An overview of guidelines for the management of hospital-acquired and ventilator-associated pneumonia caused by multidrug-resistant Gram-negative bacteria

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Purpose of review
Multidrug-resistant (MDR) Gram-negative pathogens in hospital-acquired pneumonia (HAP) and ventilator-associated pneumonia (VAP) are associated with poor clinical outcomes. These pathogens represent a global threat with few therapeutic options. In this review, we discuss current guidelines for the empiric management of HAP/VAP caused by MDR Gram-negative pathogens.

Recent findings
The incidence of MDR Gram-negative bacteria is rising among cases of nosocomial pneumonia, such that it is now becoming a significant challenge for clinicians. Adherence to international guidelines may ensure early and adequate antimicrobial therapy, guided by local microbiological data and awareness of the risk factors for MDR bacteria.

Summary
Due to the increasing prevalence of HAP/VAP caused by MDR Gram-negative pathogens, management should be guided by the local ecology and the patient's risk factors for MDR pathogens. The main risk factors are prior hospitalization for at least 5 days, prior use of broad-spectrum antibiotics, prior colonization with resistant pathogens, admission to hospital settings with high rates of MDR pathogens, and septic shock at the time of diagnosis with nosocomial pneumonia.

Keywords
Gram-negative, hospital-acquired pneumonia, multidrug-resistance, pneumonia, ventilator-associated pneumonia

INTRODUCTION: WHY IS THIS TOPIC IMPORTANT?

Hospital-acquired pneumonia (HAP) and ventilator-associated pneumonia (VAP) are important health problems worldwide [1–3], with both being associated with substantial morbidity and mortality [4▪]. HAP is currently the main cause of death from nosocomial infection in critically ill patients, with an incidence of five to 10 cases per 1000 hospital admissions; by contrast, VAP affects approximately 10–25% of all patients in ICUs. The estimated mortality rate of HAP is 20–30%, but it is higher (20–50%) in VAP [5▪,6].

Gram-negative bacteria are responsible for most bacterial cases of HAP/VAP (50–80%) [5▪,7]. The most frequently reported Gram-negative bacteria are *Pseudomonas aeruginosa*, *Acinetobacter baumannii*, and *Enterobacteriaceae*, with distributions that vary by country and continent [8–10]. Antimicrobial resistance among these organisms has increased in the last 2 decades, representing a global threat and leaving few therapeutic options [11,12]. Specifically, multidrug-resistant (MDR) Gram-negative pathogens are associated with poor clinical outcomes, in part due to inappropriate or delayed antibiotic therapy [5▪,13,14].

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KEY POINTS

- MDR Gram-negative bacteria are related to high mortality in critically ill patients, especially in cases of HAP or VAP.
- Prior use of broad-spectrum antibiotics, prior colonization with resistant pathogens, and shock are among the main risk factors associated with pneumonia caused by MDR Gram-negative bacteria.
- It is important to know the local epidemiology and risk factors associated with MDR Gram-negative infection to ensure prompt and adequate antimicrobial therapy.
- Adherence to current guidelines may ensure correct clinical management.

The 2016 Infectious Diseases Society of America/American Thoracic Society guidelines [2] (the American guidelines) and the 2017 International European Respiratory Society/European Society of Intensive Care Medicine/European Society of Clinical Microbiology and Infectious Diseases/Asociación Latinoamericana del Tórax guidelines [3] (the European guidelines) provide clinical recommendations for the management of MDR Gram-negative pathogens in cases of HAP/VAP. Both guidelines highlight the importance of a prompt and adequate empiric therapy based on the patient's risk stratification for MDR pathogens and on local microbiological and antibiotic resistance data. However, the two guidelines are differentiated by some important issues in the management of HAP/VAP caused by MDR Gram-negative bacteria. These include differences in MDR risk factors, diagnostic strategies, and the use of pharmacological/pharmacodynamic endpoints to guide therapy [15,16].

In this review, we summarize the most recent evidence on HAP/VAP caused by MDR Gram-negative bacteria, the current main controversies, parallelisms, and conceptual differences between the two most frequently used guidelines.

