

Hospital-acquired pneumonia: risk factors and prognosis, microbial etiology, treatment, and prophylaxis

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ABSTRACT

Hospital-acquired pneumonia (HAP) is a group of nosocomial infections that includes a variety of different phenotypes of pneumonia. This heterogeneity, along with the time-dependent nature of the disease, contributes to the difficulty in determining its exact incidence and mortality, despite being one of the most common and lethal hospital acquired infections, particularly in critically ill patients. Many cases of infection are sustained by multi-drug resistant pathogens and require rapid diagnosis and identification of the responsible pathogen and appropriate antibiotic treatment. This review aims to summarize the main evidence in the clinical management of HAP, focusing on the identification of risk factors, prevention, and innovations in the areas of diagnosis and treatment.

Keywords: Hospital-acquired pneumonia. Ventilation-associated pneumonia. Multidrug resistance. Nosocomial infections. Antimicrobial treatment.

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INTRODUCTION

Hospital acquired pneumonia (HAP) represents a heterogeneous group of severe lung parenchyma infections occurring after at least 48 h from the hospital admission. The term HAP refers to both healthcare-acquired pneumonia and ventilator-associated pneumonias (VAP), with the latter being generally characterized by greater severity and worse prognosis¹. HAP occurs at a rate of 5-20/1,000 hospital admissions, being the second most common cause of nosocomial infection yet the first one in the intensive care unit (ICU) setting². The development of HAP has been also associated to a relevant mortality (from 20 to 70% according to different case series) and increment of duration of the hospitalization period with high costs for the healthcare system^{3,4}. The etiology of HAP varies depending on the hospital and geographic context but is predominantly characterized by nosocomial pathogens. These pathogens are often difficult to treat due to the prevalence and diversity of multi-drug resistance (MDR) mechanisms and their presence has been related to negative outcomes⁵⁻⁷. The latest European guidelines for the management of nosocomial pneumonia were published in 2017, offering recommendations based on the evidence available at the time⁸. However, the clinical management of these infections has evolved since then and the application of the guidelines recently showed limited efficacy in the treatment of HAP presenting with septic shock at the time of diagnosis⁹. The introduction of rapid diagnostic assays and next-generation antimicrobial agents deeply changed the management of HAP and VAP, allowing for precision medicine approaches and minimizing the overuse of broad-spectrum antibiotics, but the evidence

supporting the effectiveness of these methodologies is still limited¹⁰⁻¹². The present review aims to outline the complexity and heterogeneity of HAP with the objective to summarize the knowledge to assist intensive care physicians in the clinical management of these infections.

DEFINITION

As previously said, HAP indicates a wide group of pulmonary infections including different kind of conditions developing after 48 h in the hospital setting¹³. HAP is traditionally categorized in HAP and VAP, however also other subgroups have been proposed by literature.

Some American studies suggested the definition of healthcare-associated pneumonia in patient with the following risk factors: hospitalized for at least 2 days within the preceding 3 months; residents in extended care facilities; undergoing chronic infusion therapy or dialysis. It was hypothesized that such patients had a high risk to be caused by MDR microorganisms¹⁴, however, recent European data found substantial similarities in the etiology of HCAP and community-acquired pneumonia, challenging the definition of HCAP itself¹⁵.

In recent years, an additional group of patients with severe HAP who ultimately require mechanical ventilation has been recognized and defined as ventilated hospital-acquired pneumonia (VHAP)¹⁶. Patients with VHAP have been shown to be more similar to those with VAP in terms of causative agents and prognosis and therefore warrant a differentiated clinical management approach^{8,17-19}.

Another category that has gained importance in recent years is ventilator-associated tracheobronchitis (VAT), acquired in the ICU and characterized by signs of respiratory infection without new radiologic infiltrates²⁰. The impact of this condition has been shown to be significant in terms of incidence; however, recent studies suggest an uncertain effect of this condition on prognosis and argue against the necessity of antibiotic treatment when this pathology is identified in intubated patients^{16,21}.

Finally, HAP has historically been defined as “early” or “late” depending on the time of onset from the admission into the hospital setting^{22,23}. A late onset of pneumonia was related to the risk of developing infections supported by MDRs, however, recent studies challenged this classification reporting similar etiologies in the two different groups^{7,24}. This difference has likely been progressively lost over time and may be linked to the global increase MDR microorganisms, which is reshaping the ecological balance within ICUs.

EPIDEMIOLOGY

HAP is a common complication of hospitalization, accounting for 22% of all hospital-acquired infections²⁵. In ordinary inpatient wards, the average incidence of HAP is estimated at 3 cases/1,000 hospital admissions, with a higher risk in elderly patients with underlying comorbidities and subjected to prior hospitalizations lasting more than 5 days²⁶. Conversely, most studies on HAP in critically ill patients focus on VAP, which weighs from 48 to 90% of HAP cases in ICUs²⁷. Non-ventilated patients are less likely to

develop HAP than ventilated patients, with a risk of 0.58 cases/1,000 patient-days, against an incidence rate ranging from 1.58 and 5.44 cases/1,000 ventilation days, depending on whether invasive or non-invasive ventilation is chosen²⁸. These data strongly suggest that intubation, rather than ventilation support itself, plays a key role in determining HAP risk in ICU patients while confirming that the incidence in non-ventilated patients is non-insignificant¹⁶.

Globally, VAP affects 9-27% of mechanically ventilated patients²⁹, with significant differences between case series. U.S. hospitals report an incidence of 1-2.5 cases/1,000 ventilator days³⁰, compared to 18.3 in Europe³¹, and 9-18.5 in Asia, depending on the country's income group³². These discrepancies reflect varying resource availability and challenges in establishing a standardized VAP definition³³. Incidence rates also vary depending on the underlying medical conditions of the patient, with respiratory comorbidities such as chronic obstructive pulmonary disease³⁴, acute respiratory distress syndrome³⁵, and severe cases requiring extracorporeal membrane oxygenation support³⁶ associated with a higher incidence of VAP. While older age is generally associated with greater comorbidities, age itself does not significantly increase VAP incidence rates, unlike male gender, active malignant neoplasia, and recent major trauma, which are independent risk factors within specific age groups^{37,38}.

Mortality due to VAP is difficult to quantify because of the time-dependent character of this condition, being associated with length of stay and days of mechanical ventilation; in fact, it is the patients who survive the longest

who have the highest risk of developing VAP. Moreover, once acquired, VAP delays the moment of ICU discharge, consensually increasing the overall daily hazard for ICU mortality, and death from all causes⁴. For this reason, the mortality for all causes associated with VAP ranges between 20% and 50%, according to different case series¹⁶, while mortality directly attributable to it is estimated to be between 9 and 13% according to recent meta-analyses³⁹. This discrepancy is due to the effect of randomization in reducing the impact of time-dependent biases and better discriminating between mortality from VAP and ICU death from other causes. Interestingly, the highest attributable mortality was observed in surgical patients with mid-range severity scores on admission⁴. Historically, VAP mortality is considered higher than that of HAP, as the latter includes patients who are not critically ill enough to require invasive mechanical ventilation⁴⁰. However, in critically ill patients, crude mortality is similar between HAP and VAP, suggesting that the incidence of HAP is more influenced by airway management invasiveness, while mortality is mostly related to patient comorbidities²⁷. Consistent with this, the highest mortality is observed in patients with HAP who required intubation because of the infection (VHAP), as this is a marker of failure to contain the infection and pneumonia progression⁴¹.

MICROBIAL ETIOLOGY AND RISK FACTORS FOR MDRS

Globally, the most frequently involved pathogens in the development of HAP are methicillin-resistant *Staphylococcus aureus*

(MRSA), *Pseudomonas aeruginosa*, *Klebsiella pneumoniae*, *Escherichia coli*, and *Acinetobacter baumannii*⁴². However, the relative prevalence of these microorganisms varies across different geographical regions. In the USA, *S. aureus* is by far the most frequently isolated microorganism among HAP patients (40%), *P. aeruginosa* is the second most common (16-19%, in patients with HAP and in those in the VAP subgroup, respectively), while *E. coli* and *K. pneumoniae* are found in 12 and 13% of cases, with a slight decrease in *E. coli* prevalence in VAP patients (8.7%)⁴³. In Western Europe⁴⁴, the most frequent pathogens are *P. aeruginosa* (18, 2-17.5%, in patients with HAP and VAP, respectively), *S. aureus* (12.1-12.2%), *K. pneumoniae* (10.3-6.9%), and *E. coli* (7.5-6.7%). However, in ICU patients, infections from *Enterobacter cloacae* (7.3%), *Serratia marcescens* (7%), and other non-fermenting Gram-negative bacilli such as *Stenotrophomonas maltophilia* and *A. baumannii*, responsible for 5.5% and 0.7% of VAP cases, respectively, also become significant⁴⁵. In addition, in other geographical areas like Eastern Europe, the frequency of infections from *A. baumannii* is very high, reaching up to 20%⁴⁶, justifying its inclusion among the microorganisms most involved in the etiology of HAP⁴².

