EXPERT OPINION

Pharmacotherapy for hospital-acquired pneumonia

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Introduction: Hospital-acquired pneumonia is the most common life-threatening hospital-acquired infection, and the majority of cases are associated with mechanical ventilation. Once pneumonia develops, the appropriateness of the initial antibiotic regimen is a vital determinant of outcome. The slow rate of development of newer antimicrobials has led to the rediscovery of the 'old' and 'forgotten' antibiotic 'Colistin', and it is increasingly being used as salvage therapy in patients with multidrug-resistant gram-negative bacteria infections.
Areas covered: This article covers medical literature published in any language since 1990 until November 2011, on 'hospital pneumonia', identified using PubMed, MEDLINE and clinicaltrial.gov. The search terms used were 'ventilator associated pneumonia', 'management' and 'new antibiotics'.
Expert opinion: Many controversies still remain in the management of hospital-acquired pneumonia. A continuous evaluation of the antimicrobial therapeutic options, along with their pharmacodynamic and pharmacokinetic profiles, is mandatory to optimize therapy and reduce hospital pneumonia-related mortality.

Keywords: antibiotic, combination treatment, de-escalation, hospital-acquired pneumonia

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1. Introduction

Hospital-acquired pneumonia (HAP) is the second most prevalent nosocomial infection in hospitalized patients, with ventilator-associated pneumonia (VAP) being the leading nosocomial infection in the intensive care unit (ICU). By definition it is pneumonia occurring 48 h or more following admission to hospital. Data from The National Nosocomial Infection Surveillance showed that 27% of all nosocomial infections in ICUs in the USA and Canada were due to pneumonia, with 86% of nosocomial pneumonias associated with mechanical ventilation [1]. HAP can further be classified as ICU HAP or non-ICU HAP depending upon whether this infection is acquired in the ICU or in other clinical areas.

It is associated with increased ICU and hospital stay, an increased use of antibiotics and greater hospital costs. The crude mortality of VAP may be as high as 30 – 70%, although the difficulty in determining the exact cause of death in critically ill patients prevents this figure from being established with certainty [2].

The administration of accurate and timely initial empirical antibiotic therapy has been shown to have a major impact on mortality from nosocomial pneumonia [3]. In fact, Alvarez Lerma *et al.* [4] in a large series of HAP patients demonstrated that patients who received adequate antibiotic treatment had lower mortality than those with inadequate therapy (16 vs 25%). The percentage of inadequate treatment has varied in the literature between 22 and 73%.

This review focuses on the recommended pharmacotherapy of HAP/VAP based on the guidelines of American Thoracic Society/Infectious Diseases Society of America (ATS/IDSA) [5] and European Respiratory Society/European Society for Clinical Microbiology and Infectious Diseases [3] and recent studies, giving a brief

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Article highlights.

- Hospital-acquired pneumonia (HAP) or ventilator-associated pneumonia (VAP) are associated with longer attributable lengths of stay in hospital and greater hospital mortality comparing to other nosocomial infections.
- Empiric therapy of patients with severe HAP or VAP requires the use of antibiotics at optimal doses, to ensure maximum efficacy.
- Combination therapy should be used if patients are likely to be infected with multidrug-resistant (MDR) pathogens, especially *Pseudomonas aeruginosa*.
- Aerosolized antibiotics (colistin and tobramycin) may be a useful adjunct to intravenous antibiotics in the treatment of MDR pathogens where toxicity is a concern (2A).
- A few novel drugs in the pipeline, as telavancin, ceftobiprole and avibactam, remain to be fully assessed in HAP/VAP caused by MDR pathogens, especially methicillin-resistant *Staphylococcus aureus*.

This box summarizes key points contained in the article.

summary of the use of older and existing agents and forthcoming, newer antimicrobial agents. Healthcare-associated pneumonia (HCAP) has been reevaluated the last years [6] and we do not believe that it belongs to HAP, as ATS/IDSA guidelines, in 2005, have proposed [5].

2. Etiology

Establishing the etiological agent(s) of HAP/VAP may be difficult because distinguishing between mere colonization of the tracheobronchial tree versus true nosocomial pneumonia is often problematic. The bacterial epidemiology of HAP based in microbiological testing, which includes the qualitative and quantitative analysis of the respiratory secretions obtained using bronchoscopic (directed) or non-bronchoscopic (blind) techniques – Bronchoscopic Protected Specimen Brush and Bronchoalveolar Lavage, or also by taking tracheal aspiration samples.

In the clinical practice, in a multicenter study carried out in nine European countries, bronchoscopic techniques were used in < 20% of patients, while quantitative tracheal aspiration represented 70% of the cases [7]. As American guidelines recommend, the choice of the diagnostic technique depends on local resources and expertise [5].

Nowadays, molecular diagnostics play an increasing role in pathogen detection in critically ill patients, which could ultimately improve antibiotic stewardship and clinical outcomes [8]. Real-time PCR, *in situ* DNA hybridization and mass spectrometry are currently the leading investigation methods.