MULTIDRUG-RESISTANT GRAM-NEGATIVE HOSPITAL-ACQUIRED PNEUMONIA/VENTILATOR-ASSOCIATED PNEUMONIA: WHAT IS THE SCALE OF THE PROBLEM?

Several prospective and retrospective studies have evaluated the prevalence of MDR Gram-negative pathogens in HAP/VAP, showing an increase in their frequency in Europe and the USA [10,17–26,27▪] (Table 1).

Table 1. Hospital-acquired pneumonia/ventilator-associated pneumonia caused by multidrug-resistant Gram-negative pathogens: prevalence and outcomes

Author/Year/Country	Study design	Population	Prevalence MDR Gram-negative pathogens
Kanafani *et al.*/2019/Lebanon	Retrospective	VAP ($n=162$)	90% MDR *Acinetobacter baumannii*
Perez *et al.*/2019/Greece, Spain, Italy	Prospective	VAP ($n=53$)	4% PDR *Pseudomonas aeruginosa* 36% XDR *P. aeruginosa* 30% MDR *P. aeruginosa*
Čiginskienė *et al.*/2019/Lithuania	Retrospective	VAP ($n=60$)	13% MDR *A. baumannii* 68% XDR *A. baumannii* 18% PDR *A. baumannii*
Sosa-Hernandez *et al.*/2019/Mexico	Retrospective	VAP ($n=48$)	48% MDR *A. baumannii* 15% MDR *P. aeruginosa* 2% *Klebsiella pneumoniae* ESBL
Wang *et al.*/2018/China	Prospective	VAP ($n=76$)	53% ESBL *K. pneumoniae* and *E. coli*
Fernández *et al.*/2017/Spain	Retrospective	ICUAP ($n=222$) [VAP = 159, HAP = 63]	34% MDR *P. aeruginosa*
Guzek *et al.*/2017/Poland	Retrospective	VAP ($n=2033$)	26% *Enterobacteriaceae* sp. ESBL 3% *P. aeruginosa* MBL
Ferrer *et al.*/2015/Spain	Prospective	VAP ($n=179$) Nonventilator-ICUAP ($n=77$) Cases with defined cause	11% MDR Gram-negative pathogens
Micek *et al.*/2015/EU-USA	Retrospective	HAP due *P. aeruginosa* ($n=740$)	31% MDR *P. aeruginosa*
Behnia *et al.*/2014/US	Retrospective	HAP/VAP ($n=43$)	75% *K. pneumoniae* ESBL
Di Pasquale *et al.*/2014/Spain	Prospective	HAP (135)/VAP (280)	28% MDR *P. aeruginosa* 29% *K. pneumoniae* ESBL

ESBL, extended-spectrum β-lactamase; HAP, hospital-acquired pneumonia; ICUAP, intensive care unit acquired pneumonia; MBL, metallo-beta-lactamase; MDR, multidrug-resistant; PDR, pan drug resistant; VAP, ventilator-associated pneumonia; XDR, extensively drug resistant.

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In 2015, Micek *et al.* compared the characteristics of patients with and without MDR *P. aeruginosa* strains. Compared with pneumonia caused by less-resistant strains, pneumonia due to MDR *P. aeruginosa* was associated with longer ICU stays, prolonged mechanical ventilation, and higher mortality [17]. In the same year, Martin-Loeches *et al.* [28] investigated the prognostic impact of multidrug-resistance on ICU-acquired pneumonia in a cohort of 343 patients. The authors reported higher ICU mortality rates in patients with MDR pathogens. In a 2017 study of the risk factors for MDR *P. aeruginosa* in ICU-acquired pneumonia, Fernández-Barat *et al.* [27▪] reported that 34% of cases had MDR *P. aeruginosa* and that chronic renal disease independently predicted MDR pneumonia in these cases. In 2018, Bickenbach *et al.* [29] investigated the influence of MDR bacteria on the outcomes of patients with prolonged weaning after pneumonia and/or septic pneumonic shock. The authors reported that approximately one-quarter of infections in these cases were caused by MDR pathogens, with a marked increase of pan-resistant bacteria, especially *P. aeruginosa* and *A. baumannii*, during mechanical ventilation. The authors concluded that the success of weaning could be influenced by the presence of MDR pathogens.

