Review Article

Diagnosis, management and treatment of nosocomial pneumonia in ICU: a narrative review

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Background and Objective: Despite recent advances in prevention, diagnosis, and treatment, hospital-acquired pneumonia (HAP) and ventilator-associated pneumonia (VAP) are overriding among the most life-threatening infections in hospitalized patients and they may have serious consequences in term of clinical and economic burdens. This review will focus on current epidemiology, diagnosis and treatment of HAP/VAP.

Methods: We performed literature research using the electronic database PubMed. The most relevant original articles, reviews and short communications were assessed through non-systematic literature search of the last 5 years up to June 2022.

Key Content and Findings: Though incidence of HAP/VAP has been decreasing in the last decades, they are still associated with high morbidity and mortality, prolonged hospitalization, extensive antimicrobial use and significant health-care costs. In the last years novel microbiological technics including molecular tests based on rapid immunoassay or nucleic acids using amplifications tests (NAATs) have been developed, generally characterized by rapid turnaround time and good sensitivity and specificity. Similar novel β-lactam/β-lactamase inhibitor combinations are available with significant activities against most of circulating multidrug-resistant organisms.

Conclusions: HAP/VAP still represents one of the most challenging complications affecting hospitalized patients. This narrative review may provide to clinicians a complete and updated summary on prevention, diagnosis and management of HAP/VAP.

Keywords: Pneumonia; fast microbiology; treatment; multidrug-resistant organisms

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Introduction

Hospital-acquired pneumonia (HAP) and ventilator-associated pneumonia (VAP) remain leading causes of morbidity and mortality despite recent advances in prevention, diagnosis, and treatment.

HAP is a lung infection occurring in the nosocomial setting which develops after 48 hours of hospitalization and does not appear in incubation at the hospital admission. Among nosocomial pneumonia, VAP is an infection developing in patients admitted to intensive care unit (ICU) after 48 hours of endotracheal intubation (1).

In order to standardize strategies for prevention of VAP, ventilator-associated events/conditions (VAE/VAC), and non-ventilator hospital-acquired pneumonia (NV-HAP),

from 2013 the Center of Disease Control and Prevention (CDC) had implemented new surveillance pneumonia definitions (2). Indeed, the definition of VAE/VAC—that is an increase in the daily minimum positive end expiratory pressure (PEEP) of ≥3 cmH_2O sustained for ≥2 days after ≥2 days of stable or decreasing daily minimum PEEP, or an increase in the fraction of inspired oxygen (FiO_2) of ≥20 points sustained for ≥2 days after ≥2 days of stable or decreasing daily minimum FiO_2 level—was created to frame the wide spectrum of complications related to mechanical ventilation (MV). Among them, infection-related ventilator-associated complications (IVAC) are considered VAE/VAC associated with possible pulmonary infection or non-pulmonary infection leading to respiratory deterioration (i.e., an abnormal temperature—<36 or >38 ℃—and/or white blood cell count—≤4,000 or ≥12,000 cells/mm^3—and administration of 1 or more new antibiotic for ≥4 days). Possible VAP (PVAP) refers to an IVAC with presumable lung infection supported by positive respiratory secretion or pleural fluid cultures for potentially pathogenic organisms, positive assays for respiratory viruses or *Legionella*, or suggestive histopathology concurrent with the IVAC (2,3). However, some studies observed that IVAC algorithm had low sensitivity and low positive predictive value for the identification of VAP, as well as it even captured critically ill patients needing enhanced ventilator support due to a range of conditions other than pneumonia (4-6). For the purpose of this paper, which focuses on diagnosis and management of pneumonia occurring in hospitalized and mechanically ventilated patients, we will still use the terms of HAP and VAP.

Both HAP and VAP are associated with high morbidity and mortality rates, prolonged length of stay, greater antimicrobial use, and significant healthcare costs (7). Several reports estimated that VAP prolongs the length of MV and hospitalization compared with similar patients without VAP. In addition, the cost associated with VAP has been estimated at approximately $40,000 per patient in United States (US) (8,9). Therefore, the prevention of VAP has become a crucial objective for most infection control programs (10). Indeed, ICU practice has evolved over the past 15 years targeting to the final goal to reduce as much as possible pneumonia development (11). We present the following article in accordance with the Narrative Review reporting checklist (available at https://jeccm.amegroups.com/article/view/10.21037/jeccm-22-32/rc).