In certain patient populations, such as those undergoing invasive mechanical ventilation or immuno-compromised individuals, viral or fungal etiology also becomes important⁴². The latter is a major concern in immunocompromised patients, with *Aspergillus* infection being the most common, as its proliferation is strongly associated with sustained neutropenia⁴⁷. Historically, the viruses most involved in HAP are the *influenza virus* and respiratory syncytial virus, with *adenovirus*, *rhinovirus*,

cytomegalovirus, metapneumovirus, and parainfluenza virus less commonly involved. Herpes simplex virus is also noteworthy. Still, its presence in the lower respiratory tract of ICU patients is difficult to interpret, as it could indicate infection, reactivation due to immunosuppression, or simply contamination from the upper respiratory tract^{37,48}. The advent of the severe acute respiratory syndrome coronavirus 2 pandemic has impacted the incidence of hospital infections, increasing the incidence of VAP³⁷. In this context, the most identified causative pathogens were Gram-negative bacteria from the *Enterobacteriaceae* family and *S. aureus* among Gram-positives. In these patients, factors such as increased sedation needs, prolonged invasive mechanical ventilation, the prone position, and immunosuppression caused by COVID-19 led to an increase in infections from MDR pathogens compared to the pre-pandemic period, with a particular rise in carbapenem-resistant *K. pneumoniae* and MRSA⁴⁹.

The impact of MDR HAP is largely influenced by local epidemiology, highlighting significant differences in the presence of MDR strains between Europe and the USA⁴⁶. In fact, the percentage of MRSA in Western Europe is around 16%, while in Eastern European countries and the USA, it reaches 38.6-40.1%, respectively. Among the *Enterobacteriales*, *K. pneumoniae* is a primary concern due to the development of carbapenemases, especially in Eastern Europe (23.6%), while the frequency of this resistant strain is less common in the rest of Europe and the USA, with percentages around 1%. The subtype of carbapenemase also appears to differ, with a predominance of OXA-48 and MBLs in Eastern Europe and KPC in other areas. This geographical region

is also concerning due to the higher prevalence of *P. aeruginosa* and *A. baumannii* resistant to meropenem, representing 51% and 90%, respectively⁴⁶.

In addition to local microbial ecology, the likelihood of developing VAP caused by MDR pathogens varies depending on several cumulative risk factors, such as the length of hospitalization and ICU stay, the timing of invasive ventilatory support, and previous exposure to antibiotic treatments⁵⁰. Typically, early-onset VAP, occurring within 4 days of initiating ventilatory support, is caused by non-MDR microorganisms found in the common oropharyngeal flora, while late-onset VAP is often caused by MDR pathogens⁴². Both the American¹⁹ and European⁸ guidelines have aimed to identify the risk factors for MDR to guide the empirical treatment of HAP but provide different recommendations. The American guidelines are more complex, distinguishing risk factors for HAP and VAP and considering more elements related with organ failure defined by a condition of shock, acute respiratory distress syndrome, or need for continuous renal replacement therapy. In contrast, the European guidelines are simplified, considering only a high prevalence of MDR microorganisms ($\geq 25\%$), and the severity of the patients according to the predicted mortality risk and the presence or absence of septic shock⁵¹. The definition of risk factors for MDRs in a life-threatening infection such as HAP is crucial to determine an appropriate empirical treatment. However, there is no conclusive evidence that these criteria are actually able to discriminate patients with HAP sustained by MDR and a recent study suggested that the guidelines' criteria may be lacking of accuracy⁵². Table 1 shows and

TABLE 1. MDR risk factors considered by American and European guidelines to guide the empirical antibiotic treatment of HAP

American (IDSA/ATS 2016)	European (ERS/ESICM/ ESCMID/ALAT 2017)
Recent exposure to antibiotics	Local ecology: prevalence of MDR isolates \geq 25%
Hospitalization period \geq 5 days	Severity: Mortality risk \geq 15% Presence or absence of septic shock
Organ failure severity: Shock ARDS Need for CRRT	Severity: Mortality risk \geq 15% Presence or absence of septic shock

HAP: hospital-acquired pneumonia; ARDS: acute respiratory distress syndrome; CRRT: continuous renal replacement therapy.

confronts the risk factors suggested by both European and American guidelines for HAP⁵³.

DIAGNOSIS

The diagnosis of HAP is based on three key elements: the presence of a clinical suspicion³ supported by imaging evidence of a newly detected infiltrate, and a positive microbiological culture test^{8,19}.

Clinical suspicion of infection arises from the appearance of at least one of the following: temperature $> 38^{\circ}\text{C}$, alteration in the white blood cell count, and in mental status. In this case, the presence of at least two ancillary criteria such as the appearance of purulent endotracheal secretions, dyspnea or tachypnea, rales or bronchial breath sounds, and worsening of respiratory exchange⁵⁴ increase the chance of pneumonia. However, none of these criteria, either alone or in association with evidence of an infiltrate on the chest

X-ray (CXR), are sufficient to make a diagnosis⁵⁵, as these findings lack sufficient specificity in critically ill patients⁵⁶. Scores like the clinical pulmonary infection score⁵⁷ aim to improve diagnostic accuracy by combining clinical, radiographic, and laboratory criteria. However, they are more useful for determining when to safely stop antibiotics⁵⁸ rather than for initiating therapy⁵⁹, which is why current guidelines^{8,19} do not recommend their use for diagnosis.

Conventionally, a CXR is performed when pneumonia is suspected to identify new infiltrates or signs of worsening, although the specificity and sensitivity of this test are not sufficient to avoid false negatives. In fact, no radiographic sign has a diagnostic accuracy $> 68\%$ ⁶⁰. On the other hand, a computed tomography scan can identify pneumonia with greater sensitivity⁶¹ and sometimes assist in identifying the causative microorganism⁶². However, due to high costs and increased radiation exposure, it cannot be used on a large scale⁶³. Recently, several studies have assessed the possibility of introducing lung ultrasound as an imaging technique, finding its sensitivity and specificity in detecting pneumonia to be superior to 90%^{64,65}.

In terms of microbiological diagnosis, the main variables to consider are the site of sample acquisition, which can be from the upper or lower respiratory tract, and the use of quantitative, semi-quantitative, or qualitative techniques to support the diagnosis. The acquisition of a sample from the lower airways involves invasive techniques, by means of fiberoptic bronchoscopy to perform procedures such as bronchial aspirate, protected specimen brush, or bronchoalveolar lavage

TABLE 2. Diagnostic threshold and relative performance of different techniques for microbiological diagnosis of HAP⁷²

Characteristic	BAS	PSB	BAL
Diagnostic threshold (UFC/mL)	10 ⁵	10 ³	10
Sensitivity (%)	76	66	73
Specificity (%)	75	90	82
Relative performance	Most sensitive	Most specific	Most accurate

HAP: hospital-acquired pneumonia; BAS: bronchial aspirate; PSB: protected specimen brush; BAL: bronchoalveolar lavage; UFC: colony-forming unity.

(BAL). These techniques allow direct visualization of the bronchi and the collection of a sufficient sample volume for additional investigations beyond culture tests, helping to reduce inappropriate use of antibiotics. On the other hand, the sample acquisition requires adequately trained personnel to minimize the risk of complications such as bleeding, pneumothorax, and barotrauma. The acquisition of an endotracheal aspirate is quicker and carries fewer complications, making it possible for less specialized personnel to perform it. However, it has a lower ability to differentiate between true pneumonia and microbial contamination or tracheo-bronchitis, posing a risk of unjustified antibiotic use⁶⁶. Since data do not show differences in outcomes when either method is applied⁶⁷, international guidelines are not in agreement: the European guidelines⁸ advocate for obtaining a sample using an invasive technique, while the American guidelines¹⁹ suggest collecting a sample from the upper airways. An intermediate approach between these strategies is the mini-BAL, which is performed obtaining a sample theoretically from the lower airways but without the use of an invasive tool like a bronchoscope. However, this technique still carries complications similar to those related to bronchoscope use and,

as it is performed with a blind catheter, does not provide full assurance of the site of sample acquisition⁶⁸. Finally, quantitative culture techniques are more reliable compared to qualitative ones, as the patient develops pneumonia when a pathogen reach concentrations in the lower airways ranging between 10³ and 10⁵ colony forming units/mL, depending on the acquiring method chosen⁶⁹. Diagnostic thresholds for each technique are resumed in table 2. On the other hand, observation under the microscope with Gram staining provides quick support for the diagnosis, but its negative result does not exclude VAP, due to its sensitivity and specificity characteristics of 68% and 95%, respectively⁷⁰.