IS THERE A GOLD-STANDARD METHOD FOR THE MICROBIOLOGICAL DIAGNOSIS OF HOSPITAL-ACQUIRED PNEUMONIA/ VENTILATOR-ASSOCIATED PNEUMONIA?

Adequate antibiotic therapy for HAP/VAP should be guided by the results of microbiological cultures of lower respiratory samples [2,3]. On the contrary, arguments about the best method of respiratory sampling (invasive versus noninvasive) and the most accurate method of diagnosis (quantitative versus semiquantitative cultures) have not been resolved [16].

Invasive respiratory sampling includes bronchoscopic techniques (e.g., bronchoalveolar lavage or protected specimen brush) and blind bronchial sampling (e.g., mini-bronchoalveolar lavage). Gas exchange may worsen during bronchoscopy, especially in patients with severe acute respiratory distress syndrome (ARDS) and septic shock; moreover, they require the participation of expert clinicians and may be associated with higher costs [30]. By contrast, noninvasive diagnostic methods (e.g., endotracheal aspiration) may over identify pathogens. In patients with suspected VAP, Solé Violán *et al.* [31] found that VAP bacteria were identified in 86% through endotracheal qualitative aspirates and in 43% through bronchoscopic distal quantitative methods. This difference could explain the reduction of antibiotic-free days and antibiotic exposure between the two techniques in previous research.

In 2014, Berton *et al.* [32] reviewed randomized controlled trials comparing respiratory quantitative or qualitative cultures obtained invasively or noninvasively from immunocompetent patients with VAP. The authors found that the use of quantitative cultures did not reduce mortality, ICU stay, duration of mechanical ventilation, and antibiotic change when compared with qualitative cultures. Similar results were found when comparing invasive and noninvasive strategies.

The American guidelines [2] recommend noninvasive sampling with semiquantitative cultures to diagnose VAP (weak recommendation, low-quality evidence). Conversely, the European guidelines [3] recommend obtaining distal quantitative cultures before antibiotic treatment in clinically stable patients with suspected VAP. The goal of this latter approach is to limit antibiotic use and improve the accuracy of the results (weak recommendation, low-quality evidence). The European guidelines also recommend obtaining a lower respiratory tract sample (e.g., distal quantitative or proximal quantitative or qualitative culture) even in patients with HAP, which is also used to narrow the initial spectrum of empiric antibiotic therapy (strong recommendation, low-quality evidence). Of course, lower respiratory samples should be obtained before any change in antimicrobial therapy given that such change significantly reduces the sensitivity and specificity of both qualitative and quantitative samples.

Although molecular methods are not currently recommended by international guidelines for the microbiological diagnosis of nosocomial pneumonia, recent evidence supports the idea that genotypic and phenotypic assays have a role in clinical practice [33,34]. These molecular assays may improve the ability to identify pathogens and their resistance patterns more rapidly and precisely, may help clinicians to start early and appropriate antimicrobial therapy, and to reduce the use of broad-spectrum antimicrobials. This can guide de-escalation therapy and stewardship, though there is a need for additional validation studies to assess the utility and efficacy of these assays systematically with the aim of improving the microbiological diagnosis of HAP/VAP.

WHICH FACTORS SHOULD GUIDE EMPIRIC ANTIBIOTIC THERAPY IN PATIENTS AT RISK FOR HOSPITAL-ACQUIRED PNEUMONIA/ VENTILATOR-ASSOCIATED PNEUMONIA CAUSED BY MULTIDRUG-RESISTANT GRAM-NEGATIVE PATHOGENS?