Methods

In this review we will focus on epidemiology, microbiology diagnosis and approach to treatment for HAP and VAP. Literature search was performed through the scientific database PubMed and assessed literature of the last 5 years up to June 2022. The most relevant observational studies, randomized controlled trials (RCTs) and meta-analysis focusing on epidemiology, diagnosis and treatment were reviewed. Given the narrative nature of this review, non-systematic literature search was performed. For further details about search method see *Table 1*.

Epidemiology

To estimate the epidemiology of HAP and VAP is difficult due to several factors: differences in definitions and their application, diagnostic limitations, differences in microbiological sampling methods and different monitoring system across countries (1,11-13).

Though it is one of the most common nosocomial infections, epidemiologic data on HAP in non-ICU patients are limited and fragmented. Estimated incidence ranges from 5 to more than 20 cases per 1,000 admissions and from 2.5 to more than 6.1 cases per 1,000 non-ICU patients (14,15).

In the US, various formalized systems for ongoing national surveillance provide systematized information concerning infection rates, including pneumonia (16-18). One of the most recent large experience comes from a multicenter retrospective cohort study of 17,819 hospitalized patients from 253 US hospitals in 2012–2019 period (19). Among all patients enrolled, 26.5% had NV-HAP, 25.6% ventilated HAP (V-HAP), and 47.9% VAP. VAP was predominated in the Northeastern US and in large urban teaching hospitals. Instead, patients with NV-HAP pneumonia were older (mean age 66.7±15.1 years), whereas those with V-HAP were younger (59.7±16.6 years). Hospital mortality was higher among patients with V-HAP (29.2%) and lower in NV-HAP (11.7%), VAP accounted for 21.3%.

In Europe and incoming countries, no such reporting systems exist, and epidemiology of VAP/HAP in ICUs is inferred from national and international studies. Extensive, but old, data come from the EPIC study, conducted in 17 countries in Western Europe (Austria, Belgium, Denmark, Ireland, Finland, France, Germany, Greece, Italy, Luxembourg, The Netherlands, Norway, Portugal, Spain,

Table 1 Search strategy summary

Items	Specification
Date of search	February 2022–June 2022
Databases and other sources searched	PubMed
Search terms used	Hospital-acquired pneumonia OR HAP OR Ventilator-associated pneumonia OR VAP OR Nosocomial pneumonia*
	* AND risk factors
	* AND diagnosis OR molecular diagnostic test OR rapid diagnostic test
	* AND management OR antibiotic therapy OR antibiotic treatment
	* AND prevention OR preventive strategies OR surveillance
Timeframe	2017–2022
Inclusion and exclusion criteria	Inclusion criteria:
	Observational studies, RCTs, guidelines, narrative reviews, systematic reviews and meta-analysis
	English language
	Exclusion criteria:
	Case reports and case series
	Non-English language
Selection process	Each author independently searched and reviewed the relative literature and wrote a specific section of the paper (MM: introduction, methods, diagnosis; RP: epidemiology, microbiology, MR: risk factors, LB: therapeutic management). LB reviewed and homogenised the contents of all paragraphs

Sweden, Switzerland, and the United Kingdom) (12). A total of 1,417 ICUs provided 10,038 patient case reports. Pneumonia accounted for 46.9% of cases. No data on VAP/HAP classifications were provided, but ICU pneumonia was reported as a risk factor for death (12). A more recent report on pneumonia in European ICUs comes from the EU-VAP/CAP study (20). In this prospective observational study, 2,436 patients were enrolled from 27 ICUs in 9 European countries (Belgium, France, Germany, Greece, Italy, Ireland, Portugal, Spain, and Turkey). Among all patients enrolled, 34% developed pneumonia during ICU stay, with 18.3 VAP episodes per 1,000 ventilator-days. The authors marked the local differences in management of nosocomial pneumonia among all centers (20).

