *Staphylococcus aureus*.
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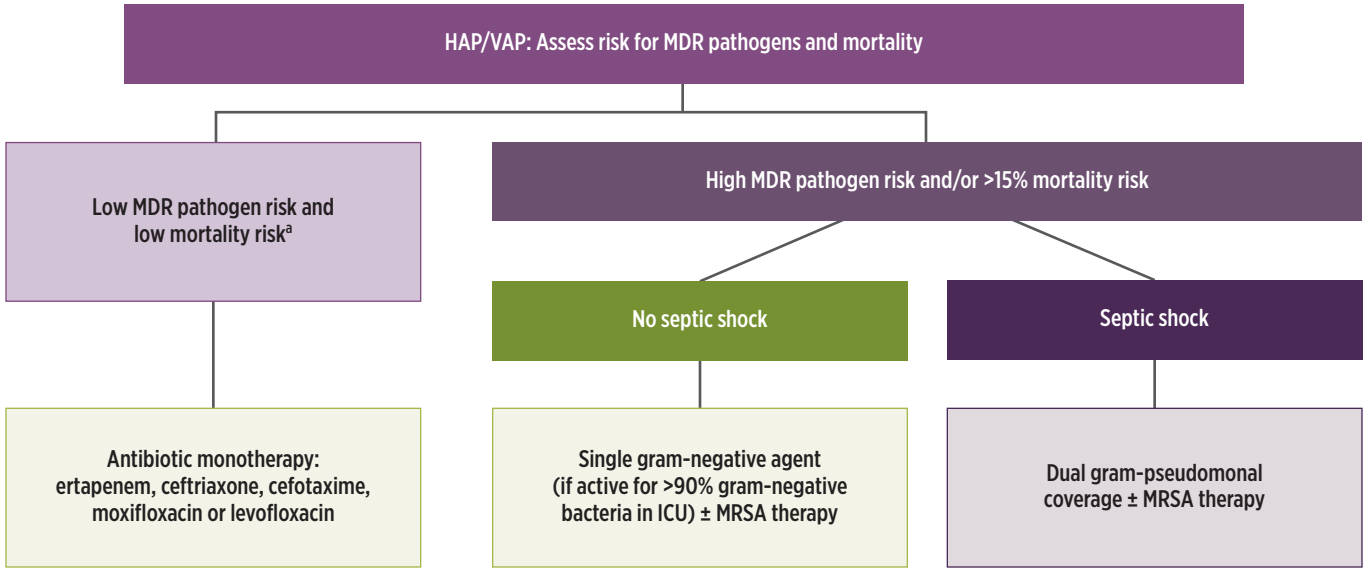

Figure 4. ERS/ESICM/ESCMID/ALAT algorithm for empiric antibiotic treatment in HAP/VAP.[70]

[a] ≤15% chance of dying (associated with better outcomes using monotherapy vs combination therapy for serious infection).
ALAT, Latin American Thoracic Society; **ERS,** European Respiratory Society, **ESCMID,** European Society of Clinical Microbiology and Infectious Diseases; **ESICM,** European Society of Intensive Care Medicine; **HAP,** hospital-acquired pneumonia; **ICU,** intensive care unit; **MDR,** multi-drug resistant; **MRSA,** methicillin-resistant *Staphylococcus aureus*; **VAP,** ventilator-associated pneumonia.
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Tailoring and Optimization of Therapy

All patients with HAP/VAP should be evaluated for clinical response and the results of microbiologic studies after initial empiric antimicrobial therapy so treatment can be tailored according to the susceptibility patterns of identified pathogens.[5] Tailoring antibiotic therapy has *not* been associated with increased mortality, recurrent pneumonia, or increased ICU LOS.[88,89]

Most patients with HAP/VAP receive treatment for 7 days.[5] This duration appears to be as effective as longer durations in most situations and may reduce the emergence of resistant organisms.[5,90] It also almost certainly reduces costs and AEs. A potential negative outcome of a short-course regimen is that antibiotics may be discontinued prematurely, leading to recurrence; however, the evidence suggests that this is uncommon.[5]

Dose Optimization

Antibiotic resistance is defined by the minimum inhibitory concentration (MIC), the lowest concentration (mg/L) of an antibiotic that prevents visible growth of a microorganism on agar or in broth.[91] Higher MICs may lead to worse clinical outcomes.[92] As antimicrobial MICs among gram-negative pathogens continue to rise, susceptibility rates decline, and dosing typically requires modification.[91] Simply increasing doses could be expected to increase exposure; however, not all antibiotics kill bacteria by concentration-dependent mechanisms. Others kill in a concentration-independent (time-dependent) manner. Dose adjustment based on an understanding of these mechanisms reduces mortality, improves clinical cure rates, and reduces ICU LOS.[5]