Effective management of MDR infections in ICU requires knowledge of local microbial cause, prompt

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VAP/HAP High Risk

American guidelines (2016)	European guidelines (2017)
Previous antibiotic use	Previous antibiotic use
≥5 days of hospitalization	≥5 days of hospitalization
Septic shock	Septic shock
ARDS before VAP	*Hospital settings with high rates of MDR pathogens*
Acute renal replacement therapy before VAP onset	*Previous colonization with MDR pathogens.*

FIGURE 1. Hospital-acquired pneumonia/ventilator-associated pneumonia high risk.

use of appropriate antibiotic therapy, antimicrobial stewardship, and accurate patient risk stratification [2,3,35,36]. However, it is notable that the risk factors for MDR differ between the American [2] and European [3] guidelines (Fig. 1).

The American guidelines [2] identify five risk factors that are frequently associated with MDR nosocomial pneumonia: previous intravenous antibiotic therapy within 90 days (for both VAP and HAP), hospitalization for at least 5 days before the occurrence of VAP, septic shock at the time of VAP, ARDS preceding VAP, and need for renal replacement therapy before VAP onset. Empirical therapy recommended for patients with none of these risk factors, when treated in ICUs with a low prevalence (<10%) of MDR pathogens, is a narrow-spectrum antibiotic with activity against nonresistant Gram-negative microorganisms (weak recommendation, low-quality evidence). The suggested therapy for patients at high risk for MDR pathogens, those presenting with lung disease, and those treated in ICUs with an unknown or high prevalence (>10%) of MDR pathogens, is dual antibiotic therapy against Gram-negative microorganisms (weak recommendation, low-quality evidence).

In a validation study of the 2016 American guidelines, Ekren *et al.* [37] reported that the risk factors mentioned for MDR pneumonia had a high sensitivity but a very low specificity and poor overall performance, leading to excessive broad-spectrum empirical therapy. Among the five risk factors, only antibiotic use in the past 90 days (negative predictive value 79%) and at least 5 days of hospitalization (negative predictive value 80%) before pneumonia were strongly associated with the presence of MDR pneumonia. Significantly, the presence of ARDS preceding VAP had a negative predictive value of 71% for the presence of MDR pathogens.

The European guidelines [3] do not include ARDS or renal replacement therapy in the definition of patients at high risk for MDR pathogens. These two variables are related to disease severity in patients with nosocomial pneumonia, but not to the risk of MDR pathogens. Instead, these guidelines include hospital settings with high rates of MDR pathogens as well as prior colonization with MDR pathogens as determinants of risk for MDR pathogens [3]. In patients at low risk of MDR pathogens and mortality who are treated in ICUs with a low prevalence of MDR pathogens (<25%), the European guidelines suggest using narrow-spectrum antibiotics that are active against nonresistant Gram-negative microorganisms (weak recommendation, very low-quality evidence). In patients at high risk of MDR pathogens and mortality who are treated in ICUs with a high prevalence of MDR pathogens (>25%), the guidelines recommend that empiric antibiotic treatment should be guided by the patient's hemodynamic status. Patients