An extensive and recent report on nosocomial pneumonia in middle-income countries has been provided by the International Nosocomial Infection Control Consortium (INICC) (21). The INICC is an international research network comprising centers from Latin America, Eastern Europe, Eastern Mediterranean, Southeast Asia, and Western Pacific aimed to measure and prevent nosocomial infection (22). The Consortium collected prospective data on nosocomial infections from 861,284 patients hospitalized in 703 ICUs in a 6-year period from January 2010 to December 2015. The overall rate of VAP was 13.1 per 1,000 ventilator-days, higher than rates from hospitals in North America, Western Europe in the same period (0.9 per 1,000 ventilator-days) (21). Such higher rates could be due to the extremely low nurse-to-patient staffing ratios, the hospital overcrowding, the lack of medical supplies, and an insufficient number of experienced nurses or trained healthcare workers (23-25).

Overall, prevalence of VAP has decreased in the last decades, principally as a result of implementation of prevention protocols. Main novel strategies have been priority use of high-flow nasal oxygen or non-invasive positive pressure ventilation (NIPPV) in place of intubation/reintubation, reduced duration of sedation and MV, daily oral care, early enteral feeding, correct in-bed positioning and early mobilization (3,26).

Microbiology

The prevalence of bacterial microorganisms responsible

for HAP/VAP varies according to many factors. Among all the geographic areas, the length of hospital/ICU stays, the duration of MV in case of VAP, the previous exposure to antimicrobial therapies and also the local ecology (27-29), seem the most relevant, as exposed above.

In contrast to community-acquired pneumonia (CAP) in which the dominant typical pathogens are *Streptococcus pneumoniae*, *Mycoplasma pneumoniae* and *Haemophilus influenzae* (30), the aetiology of HAP/VAP is quite different. It is noteworthy that obtaining microbiological culture from the lower respiratory tract in patients developing VAP is relatively easy through the endotracheal tube. This collection appears more difficult to obtain in patients developing HAP, so microbial aetiologies remain poorly documented (20). However, microbial aetiologies in HAP and VAP are mostly identical (31).

In a previous cited large retrospective study conducted in the US (19), the most common pathogen in VAP/HAP was *Staphylococcus aureus* [both methicillin-resistant (MRSA) and susceptible (MSSA)]. Among Gram negative strains, *Pseudomonas aeruginosa* was the most prevalent, followed by *Klebsiella pneumoniae* and *Escherichia coli* (19). The SENTRY Antimicrobial Surveillance Program collected 12,851 bacterial isolates from patients hospitalized with VAP in US and European centres between 2009–2012. Also in this report *S. aureus* was the most frequent microorganism isolated in the US (34.8% of case). In Europe the aetiology was inverted and *P. aeruginosa* was the most frequent, followed by *S. aureus*.

More generally, Gram-negative organisms represented a large part of VAP/HAP aetiology, ranging from 61.5% and 76.1% of isolates in US and Europe respectively (32). Among Gram negative strains, *P. aeruginosa* was the most frequently isolated organism (20.9% for both regions). Other Gram negative isolates were: *Klebsiella* spp. accounted for 11% and 9% in Europe and US, respectively; *Enterobacter* spp. and *Escherichia coli* rates were similar in US and Europe (around 5.5–5.9% in both US and Europe). *Acinetobacter* spp. and *Stenotrophomonas maltophilia* were isolated in a minor number of cases (less than 11% in both US and Europe) (32).

The aetiology of infection appeared similar in another multicenter prospective cohort of 280 patients with VAP enrolled in 27 European ICUs (33). Overall, Enterobacterales accounted for 31% of cases, mainly *E. coli* and *Klebsiella* spp. *Pseudomonas aeruginosa* alone was again one of the most frequently pathogen isolated, accounted for 18% of cases. Among Gram positive strains, MRSA was isolated in 13% of patients enrolled (33). Similar results from other studies reported same pathogens responsible for VAP/HAP (34-36).

Regarding antimicrobial susceptibility profiles, accurate and complete data come once again from the SENTRY registry (37). In a recent report (38), a large number of bacterial isolates from respiratory cultures were collected from 2016 to 2019 from 12 hospitals in Western and Eastern Europe and in the US. *P. aeruginosa* susceptibility to piperacillin/tazobactam and meropenem was 75.4% and 76.9% in Western Europe, 57.4% and 48.3% in Eastern Europe and 76.1% and 74.8% in the US, respectively. Carbapenem resistance among Enterobacterales in 2019 was 1.7% and 2.2 % in the US and Western Europe, respectively. Carbapenem resistance was worryingly higher in Eastern Europe accounted for 16.6% of isolates. Only 10.4% of *A. baumannii* isolates from Eastern Europe were meropenem susceptible compared with 45.8% in Western Europe and 58.8% in the US. Methicillin-resistant *S. aureus* rates were 21.4% and 28.7% in Western and Eastern Europe, respectively, in the US these decreased from 44.8% in 2016 to 40.1% in 2019.