To improve the accuracy of diagnostic methods, various biomarkers have been investigated: procalcitonin (PCT), C-reactive protein (CRP), soluble triggering receptor expressed on myeloid cells type 1, and the mid-region fragment of pro-adrenomedullin⁵³. However, none of these are deemed sufficiently reliable to be used as a gold standard for the identification of nosocomial pneumonia. Among the investigated factors, CRP appears to be the most robust parameter, particularly regarding the trend of its curve over time. In fact, kinetics of CRP in the days before VAP

diagnosis, namely, the slope of CRP, could be useful in VAP prediction, since an average increase in CRP of 1 mg/dL/day results in a 62% greater chance of infection when compared with a patient with no CRP increase⁷¹.

In recent years, several rapid molecular assays have been developed for the diagnosis of HAP, aiming to provide rapid pathogen identification and guide antibiotic treatment⁷². The most commonly used assays are based on polymerase chain reaction, allowing for the identification of the primary pathogens involved in nosocomial pneumonia and their main resistance mechanisms in < 1 h⁷³⁻⁷⁵. These techniques can be applied to any respiratory-derived microbiological sample and hold the promise of revolutionizing the approach to severe pneumonia and empirical treatment due to their high sensitivity and specificity. Nonetheless, the use of rapid diagnostic assays has also been shown to increase the risk of overdiagnosis and overtreatment, as they can detect DNA fragments from non-viable pathogens⁷⁶. Several ongoing studies are currently investigating the impact of these techniques on the incidence of negative outcomes and their ability to guide antibiotic therapy, but no conclusive results are available yet⁷⁷.

PATHOGENESIS AND PREVENTION

HAP occurs in debilitated patients who remain hospitalized for prolonged periods. The pathogenesis of this infection has been linked to bacterial translocation processes, which take place in these patients due to a weakening of the body's natural defense

mechanisms. It has been demonstrated that the translocation of bacterial species through micro-aspiration of material from the digestive tract or bloodstream plays a crucial role in the development of pneumonia. Studies on the pulmonary dysbiosis occurring in critically ill patients appear to support this mechanism⁷⁸.

In these cases, deep alterations in the respiratory microbiome have been observed in terms of absolute increase of the microbial burden, loss of biological diversity, and depletion of the protective commensal species that constitute the normal microbial flora of the respiratory system⁷⁹. Specifically, there is a progressive reduction in biodiversity, allowing the predominant pathogen to increase its biomass to the point of causing infection in a patient whose immune defenses are simultaneously weakened⁸⁰. Such alterations have shown a strong correlation with the development of HAP and circumstances that promote the aspiration of microorganisms from the oropharynx or digestive tract to the lower airways have been demonstrated to increase the likelihood of developing pneumonia⁸¹. Patients with swallowing impairment, ineffective cough reflex, as well as intubated patients, are therefore at high risk for the onset of HAP. For this reason, invasive mechanical ventilation represents a primary risk factor for nosocomial pneumonia, due to the need for endotracheal intubation, and sedative drugs which reduce their ability to cough and may lead to the development of VAP⁴⁵.

Therefore, the most effective preventive interventions are those aimed at avoiding

intubation, preferring non-invasive positive pressure ventilation strategies or the use of high-flow nasal oxygen^{82,83}, as well as those aimed at minimizing sedation^{84,85}, when applicable. In this context, protocols for light sedation obtained through multimodal strategies that favor dexmedetomidine and propofol over benzodiazepines⁸⁶ and that include daily awakening trials for the patient⁸⁷ are also recommended.

However, several other measures have proven effective in reducing the incidence of infection, although they have not demonstrated the same strength in other outcomes, such as the duration of mechanical ventilation, length of ICU stay, the need for antibiotic use, and mortality⁴². This is why the literature on HAP prevention appears difficult to interpret. As a result, American¹⁹ and European⁸ guidelines have adopted completely different approaches to the topic. The American guidelines chose not to issue any recommendation, as the Society for Healthcare and Epidemiology of America had already expressed on the subject in 2008 and 2014, with a further update in 2022⁸⁸; the European guidelines, on the other hand, sought to clarify some of the preventive measures with greater interpretative uncertainty, such as the use of 0.12-0.2% chlorhexidine in oral care and the use of selective oropharyngeal decontamination (SOD) and selective digestive decontamination (SDD) protocols⁵¹.

Indeed, the use of chlorhexidine has been associated with a significant reduction in pulmonary infections without affecting the use of antibiotics, length of stay, or ventilation times. However, this advantage was accompanied by a non-significant increase in

mortality^{89,90}, possibly due to the microaspiration of small amounts of disinfectant. Therefore, in the absence of clear clinical benefits and in the face of a potential increase in mortality, European guidelines do not recommend its use. Regarding antibiotic prophylaxis with topical application of tobramycin, colistin, and amphotericin B in the form of an oropharyngeal paste (SOD) and via nasogastric tube, in addition to intravenous administration of cefotaxime (SDD), there was a reduction in the incidence of pneumonia⁹¹ and mortality⁹². Therefore, European guidelines support the use of these prophylaxes, favoring SOD as it does not involve the use of intravenous antibiotics. However, to minimize the effects of these treatments on the potential emergence of antibiotic resistance, their use is recommended in regions where the occurrence of resistant strains is < 5%⁸.

The main measures explored for their potential role in nosocomial pneumonia prevention are resumed in table 3, aimed to provide the most comprehensive overview possible on the subject. Some of these strategies are included within bundles of care, which are sets of different techniques aimed at maximizing the reduction of the incidence of HAP, with particular reference to the subgroup of late-onset VAP⁹³. The efficacy of the individual techniques remains debated; however, their combination in bundles of care could be beneficial. There is no conclusive evidence about the impact on mortality, even given the presence of bundle application protocols that differ from center to center⁸⁸. Nevertheless, HAP bundles of care's ability to reduce the duration of invasive mechanical ventilation and the incidence of HAP has already been observed⁹⁴.

TABLE 3. Overview of the main preventive strategies for nosocomial pneumonia⁹¹

Intervention	Quality of evidence	Indication	Rational
Limit the use of invasive mechanical ventilation	High	Essential	High-flow nasal oxygen and non-invasive positive pressure ventilation might represent an alternative to invasive mechanical ventilation in absence of contraindications
Reduce sedation when possible	High	Essential	Use the minimum necessary sedation, preferring multimodal strategies with propofol and dexmedetomidine over benzodiazepines, and a light sedation protocol with daily interruptions
Change the ventilation circuit only when necessary	High	Essential	Changing the ventilation circuit at scheduled intervals has no impact on the incidence of pneumonia and leads to an unjustified increase in hospital costs
Prioritize enteral nutrition	High	Essential	Enteral nutrition is preferred over parenteral nutrition when possible
Oral care of the patient	Moderate	Essential	Daily brushing of the teeth and oral care without using chlorhexidine may have a preventive impact on pneumonia.
Head of the bed inclined at 30-45°	Low	Additional	Raising the patient's head reduces microaspiration of secretion and the incidence of pneumonia but has no impact on mortality
Antibiotic prophylaxis SOD (selective oral decontamination) and selective digestive decontamination	Moderate	Additional	The application of prophylaxis is justified in settings where the frequency of encountering resistant microorganisms is below 5%
Drainage of subglottic secretions	Moderate	Additional	The use of endotracheal tubes that allow for the drainage of subglottic secretions positively impacts the incidence of VAP, but not other outcomes ¹²⁹ and is justified in patients expected to undergo intubation for at least 48 h
Early tracheostomy	Moderate	Additional	It reduces the incidence of VAP but not mortality ¹³¹ ; its application should be evaluated on a case-by-case basis.
Assessment of the structure and pressure of the endotracheal tube cuff	Moderate	Not recommended	ultrathin polyurethane, tapered endotracheal tube cuffs, and automatic cuff pressure control has not shown benefits
Stress-ulcer prophylaxis	Moderate	Contraindicated	It does not impact pneumonia but may prevent gastrointestinal bleeding
Monitoring of residual gastric volume	Moderate	Contraindicated	The addition of this monitoring has not shown greater effectiveness compared to controls ¹⁴⁰

TREATMENT

The treatment of HAP/VAP presents a challenge that requires combining the administration of early and appropriate empiric therapy that can possibly be de-escalated to

targeted once microbiological test results are available. Nevertheless, delayed and inappropriate empirical therapy still remain frequent in clinical practice^{47,95}, being strongly correlated with the incidence of adverse outcomes⁹⁶. For such reason, both American and