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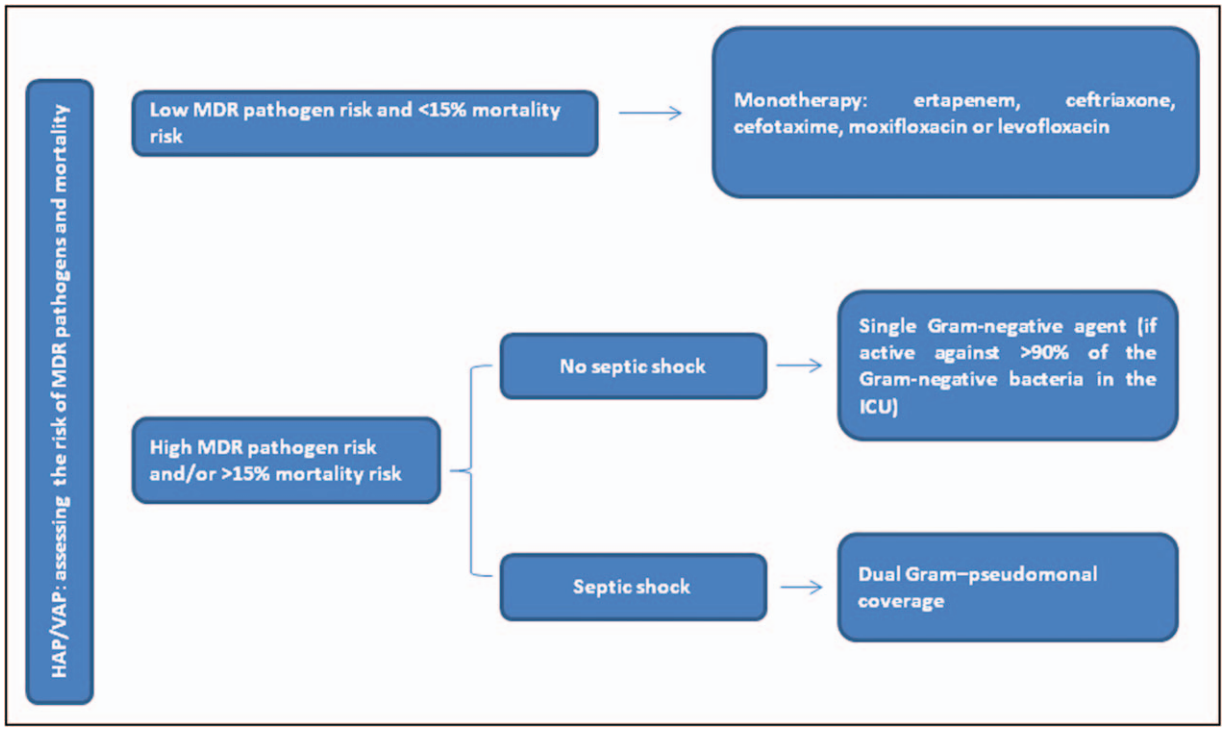

FIGURE 2. Algorithm for the empiric antibiotic treatment of hospital-acquired pneumonia/ventilator-associated pneumonia caused by multidrug-resistant Gram-negative pathogens.

with no septic shock at diagnosis, monotherapy is considered appropriate provided that the agent is active against more than 90% of the Gram-negative organisms typical of that ICU. For patients in septic shock, broad-spectrum empiric antibiotic therapy is recommended that targets *P. aeruginosa*, *Enterobacteriaceae* positive for extended spectrum beta-lactamases, and *A. baumannii* (if highly prevalent in the treating ICU) (strong recommendation, low-quality evidence).

Figure 2 summarizes a proposed algorithm for the empirical treatment of MDR Gram-negative pathogens.

WHAT ARE THE CURRENT RECOMMENDATIONS FOR THE DURATION OF ANTIBIOTIC THERAPY IN PATIENTS WITH MULTIDRUG-RESISTANT GRAM-NEGATIVE PATHOGENS?

It is recommended that the duration of the antibiotic therapy be individualized to a patients' baseline characteristics, the pneumonia presentation, and the initial response to treatment. In two recent systematic reviews [38,39], the authors analyzed randomized controlled trials comparing antibiotic therapy of short (7–8 days) and long (10–15 days) durations in immunocompetent patients with VAP. They found no difference by treatment duration in the mortality rate (including patients with nonfermenting Gram-negative bacteria), length of mechanical ventilation, length of ICU stay, and relapse rate. However, there was a strong trend toward fewer relapses in the longer treatment group. This result is clearly supported by data from Chastre *et al.* [40], in which most patients with relapse had VAP due to nonfermenting Gram-negative bacteria. Treatment of short duration was associated with significantly more antibiotic-free days and a lower incidence of secondary infections, including VAP, caused by MDR pathogens. Adverse events were reported differently across studies, but in general, treatment of short duration has been associated with better tolerability.

Although they do so with a moderate quality of evidence, both the American and the European guidelines suggest a 7-day course of antibiotics for patients with nosocomial pneumonia, including those with VAP caused by nonfermenting Gram-negative and *Acinetobacter* spp. with good clinical response. However, they do advocate longer antibiotic courses (14 days) in the following cases:

(1) Patients with immunodeficiency, cystic fibrosis, empyema, lung abscess, cavitation, or necrotizing pneumonia.
(2) Patients with inappropriate initial empiric therapy.