The high rate of complex antimicrobial susceptibility profiles in the US and Europe is of concern due to the high impact on morbidity and mortality and the difficult therapeutic strategies to use, as explained below (32,39-41).

Risk factors

The occurrence of VAP and HAP among hospitalized patients is the result of complex interactions among environmental exposure, host susceptibility and pathogen virulence.

The most common pathogenetic route of HAP/VAP is micro-aspiration of pathogens colonizing the oropharyngeal and gastroenteric tract. In this sense, patients with higher risk of aspiration (elderly, those with dysphagia, or mechanically ventilated) are more prone to develop HAP/VAP.

Host characteristics favoring HAP may be similar to CAP. Social-demographic features like age >60 years, male sex or poverty have been associated with pneumonia onset in hospitalized patients in many observational studies (42-44). Different chronic or degenerative comorbidities emerged as potential risk factors, too. Conditions bringing to impairment of lung structure or function like asthma, chronic obstructive pulmonary disease (COPD) and interstitial lung diseases are common predisposing factors

for HAP (44,45). Additionally, malnutrition, anemia, diabetes, chronic renal failure, cirrhosis, dementia or neurological impairment, recent thoracic surgery frequently affect hospitalized patients who develop pneumonia (45-49). Beyond host factors, hospital organization bringing to understaffing (e.g., like high bed-to-nurse ratio) or environmental conditions favoring close contacts (e.g., room crowding, permanence of caregivers) may promote HAP development (44). In a cohort study of 66,000 hospitalized patients, 314 developed NV-HAP. In this group, time-varying exposures associated with pneumonia onset were tube feeding [adjusted hazard ratio (aHR) =3.24; 95% CI: 2.17–4.83], impaired mental status (aHR =2.32; 95% CI: 1.63–3.31), and severely impaired mobilization (aHR =2.06; 95% CI: 1.50–2.84). The authors observed that the relation with NV-HAP came down within 7.1–13.2 days after these exposures were removed (47).

Although oro-tracheal intubation is an important intervention to give an effective life support of critically ill patients, onset of VAP is strictly related to the dwell time of the endotracheal tube. The presence of an artificial device modifies the mucosal defense function; organisms could directly pass through the gap between the airway and the tube, firstly colonizing and then infecting the lower respiratory tract. This implies that the pathogens involved in nosocomial pneumonia depend on the local epidemiology of the ICU.

Generally, a time of MV >2 weeks is considered a risk factor for nosocomial pneumonia, as well as the length of ICU stay and hospitalization lasting >5 days (33,50,51). Interestingly, a prospective study revealed that the risk of pneumonia increases along with the number of ventilation days, reaching an incidence of 65% at 30 days of MV (52). Different invasive operation may lead to anatomic barrier disruption and subsequently lower tract respiratory infection. Of these, needing of emergency intubation or re-intubation, tracheostomy, indwelling gastric tube for enteral nutrition, gastric aspiration, several changes of the ventilator circuit fiberoptic bronchoscopy, multiple central lines, acute renal replacement therapy may be associated with VAP according to several studies (51,53-55). In addition, complications such as pneumothorax or hemothorax may cause a direct lung parenchymal damage that could lead to pneumonia (55). Some core pharmacological treatments in ICU may also be detrimental, for instance stress ulcer prophylaxis with proton pump inhibitors, antacids or anti-H2 receptors, neuromuscular blockers, excessive sedation, steroids as well as antibiotic therapy in the previous 90 days which is also involved in multi-drug resistant organisms (MDRO) selection (51).

Some patient baseline characteristics are significantly involved in VAP development. Age ≥60 years is considered an independent risk factor for VAP development (56,57), and the risk is directly proportional to 1-year increase in age (58).