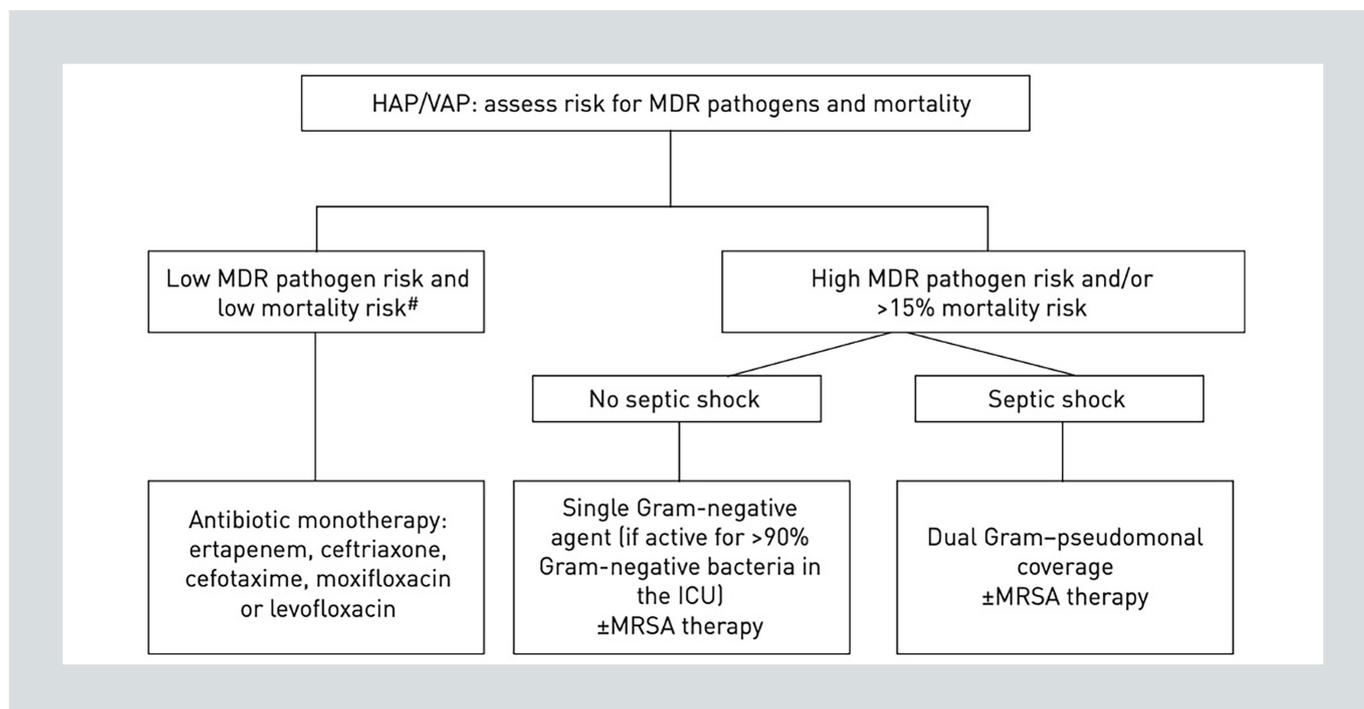


FIGURE 1. Treatment algorithm for empirical antibiotics in nosocomial pneumonia. #Low risk for mortality is defined as a $\leq 15\%$ chance of dying⁵³, a mortality rate that has been associated with better outcome using monotherapy than combination therapy when treating serious infection. HAP: hospital-acquired pneumonia; MDR: multidrug-resistant; MRSA: methicillin-resistant *Staphylococcus*. HAP: hospital-acquired pneumonia; MDR: multidrug resistant; MRSA: methicillin-resistant *Staphylococcus aureus*; VAP: ventilator-associated pneumonia (reprinted with permission from Torres et al.¹⁹).

European guidelines for HAP/VAP recommend risk-based treatment algorithm to help the prescription of an effective empirical therapy^{19,51}. The ERS/ESICM/ESCMID/ALAT guidelines⁸, calibrated to the European context, suggest empirical treatment focused on the use of narrow-spectrum anti-gram negative agents as the first line of treatment in low-risk patients, with the need to resort to MRSA agents or broader-spectrum anti-gram negative molecules (anti-pseudomonal agents) in case of the presence of risk factors for MDRs and/or presence of septic shock at the time of diagnosis of pneumonia (Fig. 1).

Table 4 summarizes the recommended treatment options and posology according to the 2017 ERS/ESICM/ESCMID/ALAT guidelines for the management of HAP by Torres et al.

The application of these recommendations has recently been shown to be effective in reducing the incidence of adverse outcomes in a historical cohort of critically ill patients; however, it failed to demonstrate any benefit in the population of the most severe patients that presented septic shock at the time of diagnosis⁹. This lack of efficacy could be related to a low statistical power of the study, due to an insufficient sample size. However, the need for dual anti-pseudomonal coverage, on which the recommendations of the European guidelines are based has been questioned in the last few years and recent evidence suggests that it does not result in outcome benefits by potentially leading to greater microbiome injury and therefore to increased risk of adverse events^{97,98}. Moreover, the posology recommended by the

TABLE 4. European recommendations for the HAP according to the presence/absence of risk factors

Risk	Recommended treatment	Recommended posology
Low MDR risk and low mortality risk ($\leq 15\%$ chance of dying)	Aminopenicillin plus β -lactamase inhibitor or second-generation cephalosporin or respiratory fluoroquinolone	Amoxicillin-clavulanate 2.2 g \times 3 Ampicillin sulbactam 3 g \times 3 Cefotaxime 2 g \times 3 Ceftriaxone 2 g/day Levofloxacin 750 mg Moxifloxacin 400 mg
High MDR risk/ or mortality risk and absence of septic shock	Anti-Pseudomonas β -lactams or carbapenems or fluoroquinolone Addition of coverage for MRSA if suspected	Piperacillin/tazobactam 4.5 g \times 3 Ceftazidime 2 g \times 3 Cefepime 2 g \times 2 Imipenem 1 g \times 3 Meropenem 1 g \times 3 Ciprofloxacin 400 mg \times 3 Levofloxacin 50 mg/day Vancomycin 1 g \times 2 Linezolid 600 mg \times 2
High MDR risk or mortality risk and presence of septic shock	Anti-Pseudomonas β -lactams or carbapenems + aminoglycoside or fluoroquinolone or if <i>Acinetobacter</i> is a possible pathogen Addition of coverage for MRSA if suspected	Piperacillin/tazobactam 4.5 g \times 3 Ceftazidime 2 g \times 2 Cefepime 2 g \times 2 Imipenem 1 g \times 3 Meropenem 1 g \times 3 Amikacin 15-20 mg/kg/day Gentamicin 5-7 mg/kg/day Tobramycin 1 \times 5-7 mg/kg/day Ciprofloxacin TDS 400 mg Levofloxacin 750 mg/day Colistin 2.5 mg \times (1.5 \times CrCl + 30) \times 2 Vancomycin 1 g \times 2 Linezolid 600 mg \times 2

MDR: multi-drug resistance, MRSA: methicillin-resistant *Staphylococcus aureus*.

guidelines has also been questioned, especially in critically ill patients, in whom dynamic changes in pharmacokinetics due to the underlying disease may require higher dosages, with the need for an initial loading dose and potential dose reduction in patients with hepatic or renal impairment⁹⁹⁻¹⁰¹. Since the publication of the guidelines, the therapeutic management of HAP has, therefore, deeply changed due to the gradual introduction of new evidence from literature, but at the same time, a true revolution is underway in the management of this pathology, driven by the market introduction of rapid microbiological diagnostic tests and novel molecules for antibiotic treatment¹⁰².

The use of ceftaroline and ceftobiprole has shown a good efficacy in Gram-positive respiratory infections of the critical patient, being a possible alternative to linezolid and vancomycin for targeted treatment in pneumonia sustained by MRSA^{103,104}. The biggest revolution in recent years, however, has involved new possibilities for treating infections with gram-negative MDR microorganisms¹⁰⁵. Cefiderocol, as well as the novel associations of β -lactams/ β -lactamase inhibitors and aztreonam/avibactam, has demonstrated efficacy comparable to the treatment regimens recommended by clinical guidelines, allowing for the effective treatment of) pathogens presenting different mechanisms of antimicrobial