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(3) Patients with VAP caused by highly antibiotic-resistant pathogens (e.g., *P. aeruginosa*, carbapenem-resistant *Acinetobacter* spp., carbapenem-resistant *Enterobacteriaceae*).
(4) Patients receiving second-line antibiotic therapy (e.g., colistin or tigecycline).

These recommendations can also be extended to patients with HAP. However, in patients with a low probability of HAP (e.g., Clinical Pulmonary Infection Score <6) and no clinical deterioration within 72 h from symptom onset, routine antibiotic treatment should be limited to 3 days.

IS IT POSSIBLE TO PREVENT HOSPITAL-ACQUIRED PNEUMONIA/VENTILATOR-ASSOCIATED PNEUMONIA CAUSED BY MULTIDRUG-RESISTANT GRAM-NEGATIVE PATHOGENS?

Prevention measures comprise strategies that try to reduce the incidence of nosocomial pneumonia and improve patients' outcomes by taking the infection pathogenesis into account.

HAP is caused by the pharyngeal colonization and subsequent microaspiration and macroaspiration of specific pathogens in the lungs [30]. To date, most prevention strategies for HAP remain unproven. Recommend efforts to attenuate the risk for HAP include minimizing the length of hospitalization, improving hand and equipment hygiene practices, contact isolation precautions, proper oral care, and precautions against aspiration [41]. Oral and digestive decontamination with antibiotics may be effective in the prevention of HAP, but this strategy may increase the risk of resistance [41].

Transcolonization has been addressed as one of the main regional mechanisms underlying the occurrence of VAP [42]. It has been defined as a complete change in the microbiology of the oropharyngeal and tracheobronchial areas due to bacterial migration from the stomach to the upper airway. Transcolonization and an insufficiently tight endotracheal tube cuff combine to provide a direct route for bacteria to the subglottic airways, eventually leading to VAP [42]. Several approaches have been proposed to prevent VAP. These include the following: semirecumbent positioning; use of novel endotracheal tubes with subglottic secretion drainage; maintaining a cuff pressure of 20–30 cmH_2O; limiting prolonged ventilation under sedation; limiting the use of paralytics and weaning protocols; regular oral care with 0.12–2.0% chlorhexidine; stress ulcer prophylaxis; selective oral decontamination (SOD); and selective digestive tract decontamination (SDD) [43,44]. On the contrary, no single strategy is sufficient to prevent VAP when used in isolation.

The American guidelines [2] provide no specific recommendations on the prevention of nosocomial pneumonia. Conversely, the European guidelines [3] recommend SOD with topical antibiotics in ICU settings with low rates of antimicrobial resistance and low antibiotic use (weak recommendation, low-quality evidence). However, they do not specifically mention SDD and provide no other recommendations. This is perhaps surprising given that previous studies [45,46] in ICU settings with low levels of antibiotic resistance have reported that SDD and SOD are associated with improved clinical outcomes. Moreover, SDD has been shown to be more effective than SOD at preventing infection [47].

Despite the potential benefits of SDD, three important concerns have been raised. First, this strategy increases the risk of antibiotic resistance [48]. Second, we must consider the effect of using antibiotics in patients without bacterial infections. Third, it is known that the use of SDD is not associated with a reduction in infection rates in ICUs with moderate to high prevalence rates of antibiotic resistance [49]. A recently published randomized clinical trial [49] of decontamination strategies for mechanically ventilated patients in the ICU concluded that SDD offered no added benefit over standard care in ICUs with a high prevalence of resistant pathogens. SDD failed to reduce bloodstream infections caused by MDR Gram-negative bacteria in these ICUs.

CONCLUSION

HAP/VAP caused by MDR Gram-negative bacteria represents a serious threat. It is important to be aware of the local epidemiology, resistance patterns, and main risk factors for MDR Gram-negative pathogens to ensure correct management and appropriate antimicrobial therapy.

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Conflicts of interest

There are no conflicts of interest.

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