Several studies identified male gender as a specific risk factor (59-61). To date, it is unclear how sex could impact on VAP development, although some authors hypothesized that differences in hormones and immune responses may be involved (62). Of note, conditions that lead to a decreased pulmonary function are generally considered as risk factors. Firstly, active smoking, and especially patients with COPD were 2.35 times more likely to develop VAP compared with general population in one study (58). Moreover, other extra-pulmonary diseases such as diabetes, chronic renal failure or coronary disease are responsible for an increased risk (58). Indeed, these conditions are linked to a certain degree of immunosuppression, making the patient more susceptible to infections.

Several studies reported a strict connection between disorders of consciousness and early VAP onset (56,63,64). In fact, such condition determines loss of physiological reflexes, which are involved in coughing/swallowing and may lead to gastric aspiration. Particularly, comatose patients are strongly susceptible to VAP development and subsequent poor outcome (57).

Additionally, it is well known that burn patients are at high risk of pneumonia. Inhalational injury causes a direct lung damage consisting in natural barrier disruption and increased vascular permeability. Therefore, patients affected by inhalational injury have a two-fold increased risk of VAP if compared to patients without airwaves damages (65). However, pneumonia remains the most frequent complication after burn, even in patients without inhalational injury reaching an incidence of 65% (66). Sen *et al.* (65) demonstrated that there is a direct connection between the risk of VAP and the total burn surface area. In addition, coagulopathy, expressed by International Normalized Ratio (INR) elevation, seems to be a factor involved in pneumonia onset (67).

Diagnosis

Diagnosis of HAP is challenging. Clinical findings are typically non-specific and multiple similar non-infectious processes should be considered for differential diagnosis or

may overlap.

Common criteria for diagnosis of HAP/VAP are based on a combination of new and/or progressive lung infiltrates on chest radiograph plus two or more additional criteria that include fever (>38.5 ℃) or hypothermia; leukocytosis, purulent tracheobronchial secretions and reduction of partial pressure of oxygen (PaO_2)/FiO_2 ratio of at least 15% in the last 48 hours. Although these criteria are commonly wide accepted, their diagnostic accuracy is not completely satisfactory. In a study performed on post-mortem biopsies of patients with suspected VAP, the presence of infiltrates on the chest radiograph and two of three clinical criteria (leukocytosis, purulent secretions, fever) had a sensitivity of 69% and a specificity of 75% in diagnosing VAP (68).

Several scores have been evaluated and used to help clinicians in the diagnosis of VAP. These combine clinical, radiological and microbiological aspects. One study comparing most of available scores found that the incidence of VAP ranged from 4% to 42% and when more stringent criteria were used, a delay on antibiotic treatment was noted as well as a negative impact on mortality (69).

Several biomarkers were proposed to assist clinicians in the diagnosis of HAP/VAP. The most studied one is procalcitonin (PCT). PCT is a precursor of calcitonin secreted by thyroidal C cells normally undetectable in healthy individuals. During bacterial infections it is typically released in the bloodstream.

The culture of specimens from the lower respiratory tract (i.e., bronchial aspirate, broncho-alveolar lavage) is currently considered the gold standard for microbial diagnosis of pneumonia. Moreover, quantitative or semiquantitative culture based on the bacterial load, can help to distinguish pathogens from contaminants and make a correct diagnosis (70). However, the approach based on cultural methods has some limitations including the long turnaround time and the low sensitivity, especially when cultures are obtained from patients receiving antibiotic treatment (71). These two limitations may be overcome with the use of tests based on rapid immunoassay or nucleic acids amplifications tests (NAATs) which in turn are limited by the low number of pathogens detected and the high costs. A number of tests are available (71), generally characterized by rapid turnaround time and good sensitivity and specificity. For instance, studies using multiplex molecular test panels estimated a potential adjustment of antibiotic therapies in more than 70% of patients with respiratory tract infection, including discontinuation or de-escalation in 48.2% of patients, resulting in an average saving of 6.2 antibiotic days/patient (72). Therefore, the implementation with these tests of an antimicrobial stewardship program may compensate the high costs of the tests.

Principles of antimicrobial therapeutic management

Currently, the appropriate time to start antibiotic treatment in patients with HAP/VAP represents a challenge for clinicians. If there is general agreement on administration of antibiotics without delay in presence of signs of sepsis or shock, there are concerns about early antibiotic introduction in all patients with HAP/VAP. Indeed, early initiation of broad-spectrum antibiotic treatment is considered controversial due to difficulties in diagnosis of pneumonia and limited yield of microbiological tests, along with the risks of prolonged antibiotic exposure. For these reasons, last guidelines do not recommend a specific time-point to start antibiotic therapy (73,74). In clinically stable patients, a reasonable approach could comprise a watchful waiting while obtaining more clinical, laboratory and microbiological information to support HAP/VAP diagnosis.