TABLE 5. New molecules for the treatment of HAP

Antibiotic	Mechanism of action	Spectrum of activity	Resistance mechanisms
Ceftolozane/tazobactam	Fifth-generation cephalosporins + classical β -lactamase inhibitors	Broad-spectrum, including <i>Pseudomonas aeruginosa</i>	AmpC Ω -loop, PBP3, GalU; OXA-2/10, ESBLs, class A and B carbapenemases
Ceftazidime/avibactam	Cephalosporins + diazabicyclocotanes β -lactamase inhibitors	Broad-spectrum, including <i>Pseudomonas aeruginosa</i>	AmpC Ω -loop, MexAB \uparrow , PBP3, GalU; OXA-2/10, GES, KPC, class B carbapenemases
Imipenem/relebactam	Carbapenems + diazabicyclocotanes β -lactamase inhibitors	Broad-spectrum	OprD-, MexAB \uparrow , MexST, ParRS, PBP2, PBP1a; Class A and B carbapenemases
Meropenem/vaborbactam	Carbapenems + boronic acid β -lactamase inhibitors	Broad-spectrum	OprD-, MexAB \uparrow , PBP3, GalU; Class A and B carbapenemases
Cefiderocol	Siderophore cephalosporins	Broad-spectrum	AmpC Ω -loop, PBP3, GalU; OXA-2/10, ESBLs, class A and B carbapenemases
Aztreonam/avibactam	Monobactams + diazabicyclocotanes β -lactamase inhibitors	Limited-spectrum	MexAB \uparrow , PBP3, GalU; ESBLs and class A carbapenemases
Cefepime/zidebactam	Cephalosporins + diazabicyclocotanes β -lactamase and PBP2 inhibitors	Broad-spectrum	MexXY \uparrow , MexAB \uparrow , PBP3, GalU, PBP2; ESBLs, class A and B carbapenemases
Cefepime/taniborbactam	Cephalosporins + boronic acid β -lactamase inhibitors including MBLs	Broad-spectrum	MexXY \uparrow , MexAB \uparrow

HAP: hospital-acquired pneumonia; PBP: penicillin binding protein; MBL: metallo- β -lactamase; AmpC: ampicillin Class C resistant β -lactamase; GalU: α galactosidase; OXA: oxacylline β -lactamase; ESBL: extended-spectrum β -lactamase; Mex: multi-drug efflux resistant mechanism; GES: guiana extended spectrum β -lactamase; KPC: *Klebsiella pneumoniae* carbapenemase; ParRS: *Pseudomonas aeruginosa* resistance regulator system.

resistance¹⁰⁶⁻¹⁰⁹. The use of such molecules has already modified the approach to severe infections sustained by the, so called, difficult-to-treat pathogens, and recently both Spanish and European guidelines have included them as first lines or alternative treatment options^{110,111}. Table 5 summarizes the principal novel drugs that have been approved for the treatment of resistant enterobacterales and non-fermenting Gram-negative bacteria. The mechanisms of action, along with the antimicrobial spectrum and the possible mechanisms of drug resistance, are reported.

In recent years, the use of inhaled antibiotic therapy with colistin and aminoglycosides has been proposed for the management of

intubated patients with HAP/VAP, aiming to achieve efficacy at the pulmonary site while reducing the risk of systemic side effects and cross-resistance associated with these drugs^{112,113}. However, the overall quality of the available evidence is low and, to date, no recommendations can be made for the routine use of these strategies for the prevention and treatment of HAP^{114,115}.

In addition to selecting the appropriate molecule, however, data from the literature emphasize the importance of developing antimicrobial stewardship programs based on knowledge of local ecology, risk factors associated with the patient's history, and the appropriate timing of antibiotic treatment^{116,117}. This should include

proper de-escalation from empirical therapy and an adequate duration of targeted treatment. It has been demonstrated that a 7-day treatment regimen is sufficient for most cases of HAP, except for infections caused by MRSA, fungi, and complicated infections which may require longer treatment periods¹¹⁸. The use of unnecessary antibiotic treatment must be strictly avoided, as it has been associated with the emergence of antimicrobial resistance and an increased incidence of adverse clinical outcomes^{119,120}. Furthermore, the use of inflammatory biomarkers such as CRP and PCT has been investigated to guide de-escalation or discontinuation of therapy. However, while their trends may provide clinicians with insights into disease progression, there are no clear thresholds for their use in this.

CONCLUSION

The definition of HAP itself includes a multiplicity of clinical entities with different epidemiology and prognostic impact. The key challenges in its management include identifying risk factors, ensuring early diagnosis, implementing effective preventive strategies, and optimizing empirical and targeted antimicrobial therapy. The development of knowledge in this area is profoundly changing our approach to HAP, yet much of the evidence regarding new diagnostic and therapeutic possibilities lacks a solid foundation, and future studies will be needed to provide for new recommendations.

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REFERENCES

1. Chastre J, Luyt CE. Does this patient have VAP? *Intensive Care Med.* 2016;42:1159-63.
2. Gamazo JJ, Candel FJ, González Del Castillo J. Nosocomial pneumonia: current etiology and impact on antimicrobial therapy. *Rev Esp Quimioter.* 2023;36 Suppl 1:9-14.
3. Leone M, Bouadma L, Bouhemad B, Brissaud O, Dauter S, Gibot S, et al. Brief summary of French guidelines for the prevention, diagnosis and treatment of hospital-acquired pneumonia in ICU. *Ann Intensive Care.* 2018;8:104.
4. Melsen WG, Rovers MM, Groenwold RH, Bergmans DC, Camus C, Bauer TT, et al. Attributable mortality of ventilator-associated pneumonia: a meta-analysis of individual patient data from randomised prevention studies. *Lancet Infect Dis.* 2013;13:665-71.
5. Denis JB, Lehingue S, Pauly V, Cassir N, Gainnier M, Léone M, et al. Multidrug-resistant *Pseudomonas aeruginosa* and mortality in mechanically ventilated ICU patients. *Am J Infect Control.* 2019;47:1059-64.
6. Barbier F, Luyt CE. Understanding resistance. *Intensive Care Med.* 2016;42:2080-3.
7. Martin-Loeches I, Deja M, Koulenti D, Dimopoulos G, Marsh B, Torres A, et al. Potentially resistant microorganisms in intubated patients with hospital-acquired pneumonia: the interaction of ecology, shock and risk factors. *Intensive Care Med.* 2013;39:672-81.
8. Torres A, Niederman MS, Chastre J, Ewig S, Fernandez-Vandellos P, Hanberger H, et al. International ERS/ESICM/ESCMID/ALAT guidelines for the management of hospital-acquired pneumonia and ventilator-associated pneumonia: Guidelines for the management of hospital-acquired pneumonia (HAP)/ventilator-associated pneumonia (VAP) of 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). *Eur Respir J.* 2017;50:1700582.
9. Calabretta D, Cilloniz C, Gabarrus A, Motos A, Galli F, Ferrer M, et al. Impact of empirical treatment recommendations from 2017 European guidelines for nosocomial pneumonia. *Chest.* 2024;0012-3692(24)05398-4.
10. Papan C, Meyer-Buehn M, Laniado G, Nicolai T, Griese M, Huebner J. Assessment of the multiplex PCR-based assay Unyvero pneumonia application for detection of bacterial pathogens and antibiotic resistance genes in children and neonates. *Infection.* 2018;46:189-96.
11. Abbas M, Paul M, Huttner A. New and improved? A review of novel antibiotics for Gram-positive bacteria. *Clin Microbiol Infect.* 2017;23:697-703.
12. Bassetti M, Mularoni A, Giacobbe DR, Castaldo N, Vena A. New antibiotics for hospital-acquired pneumonia and ventilator-associated pneumonia. *Semin Respir Crit Care Med.* 2022;43:280-94.