Concentration-dependent killing is maximized by increasing 2 pharmacodynamic indices: *the ratio of maximum free drug concentration (peak concentration) to the MIC (ƒC_{max}/MIC)* and the *24-hour ratio of the area under the curve to the MIC (ƒAUC/MIC).* This mechanism applies to aminoglycosides and polymyxin antibiotics. Dosing strategies to overcome higher MICs have been developed.[91]

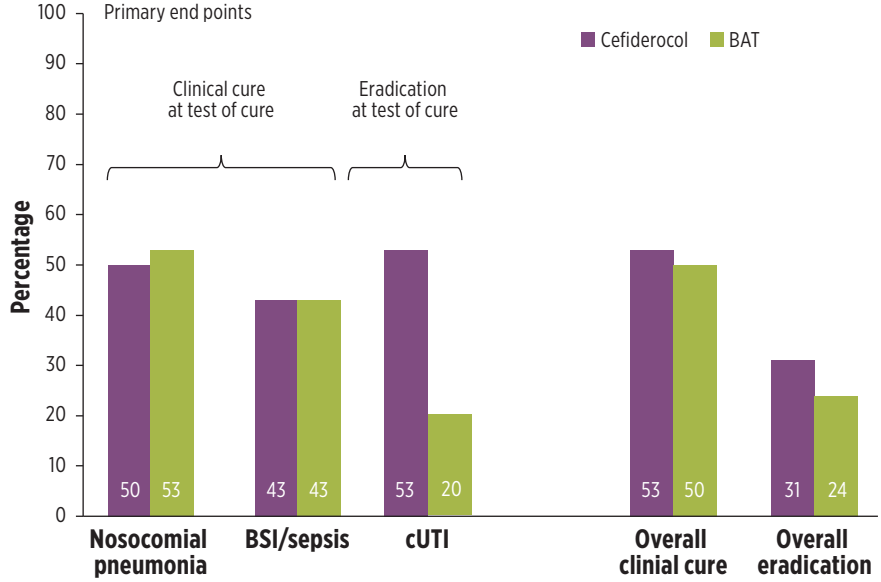
- For aminoglycosides, traditional regimens of 1 to 1.5 mg/kg (gentamycin and tobramycin) or 7.5 mg/kg (amikacin) divided into 2 to 3 daily doses have largely been replaced with high-dose, extended-interval regimens that achieve higher peak concentrations.
- Colistin also is associated with concentration-dependent killing. In a (noncomparative) series of critically ill patients with bacteremia or VAP caused by MDR gram-negative organisms, the clinical cure rate was 82% with high-dose, extended-interval colistin.[93] This was more favorable than results of ICU studies using lower, more frequent dosing.[94-96]

Time-dependent killing is maximized by increasing the duration of time the free drug concentration remains above the MIC (ƒT>MIC). β-lactams (penicillins, cephalosporins, carbapenems, and monobactams) exhibit time-dependent microbiological effects.[91]

- β-lactams require 40% to 70% ƒT>MIC to achieve bactericidal activity in gram-negative organisms.[91] Dosing methods associated with enhancing ƒT>MIC include increasing the dose, shortening the dosing interval, and extending the infusion duration from traditional, intermittent rates (eg, over 30 minutes) to prolonged infusion (eg, over 4 hours). The most effective method has shown to be a combination of increasing the dose and prolonging the infusion time.[97]
- An example of this is the dosing of meropenem used in the APEKS-NP study, 2 g every 8 hours over 3 hours, which differs from the labeled dosing of 500 mg to 1 g every 8 hours over 15 to 30 minutes (or bolus).[85,98]
- For piperacillin-tazobactam, continuous infusion has been associated with a higher probability of clinical cure vs intermittent infusion in VAP caused by a variety of gram-negative bacilli.[99]
- For cefepime, a higher-dose, extended-infusion regimen reduced infection-related mortality by 69% (P=0.029) and was associated with shorter infection-related LOS (P<0.001) and fewer superinfections in VAP patients vs a historical data set.[100]
- For the ceftazidime-avibactam combination, a higher dose (2 g of ceftazidime every 8 hours) over a prolonged infusion (2 hours) is expected reach beneficial ƒT>MIC thresholds.[91]

Conclusion

HAP and VAP remain important causes of morbidity and mortality despite improvements in prevention, antimicrobial therapy, and supportive care. The presence of antibiotic resistance, particularly MDR gram-negative pathogens, has made optimal treatment for HAP and VAP very challenging. The incidence of MDR gram-negative pathogens has increased over time, especially in the nosocomial setting. The presence of multidrug gram-negative resistance in HAP and VAP is affected by a combination of patient- and hospital-specific risk factors including recent antibiotic use, hospital LOS, presence of structural lung disease, and local resistance patterns. Increasing resistance results in limited treatment options for gram-negative infections. Fortunately, novel antimicrobials may be helpful for the treatment of resistant gram-negative infections.



Carbapenem-resistant intent-to-treat population.

Figure 5. CREDIBLE-CR: Key efficacy results.[86]

BAT, best available therapy; **BSI,** bloodstream infection; **cUTI,** complicated urinary tract infection.

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