In addition to clinical judgment, PCT testing has been proposed for driving antibiotic management of pneumonia. Actually, due to its rapid release in course of bacterial infection, PCT has been considered a helpful marker to differentiate bacterial from viral origin of low tract respiratory infections (LTRI), which may be critical for the decision to start antibiotic therapy. However, a clear PCT cut-off to rule out non-bacterial pneumonia has not been defined yet (75). A recent systematic review and metanalysis assessing clinical criteria versus PCT-driven approach to antibiotic initiation in critically ill patients, did not show differences in short-term mortality rate (76). As strong evidence on use of PCT to guide initiation of empirical therapy in VAP/HAP is still missing, recent guidelines discourage use of PCT associated with clinical criteria to start antibiotic therapy, particularly if sepsis or septic shock are suspected (74,77).

On the other hand, PCT seems a promising tool to guide cessation of antibiotic treatment. Lam *et al.* (76) observed a lower rate of mortality and antibiotic consumption using PCT for stopping antibiotics instead of using clinical judgment alone. A patient-level meta-analysis on 11 RCTs investigated safety of PCT-guided antibiotic strategy on mortality of ICU patients with infections, of which approximately 50% were LTRI. Patients managed with

PCT showed significant lower 30-day mortality and a reduction of antibiotic consumption of 1.19 days. Similar results were observed in the subgroup with LTRI, even if reduction of mortality was not significant (78). Another patient-level meta-analysis based on 26 RCTs evaluated the role of PCT in patients with acute respiratory infections in different clinical settings. Use of PCT correlated with significant reduction of antibiotic exposure of 2.4 days and of antibiotic-related adverse events. Among patients with VAP (6%), PCT use was associated with shorter duration of antibiotic treatment (2.22 days less) with a non-significant reduction in 30-day mortality (79). Finally, a randomized trial investigating PCT on VAP observed that PCT testing increased 28-day antibiotic-free survival after VAP onset [13 (range, 2–21) versus 9.5 (range, 1.5–17) days] with a consequent reduction of antibiotic consuming of 27% without affecting mortality (80). A reasonable strategy for management of HAP/VAP may include initial PCT testing then followed up every 48–72 hours in order to support the decision to continue or withdrawal antibiotics.

ERS/ESICM/ESCMID/ALAT for HAP/VAP guidelines encourage use of serial PCT determinations for stopping therapy in those conditions where safety of a short-course of antibiotics has not been established like immunocompromised patients, infections caused by multi-drug resistant (MDR) pathogens and in patients receiving inappropriate empirical therapy (73).

Choice of empirical therapy should be based on clinical severity, host factors and risk factors for MDRO.

The Clinical Pulmonary Infection Score (CPIS) has been adopted for assessing severity of VAP, while no clinical severity scores are well validated for HAP non-VAP. However, experts agree that presence of septic shock and need of ventilatory support in patients with HAP are the most effective conditions to consider because of their higher mortality (74). Patient evaluation should also highlight underlying conditions promoting severe infection like immunosuppression state or structural lung diseases.

Selection of initial antibiotics should take into account local epidemiology of antimicrobial resistance. In settings where prevalence of resistant bacteria overcomes 10–30%, empirical therapy should include coverage for MDR pathogens. Individual risk factors for MDR should be also considered, i.e., previous antibiotic exposition, prolonged hospitalization (>5 days) and prior colonization/infection with MDRO. In mild early episodes (within 5 days of hospital admission and/or intubation) occurring in patients at low risk for MDRO, a narrow-spectrum antibiotic therapy is recommended, possibly a monotherapy covering MSSA and Gram negatives.