13. Modi AR, Kovacs CS. Hospital-acquired and ventilator-associated pneumonia: diagnosis, management, and prevention. *Cleve Clin J Med*. 2020;87:633-9.
14. Falcone M, Venditti M, Shindo Y, Kollef MH. Healthcare-associated pneumonia: diagnostic criteria and distinction from community-acquired pneumonia. *Int J Infect Dis*. 2011;15:e545-50.
15. Polverino E, Torres A, Menendez R, Cillóniz C, Valles JM, Capelastegui A, et al. Microbial aetiology of healthcare associated pneumonia in Spain: a prospective, multicentre, case-control study. *Thorax*. 2013;68:1007-14.
16. Ferrer M, Torres A. Epidemiology of ICU-acquired pneumonia. *Curr Opin Crit Care*. 2018;24:325-31.
17. Ferrer M, Liapikou A, Valencia M, Esperatti M, Theessen A, Antonio Martínez J, et al. Validation of the American Thoracic Society-infectious diseases society of America guidelines for hospital-acquired pneumonia in the intensive care unit. *Clin Infect Dis*. 2010;50:945-52.
18. Giunta V, Ferrer M, Esperatti M, Ranzani OT, Saucedo LM, Bassi GL, et al. ICU-acquired pneumonia with or without etiologic diagnosis: a comparison of outcomes. *Crit Care Med*. 2013;41:2133-43.
19. Kalil AC, Metersky ML, Klompas M, Muscedere J, Sweeney DA, Palmer LB, et al. Management of adults with hospital-acquired and ventilator-associated pneumonia: 2016 clinical practice guidelines by the infectious diseases society of America and the American thoracic society. *Clin Infect Dis*. 2016;63:e61-111.
20. Martín-Loeches I, Povoia P, Rodríguez A, Curcio D, Suarez D, Mira JP, et al. Incidence and prognosis of ventilator-associated tracheobronchitis (TAVeM): a multicentre, prospective, observational study. *Lancet Respir Med*. 2015;3:859-68.
21. Rouzé A, Martín-Loeches I, Povoia P, Makris D, Artigas A, Bouchereau M, et al. Relationship between SARS-CoV-2 infection and the incidence of ventilator-associated lower respiratory tract infections: a European multicenter cohort study. *Intensive Care Med*. 2021;47:188-98.
22. Langer M, Cigada M, Mandelli M, Mosconi P, Tognoni G. Early onset pneumonia: a multicenter study in intensive care units. *Intensive Care Med*. 1987;13:342-6.
23. Wilke M, Grube R. Update on management options in the treatment of nosocomial and ventilator assisted pneumonia: review of actual guidelines and economic aspects of therapy. *Infect Drug Resist*. 2013;7:1-7.
24. Martín-Loeches I, Torres A, Rinaudo M, Terraneo S, De Rosa F, Ramirez P, et al. Resistance patterns and outcomes in intensive care unit (ICU)-acquired pneumonia. Validation of European Centre for disease prevention and control (ECDC) and the centers for disease control and prevention (CDC) classification of multidrug resistant organisms. *J Infect*. 2015;70:213-22.
25. Magill SS, Edwards JR, Bamberg W, Beldavs ZG, Dumyati G, Kainer MA, et al. Multistate point-prevalence survey of health care-associated infections. *N Engl J Med*. 2014;370:1198-208.
26. Sopena N, Sabrià M. Multicenter Study of Hospital-Acquired Pneumonia in Non-ICU Patients. Available from: <https://www.chestjournal.org>
27. Esperatti M, Ferrer M, Theessen A, Liapikou A, Valencia M, Saucedo LM, et al. Nosocomial pneumonia in the intensive care unit acquired by mechanically ventilated versus nonventilated patients. *Am J Respir Crit Care Med*. 2010;182:1533-9.
28. Kohlenberg A, Schwab F, Behnke M, Geffers C, Gastmeier P. Pneumonia associated with invasive and noninvasive ventilation: an analysis of the German nosocomial infection surveillance system database. *Intensive Care Med*. 2010;36:971-8.
29. American Thoracic Society, Infectious Diseases Society of America. Guidelines for the management of adults with hospital-acquired, ventilator-associated, and healthcare-associated pneumonia. *Am J Respir Crit Care Med*. 2005;171:388-416.
30. Dudeck MA, Horan TC, Peterson KD, Allen-Bridson K, Morrell GC, Pollock DA, et al. National healthcare safety network (NHSN) report, data summary for 2009, device-associated module. *Am J Infect Control*. 2011;39:349-67.
31. Koulenti D, Tsigou E, Rello J. Nosocomial pneumonia in 27 ICUs in Europe: perspectives from the EU-VAP/CAP study. *Eur J Clin Microbiol Infect Dis*. 2017;36:1999-2006.
32. Bonell A, Azarrafiy R, Huong VTL, Le Viet T, Phu VD, Dat VQ, et al. A systematic review and meta-analysis of ventilator-associated pneumonia in adults in Asia: an analysis of national income level on incidence and etiology. *Clin Infect Dis*. 2019;68:511-8.
33. Ego A, Preiser JC, Vincent JL. Impact of diagnostic criteria on the incidence of ventilator-associated pneumonia. *Chest*. 2015;147:347-55.
34. Rouzée A, Cottreaux A, Nseir S. Chronic obstructive pulmonary disease and the risk for ventilator-associated pneumonia. *Curr Opin Crit Care*. 2014;20:525-31.
35. Forel JM, Voillet F, Pulina D, Gacouin A, Perrin G, Barrau K, et al. Ventilator-associated pneumonia and ICU mortality in severe ARDS patients ventilated according to a lung-protective strategy. *Crit Care*. 2012;16:R65.
36. Grasselli G, Scaravilli V, Di Bella S, Biffi S, Bombino M, Patroniti N, et al. Nosocomial infections during extracorporeal membrane oxygenation: incidence, etiology, and impact on patients' outcome. *Crit Care Med*. 2017;45:1726-33.
37. Stoclin A, Rotolo F, Hicheri Y, Mons M, Chachaty E, Gachot B, et al. Ventilator-associated pneumonia and bloodstream infections in intensive care unit cancer patients: a retrospective 12-year study on 3388 prospectively monitored patients. *Supportive Care Cancer*. 2020;28:193-200.
38. Dananché C, Vanhems P, Machut A, Aupée M, Bervas C, L'Héritier F, et al. Trends of incidence and risk factors of ventilator-associated pneumonia in elderly patients admitted to French ICUs between 2007 and 2014. *Crit Care Med*. 2018;46:869-77.
39. Melsen WG, Rovers MM, Koeman M, Bonten MJM. Estimating the attributable mortality of ventilator-associated pneumonia from randomized prevention studies. *Crit Care Med*. 2011;39:2736-42.
40. Kollef MH, Shorr A, Tabak YP, Gupta V, Liu LZ, Johannes RS. Epidemiology and outcomes of health-care-associated pneumonia: results from a large US database of culture-positive pneumonia. *Chest*. 2005;128:3854-62.
41. Talbot GH, Das A, Cush S, Dane A, Wible M, Echols R, et al. Evidence-based study design for hospital-acquired bacterial pneumonia and ventilator-associated bacterial pneumonia. *J Infect Dis*. 2019;219:1536-44.
42. Papazian L, Klompas M, Luyt CE. Ventilator-associated pneumonia in adults: a narrative review. *Intensive Care Med*. 2020;46:888-906.
43. Zilberberg MD, Nathanson BH, Puzniak LA, Shorr AF. Microbiology, empiric therapy and its impact on the outcomes of nonventilated hospital-acquired, ventilated hospital-acquired, and ventilator-associated bacterial pneumonia in the United States, 2014-2019. *Infect Control Hosp Epidemiol*. 2022;43:277-83.
44. Gallego-Berciano P, Parra LM, Gallego-Munuera M, Cantero M, León-Gómez I, Sastre-García M, et al. Encuesta de prevalencia de las infecciones relacionadas con la asistencia sanitaria y uso de antimicrobianos en los hospitales de España, 2022. *Bolet Epidemiol Semanal*. 2023;31:113-32.
45. Candel FJ, Salavert M, Estella A, Ferrer M, Ferrer R, Gamazo JJ, et al. Ten issues to update in nosocomial or hospital-acquired pneumonia: an expert review. *J Clin Med*. 2023;12:6526.
46. Sader HS, Streit JM, Carvalhaes CG, Huband MD, Shortridge D, Mendes RE, et al. Frequency of occurrence and antimicrobial susceptibility of bacteria isolated from respiratory samples of patients hospitalized with pneumonia in Western Europe, Eastern Europe and the USA: results from the SENTRY Antimicrobial Surveillance Program (2016-19). *JAC Antimicrob Resist*. 2021;3:dlab117.
47. Fine LS. Non-ventilator health care-associated pneumonia (NV-HAP): pathogenesis and microbiology of NV-HAP. *Am J Infect Control*. 2020;48:A7-9.
48. Liu Y, Di Y, Fu S. Risk factors for ventilator-associated pneumonia among patients undergoing major oncological surgery for head and neck cancer. *Front Med*. 2017;11:239-46.
49. Grasselli G, Scaravilli V, Mangioni D, Scudeller L, Alagna L, Bartoletti M, et al. Hospital-acquired infections in critically ill patients with COVID-19. *Chest*. 2021;160:454-65.