The time of onset of pneumonia is an important epidemiologic consideration for acquisition of specific pathogens and outcomes in HAP [9]. Pneumonia, which occurs early in the course of ICU stay – < 4 days, is addressed as 'early onset pneumonia' and carries a better prognosis than 'late onset pneumonia'. The latter tends to be associated with multidrug-resistant (MDR) organisms and so it is characterized by higher mortality rates (**Table 1**).

Gram-negative pathogens are the most frequent cause of HAP, while gram-positive pathogens commonly isolated in HAP include *Staphylococcus aureus*, *Streptococcus* spp. with *Streptococcus pneumoniae*, accounting for 35 – 39% of all cases.

Early-onset nosocomial pneumonia was believed to be due primarily to gram-negative bacteria (GNB), such as *Haemophilus influenzae*, and methicillin-sensitive *Staphylococcus aureus* and *S. pneumoniae*. *For late-onset* nosocomial pneumonia, the most commonly encountered causative pathogens reported were higher-level antibiotic-resistant GNB, such as *Pseudomonas aeruginosa*, *Acinetobacter* spp. or methicillin-resistant *Staphylococcus aureus* (MRSA) [3,5].

In the article of the SENTRY Antimicrobial Surveillance Program during the period 1997 – 2008 [10] in patients with HAP, the results tabulated across all regions showed that the top six pathogens (*S. aureus*, *P. aeruginosa*, *Klebsiella* species, *Escherichia coli*, *Acinetobacter* species and *Enterobacter* species) caused nearly 80% of all cases. The same top six organisms prevailed in 75.8% of cases in Europe and 85.4% of cases in Latin America (data not shown). A significant change in rank was that *P. aeruginosa* was the most frequent pathogen causing HAP in Latin America (28.2%), with *Acinetobacter* species ranked third (13.3%, compared with only 4.8 – 5.6% in the other regions). *E. coli* was a prominent pathogen (third) in Europe. VAP isolates of the same species had a mean of 5 – 10% less susceptibility to frequently used extended-spectrum antimicrobials.

In general, there are significant geographical differences in the rates of resistance between some European areas and even within countries, from one hospital to another.

In 2009, 39% of *E. coli* isolated from ICU patients in the Asian/Pacific area were extended-spectrum beta-lactamase (ESBL) producers, while rates were lower in Latin America (25%), Europe (16.3%) and North America (8.7%) [11].

In the impaired host, other organisms, including opportunistic fungi and mycobacterial infections, may need to be considered.

The proportion of polymicrobial etiology and its impact on survival vary in the literature. It is commonly reported that viruses are an infrequent cause of VAP; nevertheless, it should also be acknowledged that viruses are rarely screened in patients with clinical suspicion of VAP. Daubin *et al.* [12] studied 139 ICU patients, of which 39 (28%) developed VAP. Although *P. aeruginosa* and MRSA still accounted for most of the VAP cases, Herpes simplex virus type 1 was found in 12 cases of VAP and cytomegalovirus in 1 case. Rarely, the causative organism of VAP is a fungus; *Aspergillus* spp. (mainly *Aspergillus fumigates*) may be involved in 3% of late-onset VAP [13], and invasive pulmonary aspergillosis has

Table 1. Etiology of hospital-acquired pneumonia/ventilator-associated pneumonia [5].

Early-onset HAP/VAP	Late-onset HAP/VAP
Core pathogens:	Potential pathogens
Streptococcus pneumoniae	include core pathogens*
MSSA	Plus MDR pathogens
Haemophilus influenzae	*Pseudomonas aeruginosa*
Enteric gram(-) bacilli	*Klebsiella pneumonia* (ESBL)
Escherichia coli	*Acinetobacter* species
Klebsiella pneumoniae	MRSA
Enterobacter spp.	*Legionella* pneumophila
Proteus species	
Serratia marcescens	

*Early-onset HAP/VAP.
ESBL: Extended-spectrum beta lactamase; HAP: Hospital-acquired pneumonia; MDR: Multidrug-resistant; MRSA: Methicillin-resistant *Staphylococcus aureus*; VAP: Ventilator-associated pneumonia.

been proven in 15% of critically ill patients with one or more Aspergillus-positive tracheal aspirate cultures. *Candida* spp. in respiratory specimen should not be treated unless there is clear histological evidence for such an infection.

3. Therapy

Patients in whom HAP is suspected should be given initial empirical treatment after samples for microbiological cultures are collected. A fundamental aspect to take into account at this time is to ensure that this initial treatment is appropriate and adequate, based on clinical presentation, time of onset relative to admission, and the potential for MDR pathogens [5]. One of the main challenges in the antibiotic decision is to overcome the resistance issues, which have become so important and common over the past several years.