In late HAP/VAP, a broad-spectrum antibiotic therapy with Gram positive coverage, particularly against MRSA, and at least one agent against *P. aeruginosa* and other Gram negatives is recommended. Combination of two anti-Gram negative antibiotics are suggested in patients with very severe illness or with suspected involvement of resistant pathogens in order to rise the probability of administering at least one *in vitro* active drug. In patients colonized with MDR bacteria, e.g., carbapenem-resistant Enterobacterales (CRE), the burden of colonization and the clinical severity should support the choice to include anti-CRE agent in the empirical regimen (81). Administration of empirical anti-pseudomonas combination therapy has demonstrated to improve survival of patients with bacteremic *P. aeruginosa* pneumonia rather than monotherapy (82). Addition of inhaled antibiotics to systemic therapy is currently controversial and actually it has not demonstrated to improve survival in patients with VAP. Whereas intravenous aminoglycosides and polymyxins are not recommended in guidelines due to their high renal toxicity and low tissue exposure in critically ill patients, use of inhaled aminoglycosides and polymyxins in association with their intravenous formulations may be confined to patients with MDR infections an no other therapeutic options.

Table 2 shows recommendations about antibiotic treatment for HAP and VAP according to the most updated international guidelines. Recent evidence from real-life experiences is raising concerns about risk of broad-spectrum antibiotic overuse following guideline recommendations, underlying the need of an accurate patient selection based on risks of MDR infection (83).

More recently, the range of frontline therapies for HAP/VAP has been widened, based on pivotal trials investigating new agents for MDR organisms. Ceftobiprole is a fifth-generation cephalosporin with activity against some Gram negative and Gram positive bacteria, including MRSA. Use of ceftobiprole has been authorized in European Union, Switzerland and Canada for CAP and HAP, but not for VAP (84).

New antibiotics targeting MDR Gram negative bacilli have recently received FDA and EMA approval for HAP/VAP.

As robust data confirmed its superiority versus old drugs, ceftazidime/avibactam has been considered a first-line agent for the treatment of severe infections sustained by KPC- and OXA48-like producing Enterobacterales and *P. aeruginosa* (85,86). In addition, in combination with

Table 2 Approach to empirical therapy for HAP/VAP

Without risk factors for MDR and low mortality risk	With risk factors for MDR and/or high mortality risk
Monotherapy covering MSSA and *Pseudomonas* spp (e.g., piperacillin/tazobactam, cefepime, levofloxacin, imipenem, or meropenem)	(I) Anti-MRSA agent (e.g., linezolid, ceftobiprole[#]) +
	(II) Antipseudomonal agents of different classes (e.g., piperacillin/tazobactam, cefepime, ceftazidime, ceftolozane-tazobactam, fluoroquinolone, meropenem, imipenem, aminoglycoside, aztreonam) or
	(III) Agent with antiCRE* activity (e.g., ceftazidime-avibactam[§], meropenem-vaborbactam, imipenem-relebactam) or
	(IV) Agent with activity against *Acinetobacter baumannii*° (e.g., ampicillin/sulbactam, cefiderocol)

[#], not indicated in case of VAP; *, the choice of drugs with antiCRE activity should be made upon the presence of specific risk factors, rectal carriage status and taking into account the local or center-specific epidemiology (i.e., prevalence of infections caused by CRE and most common type of carbapenemase between OXA-48, KPC and MBLs); [§], consider combination treatment when ceftazidime-avibactam is used in case of VAP; °, mainly based on center-specific epidemiology, previous colonization or infection. HAP, hospital-acquired pneumonia; VAP, ventilator-associated pneumonia; MDR, multi-drug resistant; MSSA, methicillin-susceptible *S. aureus*; MRSA, methicillin-resistant *S. aureus*; CRE, carbapenem-resistant Enterobacterales.

aztreonam, ceftazidime/avibactam retains an activity against MBL-producing Gram negative (87), thus it has been also approved for this pathogens since the paucity of other treatment options. Of value, recent data are warning toward emergence of resistance to ceftazidime/avibactam among CRE strains, in some cases even without previous exposure to the drug (88,89).

Meropenem/vaborbactam is a novel beta-lactam active against microorganisms producing group A and C beta-lactamase. Similarly to ceftazidime/avibactam, meropenem/vaborbactam received indication for infections sustained by Enterobacterales carrying KPC-carbapenemase (whereas it is not active against OXA48 and MBL) (85,86).