50. Aligui AA, Abad CL. Multidrug-resistant VAP before and during the COVID-19 pandemic among hospitalized patients in a tertiary private hospital. *Antimicrob Steward Healthc Epidemiol.* 2023;3:e192.
51. Martin-Loeches I, Rodriguez AH, Torres A. New guidelines for hospital-acquired pneumonia/ventilator-associated pneumonia: USA vs. Europe. *Curr Opin Crit Care.* 2018;24:347-52.
52. Dominedò C, Ceccato A, Niederman M, Cillóniz C, Gabarrús A, Martin-Loeches I, et al. Predictive performance of risk factors for multidrug-resistant pathogens in nosocomial pneumonia. *Ann Am Thorac Soc.* 2021;18:807-14.
53. Miron M, Blaj M, Ristescu AI, Iosep G, Avădanei AN, Iosep DG, et al. Hospital-acquired pneumonia and ventilator-associated pneumonia: a literature review. *Microorganisms.* 2024;12:213.
54. Horan TC, Andrus M, Dudeck MA. CDC/NHSN surveillance definition of health care-associated infection and criteria for specific types of infections in the acute care setting. *Am J Infect Control.* 2008;36:309-32.
55. Klompas M. Does this patient have ventilator-associated pneumonia? *JAMA.* 2007;297:1583-93.
56. Tejerina E, Esteban A, Fernández-Segoviano P, Frutos-Vivar F, Aramburu J, Ballesteros D, et al. Accuracy of clinical definitions of ventilator-associated pneumonia: comparison with autopsy findings. *J Crit Care.* 2010;25:62-8.
57. Pugin J, Auckenthaler R, Mili N, Janssens JP, Lew PD, Suter PM. Diagnosis of ventilator-associated pneumonia by bacteriologic analysis of bronchoscopic and nonbronchoscopic "blind" bronchoalveolar lavage fluid. *Am Rev Respir Dis.* 1991;143:1121-9.
58. Singh N, Rogers P, Atwood CW, Wagener MM, Yu VL. Short-course empiric antibiotic therapy for patients with pulmonary infiltrates in the intensive care unit. A proposed solution for indiscriminate antibiotic prescription. *Am J Respir Crit Care Med.* 2000;162:505-11.
59. Luyt CE, Chastre J, Fagon JY. Value of the clinical pulmonary infection score for the identification and management of ventilator-associated pneumonia. *Intensive Care Med.* 2004;30:844-52.
60. Wunderink RG, Woldenberg LS, Zeiss J, Day CM, Ciemins J, Lacher DA. The radiologic diagnosis of autopsy-proven ventilator-associated pneumonia. *Chest.* 1992;101:458-63.
61. Prendki V, Scheffler M, Huttner B, Garin N, Herrmann F, Janssens JP, et al. Low-dose computed tomography for the diagnosis of pneumonia in elderly patients: a prospective, interventional cohort study. *Eur Respir J.* 2018;51:1702375.
62. Douglas AP, Smibert OC, Bajel A, Halliday CL, Lavee O, McMullan B, et al. Consensus guidelines for the diagnosis and management of invasive aspergillosis, 2021. *Intern Med J.* 2021;51:143-76.
63. Brenner DJ, Hall EJ. Computed tomography—an increasing source of radiation exposure. *N Engl J Med.* 2007;357:2277-84.
64. Llamas-Álvarez AM, Tenza-Lozano EM, Latour-Pérez J. Accuracy of lung ultrasonography in the diagnosis of pneumonia in adults: systematic review and meta-analysis. *Chest.* 2017;151:374-82.
65. Xia Y, Ying Y, Wang S, Li W, Shen H. Effectiveness of lung ultrasonography for diagnosis of pneumonia in adults: a systematic review and meta-analysis. *J Thorac Dis.* 2016;8:2822-31.
66. Johanson WG. Nosocomial respiratory infections with gram-negative bacilli. *Ann Intern Med.* 1972;77:701.
67. Berton DC, Kalil AC, Teixeira PJZ. Quantitative versus qualitative cultures of respiratory secretions for clinical outcomes in patients with ventilator-associated pneumonia. *Cochrane Database Syst Rev.* 2014;2014:CD006482.
68. Fujitani S, Yu VL. Diagnosis of ventilator-associated pneumonia: focus on nonbronchoscopic techniques (nonbronchoscopic bronchoalveolar lavage, including mini-BAL, blinded protected specimen brush, and blinded bronchial sampling) and endotracheal aspirates. *J Intensive Care Med.* 2006;21:17-21.
69. Jourdain B, Novara A, Joly-Guillou ML, Dombret MC, Calvat S, Trouillet JL, et al. Role of quantitative cultures of endotracheal aspirates in the diagnosis of nosocomial pneumonia. *Am J Respir Crit Care Med.* 1995;152:241-6.
70. Ranzani OT, Motos A, Chiurazzi C, Ceccato A, Rinaudo M, Li Bassi G, et al. Diagnostic accuracy of Gram staining when predicting staphylococcal hospital-acquired pneumonia and ventilator-associated pneumonia: a systematic review and meta-analysis. *Clin Microbiol Infect.* 2020;26:1456-63.
71. Póvoa P, Martin-Loeches I, Ramirez P, Bos LD, Esperatti M, Silvestre J, et al. Biomarker kinetics in the prediction of VAP diagnosis: results from the BioVAP study. *Ann Intensive Care.* 2016;6:32.
72. Conway Morris A, Gadsby N, McKenna JP, Hellyer TP, Dark P, Singh S, et al. 16S pan-bacterial PCR can accurately identify patients with ventilator-associated pneumonia. *Thorax.* 2017;72:1046-8.
73. Paonessa JR, Shah RD, Pickens CI, Lizza BD, Donnelly HK, Malczynski M, et al. Rapid detection of methicillin-resistant *Staphylococcus aureus* in BAL: A pilot randomized controlled trial. *Chest.* 2019;155:999-1007.
74. Murphy CN, Fowler R, Balada-Llasat JM, Carroll A, Stone H, Akerele O, et al. Multicenter evaluation of the BioFire FilmArray pneumonia/pneumonia plus panel for detection and quantification of agents of lower respiratory tract infection. *J Clin Microbiol.* 2020;58:e00128-20.
75. Buchan BW, Windham S, Balada-Llasat JM, Leber A, Harrington A, Relich R, et al. Practical comparison of the BioFire FilmArray pneumonia panel to routine diagnostic methods and potential impact on antimicrobial stewardship in adult hospitalized patients with lower respiratory tract infections. *J Clin Microbiol.* 2020;58:e00135-20.
76. Bay P, Fihman V, Woerther PL, Peiffer B, Gendreau S, Arrestier R, et al. Performance and impact of rapid multiplex PCR on diagnosis and treatment of ventilated hospital-acquired pneumonia in patients with extended-spectrum β -lactamase-producing Enterobacterales rectal carriage. *Ann Intensive Care.* 2024;14:118.
77. Enne VI, Aydin A, Baldan R, Owen DR, Richardson H, Ricciardi F, et al. Multicentre evaluation of two multiplex PCR platforms for the rapid microbiological investigation of nosocomial pneumonia in UK ICUs: the INHALE WP1 study. *Thorax.* 2022;77:1220-8.
78. Sands KM, Wilson MJ, Lewis MA, Wise MP, Palmer N, Hayes AJ, et al. Respiratory pathogen colonization of dental plaque, the lower airways, and endotracheal tube biofilms during mechanical ventilation. *J Crit Care.* 2017;37:30-7.
79. Johnstone J, Meade M, Lauzier F, Marshall J, Duan E, Dionne J, et al. Effect of probiotics on incident ventilator-associated pneumonia in critically ill patients: a randomized clinical trial. *JAMA.* 2021;326:1024-33.
80. Roquilly A, Torres A, Villadangos JA, Netea MG, Dickson R, Becher B, et al. Pathophysiological role of respiratory dysbiosis in hospital-acquired pneumonia. *Lancet Respir Med.* 2019;7:710-20.
81. Zakharkina T, Martin-Loeches I, Matamoros S, Povoia P, Torres A, Kastelijn JB, et al. The dynamics of the pulmonary microbiome during mechanical ventilation in the intensive care unit and the association with occurrence of pneumonia. *Thorax.* 2017;72:803-10.
82. Klompas M. Prevention of intensive care unit-acquired pneumonia. *Semin Respir Crit Care Med.* 2019;40:548-57.
83. Sang L, Nong L, Zheng Y, Xu Y, Chen S, Zhang Y, et al. Effect of high-flow nasal cannula versus conventional oxygen therapy and non-invasive ventilation for preventing reintubation: a Bayesian network meta-analysis and systematic review. *J Thorac Dis.* 2020;12:3725-36.
84. Shehabi Y, Bellomo R, Kadiman S, Ti LK, Howe B, Reade MC, et al. Sedation intensity in the first 48 hours of mechanical ventilation and 180-day mortality: a multinational prospective longitudinal cohort study. *Crit Care Med.* 2018;46:850-9.
85. Devlin JW, Skrobik Y, Gélinas C, Needham DM, Slooter AJC, Pandharipande PP, et al. Clinical practice guidelines for the prevention and management of pain, agitation/sedation, delirium, immobility, and sleep disruption in adult patients in the ICU. *Crit Care Med.* 2018;46:1532-48.
86. Ouellette DR, Patel S, Girard TD, Morris PE, Schmidt GA, Truweit JD, et al. Liberation from mechanical ventilation in critically ill adults: an official American college of chest physicians/American thoracic society clinical practice guideline. *Chest.* 2017;151:166-80.