Bound for difficult-to-treat (DTR) *P. aeruginosa*, ceftolozane/tazobactam and imipenem/relebactam have been investigated in some trials including patients with HAP/VAP. While ceftolozane/tazobactam demonstrated superiority to aminoglycoside/polymyxin combination therapies for carbapenem-resistant (CR) infections (90), data on the non-inferiority of imipenem/relebactam compared to old drug combinations are limited, providing some concerns on its use as first-line therapy against CR *P. aeruginosa* (91).

Cefiderocol is a siderophore cephalosporin with *in vitro* activity against virtually all DTR Gram negative bacilli. In the APEKS-NP trial, cefiderocol showed superiority compared to high-dose extended-infusion meropenem for treatment of HAP/VAP, though few patients with CR infections were enrolled (92). However, in a following trial focused on CR Gram negative bacteria (including a wide range infection such as pneumonia), mortality was higher among patients receiving cefiderocol compared to the best available therapy, particularly in the subgroup of patients with CR *A. baumannii* infection (93). For these reasons, last US and European guidelines on treatment of MDR Gram negative infections do not recommend use of cefiderocol as first-line therapy for infections outside urinary tract and non-MBL-producing species (85,86).

Another important issue when starting antibiotic therapy is dosing schedule, which should be determined according to pharmacokinetic/pharmacodynamic data. Antibiotic extended/continuous infusion has been associated with lower mortality in critically ill patients (94). Use of therapeutic drug monitoring may be also useful to optimize antibiotic dose, particularly in case of microorganisms with elevated minimum inhibitory concentration.

Once empirical therapy is initiated, the clinical course and the yield of diagnostic testing in the first 48–72 hours should guide the subsequent therapeutic management. Routine bedside evaluations of physiological variables (e.g., temperature, blood pressure, heart and respiratory rate, oxygenation, mental status) should be performed until achievement of normal parameters or return to usual parameters in patients with abnormal variables at baseline. In addition, serial use of validated scores like CPIS, Sequential Organ Failure Assessment Score (SOFA), Acute Physiology and Chronic Health Disease Classification System II (APACHE II) could be helpful for prognostic assessment at this stage. Chest reimaging should not be

performed unless in patients who are not improving, in order to rule out lung complications needing procedural intervention.

As microbiological results are available, empirical treatment should be revised and possibly narrowed. Rapid molecular diagnostics could have a key role for early de-escalation due to their ability to get rapidly pathogen identification and antimicrobial resistance patterns.

An endorsed strategy for duration of antibiotic treatment in pneumonia consists in giving the shortest course of therapy that is likely to be effective in order to reduce risks of antibiotic resistance and adverse events.

Recommended duration of antibiotic therapy is 7–8 days once attained clinical and radiological improvement. Several RCTs demonstrated that there are no differences comparing short (7–8 days) with long (10–15 days) course of therapy for VAP with regard to mortality, length of stay in ICU, time of MV support (95). Moreover, longer courses were also associated with higher antibiotic adverse events, superinfections, and selection of more resistant microorganisms. Due to limited data on these population, in patients with immunosuppression, cystic fibrosis and infections complicated by secondary bloodstream infection, lung abscess or empyema, MRSA, MDR *P. aeruginosa* or *A. baumannii* pneumonia, short-course therapy should be avoided.

Conclusions

In this article we reviewed the current epidemiology, diagnosis and treatment of HAP/VAP. From an infectious disease physician perspective all these aspects might change the current treatment strategy of this entity. With the evolving spread of multidrug-resistant organisms (MDROs) the risk of ineffective empirical treatment may be higher than the past years. However, novel fast microbiological techniques will allow the clinicians to have prompt information on possible causative pathogens and their spectrum of antimicrobial resistance in order to modify/change and discontinue ineffective or redundant treatments especially when multiplex molecular tests are used together with antimicrobial stewardship programs. Similarly, if the availability of novel antimicrobial agents is of paramount importance, these drugs should be cautiously used in order to preserve them from fast resistance development. Efforts should be also provided to avoid some modifiable factors potentially associated with HAP/VAP, like interventions (e.g., intubation/reintubation versus NIPPV, excessive sedation, surgery) and medical conditions (e.g., pain, immobilization, neurological impairment, dysphagia). Finally, a multidisciplinary staff including ICU, infectious disease, microbiology, infection prevention and control specialists may play a key role in defining purposes, establishing programs of implementation, promoting personnel training and assessing adherence among hospital units. Moreover, a network among hospitals should be created to outline common aims and standardize clinical practice.

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