87. Fraser GL, Devlin JW, Worby CP, Alhazzani W, Barr J, Dasta JF, et al. Benzodiazepine versus nonbenzodiazepine-based sedation for mechanically ventilated, critically ill adults. *Crit Care Med*. 2013;41:S30-8.
88. Klompas M, Branson R, Cawcutt K, Crist M, Eichenwald EC, Greene LR, et al. Strategies to prevent ventilator-associated pneumonia, ventilator-associated events, and nonventilator hospital-acquired pneumonia in acute-care hospitals: 2022 update. *Infect Control Hosp Epidemiol*. 2022;43:687-713.
89. Klompas M, Speck K, Howell MD, Greene LR, Berenholtz SM. Reappraisal of routine oral care with chlorhexidine gluconate for patients receiving mechanical ventilation: systematic review and meta-analysis. *JAMA Intern Med*. 2014;174:751-61.
90. Zhao T, Wu X, Zhang Q, Li C, Worthington HV, Hua F. Oral hygiene care for critically ill patients to prevent ventilator-associated pneumonia. *Cochrane Database Syst Rev*. 2020;12:CD008367.
91. Li J, Xie D, Li A, Yue J. Oral topical decontamination for preventing ventilator-associated pneumonia: a systematic review and meta-analysis of randomized controlled trials. *J Hosp Infect*. 2013;84:283-93.
92. Price R, MacLennan G, Glen J, Collaboration S. Selective digestive or oropharyngeal decontamination and topical oropharyngeal chlorhexidine for prevention of death in general intensive care: systematic review and network meta-analysis. *BMJ*. 2014;348:g2197.
93. Burja S, Belec T, Bizjak N, Mori J, Markota A, Sinkovič A. Efficacy of a bundle approach in preventing the incidence of ventilator associated pneumonia (VAP). *Bosnian J Basic Med Sci*. 2018;18:105-9.
94. Martínez-Reviejo R, Tejada S, Jansson M, Ruiz-Spinelli A, Ramirez-Estrada S, Ege D, et al. Prevention of ventilator-associated pneumonia through care bundles: a systematic review and meta-analysis. *J Intensive Med*. 2023;3:352-64.
95. Evans L, Rhodes A, Alhazzani W, Antonelli M, Coopersmith CM, French C, et al. Surviving sepsis campaign: international guidelines for management of sepsis and septic shock 2021. *Intensive Care Med*. 2021;47:1181-247.
96. Bonine NG, Berger A, Altincatal A, Wang R, Bhagnani T, Gillard P, et al. Impact of delayed appropriate antibiotic therapy on patient outcomes by antibiotic resistance status from serious gram-negative bacterial infections. *Am J Med Sci*. 2019;357:103-110.
97. Barbier F, Dupuis C, Buetti N, Schwebel C, Azoulay É, Argaud L, et al. Single-drug versus combination antimicrobial therapy in critically ill patients with hospital-acquired pneumonia and ventilator-associated pneumonia due to Gram-negative pathogens: a multicenter retrospective cohort study. *Crit Care*. 2024;28:10.
98. Chanderraj R, Baker JM, Kay SG, Brown CA, Hinkle KJ, Fergle DJ, et al. In critically ill patients, anti-anaerobic antibiotics increase risk of adverse clinical outcomes. *Eur Respir J*. 2023;61:2200910.
99. Roberts JA, Abdul-Aziz MH, Lipman J, Mouton JW, Vinks AA, Felton TW, et al. Individualised antibiotic dosing for patients who are critically ill: challenges and potential solutions. *Lancet Infect Dis*. 2014;14:498-509.
100. Veiga RP, Paiva JA. Pharmacokinetics-pharmacodynamics issues relevant for the clinical use of beta-lactam antibiotics in critically ill patients. *Crit Care*. 2018;22:233.
101. Silva CM, Baptista JP, Santos I, Martins P. Recommended antibiotic dosage regimens in critically ill patients with augmented renal clearance: a systematic review. *Int J Antimicrob Agents*. 2023;59:106569.
102. Rodríguez A, Moreno G, Bodi M, Martín-Loeches I. Antibiotics in development for multiresistant gram-negative bacilli. *Med Intensiva*. 2022;46:630-40.
103. Torres A, Kuraieva A, Stone GG, Cillóniz C. Systematic review of ceftazolinolofosamil in the management of patients with methicillin-resistant *Staphylococcus aureus* pneumonia. *Eur Respir Rev*. 2023;32:230117.
104. Gatti M, Viaggi B, Rossolini GM, Pea F, Viale P. Targeted therapy of severe infections caused by *Staphylococcus aureus* in critically ill adult patients: a multidisciplinary proposal of therapeutic algorithms based on real-world evidence. *Microorganisms*. 2023;11:394.
105. Almyroudi MP, Chang A, Andrianopoulos I, Papatheanakis G, Mehta R, Paramythiotou E, et al. Novel antibiotics for gram-negative nosocomial pneumonia. *Antibiotics (Basel)*. 2024;13:629.
106. Falcone M, Tiseo G, Leonildi A, Della Sala L, Vecchione A, Barnini S, et al. Cefiderocol-compared to colistin-based regimens for the treatment of severe infections caused by carbapenem-resistant *Acinetobacter baumannii*. *Antimicrob Agents Chemother*. 2022;66:e0214221.
107. Bakdach D, Elajez R, Bakdach AR, Awaisu A, De Pascale G, Ait Hssain A. Pharmacokinetics, pharmacodynamics, and dosing considerations of novel β -Lactams and β -Lactam/ β -lactamase inhibitors in critically ill adult patients: focus on obesity, augmented renal clearance, renal replacement therapies, and extracorporeal membrane oxygenation. *J Clin Med*. 2022;11:6898.
108. Barbier F, Hraiech S, Kernéis S, Veluppillai N, Pajot O, Poissy J, et al. Rationale and evidence for the use of new beta-lactam/beta-lactamase inhibitor combinations and cefiderocol in critically ill patients. *Ann Intensive Care*. 2023;13:65.
109. Torres A, Wible M, Tawadrous M, Irani P, Stone GG, Quintana A, et al. Efficacy and safety of ceftazidime/avibactam in patients with infections caused by β -lactamase-producing Gram-negative pathogens: a pooled analysis from the Phase 3 clinical trial programme. *J Antimicrob Chemother*. 2023;78:2672-82.
110. Paul M, Carrara E, Retamar P, Tängdén T, Bitterman R, Bonomo RA, et al. European society of clinical microbiology and infectious diseases (ESCMID) guidelines for the treatment of infections caused by multidrug-resistant Gram-negative bacilli (endorsed by European society of intensive care medicine). *Clin Microbiol Infect*. 2022;28:521-47.
111. Pintado V, Ruiz-Garbajosa P, Aguilera-Alonso D, Baquero-Artigao F, Bou G, Cantón R, et al. Executive summary of the consensus document of the Spanish Society of infectious diseases and clinical microbiology (SEIMC) on the diagnosis and antimicrobial treatment of infections due to carbapenem-resistant Gram-negative bacteria. *Enferm Infecc Microbiol Clin (English ed)*. 2023;41:360-70.
112. Vardakas KZ, Mavroudis AD, Georgiou M, Falagas ME. Intravenous plus inhaled versus intravenous colistin monotherapy for lower respiratory tract infections: a systematic review and meta-analysis. *J Infect*. 2018;76:321-7.
113. Ehrmann S, Barbier F, Demiselle J, Quenot JP, Herbrecht JE, Roux D, et al. Inhaled amikacin to prevent ventilator-associated pneumonia. *N Engl J Med*. 2023;389:2052-62.
114. Buendía JA, Guerrero Patiño D, Zuluaga Salazar AF. Efficacy of adjunctive inhaled colistin and tobramycin for ventilator-associated pneumonia: systematic review and meta-analysis. *BMC Pulm Med*. 2024;24:213.
115. Hsu WH, Wu JY, Shiao BW, Huang PY, Chuang MH, Tsai YW, et al. The preventive effect of inhaled antibiotic against ventilator-associated pneumonia: a systematic review and meta-analysis. *Int J Antimicrob Agents*. 2024;64:107324.
116. Khan L, Naz F, Zeb M, Rehman SU. Antibiotic stewardship in hospital-acquired pneumonia. *Cureus*. 2024;16:e73623.
117. Moore LS, Baltas I, Amos J, Cooray M, Hughes S, Freeman R, et al. Antimicrobial stewardship markers and healthcare-associated pneumonia threshold criteria in UK hospitals: analysis of the MicroGuide™ application. *JAC Antimicrob Resist*. 2024;6:dlae058.
118. Metersky ML, Klompas M, Kalil AC. Less is more: a 7-day course of antibiotics is the evidence-based treatment for *Pseudomonas aeruginosa* ventilator-associated pneumonia. *Clin Infect Dis*. 2023;76:750-2.
119. Bassetti S, Tschudin-Sutter S, Egli A, Osthoff M. Optimizing antibiotic therapies to reduce the risk of bacterial resistance. *Eur J Intern Med*. 2022;99:7-12.
120. Saura O, Luyt CE. Procalcitonin as a biomarker to guide treatments for patients with lower respiratory tract infections. *Expert Rev Respir Med*. 2023;17:651-61.