The ATS/IDSA guidelines [5] recommend the following:

1) Selection of empirical treatment for HAP/VAP according to several factors, mainly risk factors for MDR bacteria (length of hospital stay, underlying diseases and previous antibiotic prescription) (**Table 2**) and local susceptibilities.
2) Dosages and intervals of administration based on pharmacokinetic (PK) and pharmacodynamic (PD) information.

3.1 Empirical antibiotic treatment

For patients with *early-onset infection* and no risks for MDR pathogens, the initial empirical therapy can be a narrow-spectrum antibiotic regimen directed at a core group of non-resistant gram-positive and gram-negative microorganisms, generally with a single agent (**Table 3**).

Patients in the *late/HCAP group* are at higher risk of MDR pathogens, especially *P. aeruginosa*, *Acinetobacter baumannii*, *Enterobacteriaceae* (e.g., *Klebsiella*, *Enterobacter*) and MRSA and thus require agents targeted at these organisms.

The anti-pseudomonal β-lactams include cefepime, doripenem, imipenem, meropenem and piperacillin/tazobactam. Facing the epidemic of ESBL-producing *Enterobacteria* and other MDR-GNB, antipseudomonal carbapenems (imipenem/cilastatin and meropenem) have become the most empirically prescribed β-lactams in European ICU for HAP/VAP [14]. Especially, in a Greek study, the combination of colistin and imipenem was synergistic in 50% of colistin-susceptible imipenem-resistant *Klebsiella pneumoniae* strains [15].

Emergence of MDR organisms has revitalized colistin, a polymyxin also called colistimethate or polymyxin E, which is an old drug that is making a comeback. It has antimicrobial activity against MDR-GNB, such as *P. aeruginosa, A baumannii* and carbapenem-resistant *Enterobacteriaceae* [16-18].

Combinations of Colistin/meromenem, colistin/rifampicin and Colistin/minocycline are synergistic *in vitro* against extensive resistant *A. baumannii*. Carbapenems in combination with colistin exhibited a synergistic effect in a few studies [19].

Synergistic effect was detected in most of the studies that examined the combination of Colistin and rifampicin [20], but in a recent multicenter clinical trial including 210 critical ill patients with XDR *A. baumanii* infections, the mortality is not reduced by addition of rifampicin to colistin, although the eradication rate of *A. baumanii* was higher with the combination therapy [21].

The main side effect of the drug is nephrotoxicity. In a retrospective cohort study of all patients receiving colisitin for ≥ 48 h over a 5-year period, Pogue and colleagues raise important safety concerns by reporting a 43% (n = 54) colistin-associated nephrotoxicity [22]. Nephrotoxicity occurred in a dose-dependent manner, with higher mean colistin doses significantly increasing the risk (5.48 vs 3.95 mg/kg/day; $p < 0.001$).

It is available in intravenous (i.v.), inhalational and topical preparations. An i.v. loading dose of 2.5 mg/kg IV q12 h × 2 doses, and the maintenance dosing beginning 24 h after first loading dose with 5 mg/kg/days divided in 2 – 3 doses (with protocolized adaptation in case of renal failure) may be an adequate scheme.

MRSA is a frequent cause of nosocomial pneumonia, and among the gram-positive–resistant organisms, MRSA represent the biggest therapeutic hurdle. Kollef *et al.* [23] in an interesting study demonstrated that patients infected with *MRSA* were more likely to receive inappropriate antimicrobial therapy, leading to higher mortality. Bacteremia, shock and mortality are significantly higher in MRSA pneumonia [3]. The ATS/IDSA recommendation is the use of vancomycin or linezolid for the treatment of suspected or proven MRSA HAP/VAP [5].

In a double-blind multicenter randomized controlled trial (RCT), Wunderink and colleagues [24] assessed the efficacy and safety of linezolid compared with a dose-optimized vancomycin strategy against MRSA nosocomial pneumonia in

Table 2. Risk factors for multidrug-resistant pathogens causing hospital-acquired pneumonia, healthcare-associated pneumonia and ventilator-associated pneumonia.

Antimicrobial therapy in preceding 90 days
Current hospitalization of > 5 days
High frequency of antibiotic resistance in the community
Presence of risk factors for HCAP:
Environment: Hospitalization for 2 or more days in the preceding 90 days
Residence in a nursing home or extended care facility
Family member with multidrug-resistant pathogen
Disease: Chronic dialysis within 30 days, i.v. antibiotics at home
Home wound care
Immunosuppressive disease and/or therapy (corticosteroids [5 mg/day for > 30 days], HIV infection, solid organ or bone-marrow transplant, radiation or chemotherapy for cancer in the last 6 months, inherited or acquired immunodeficiency)

HCAP: Healthcare-associated pneumonia.

448 adult participants. They reported higher clinical response with linezolid compared to vancomycin (57.6 vs 46.6%, p = 0.042). However, all-cause 60-day fatality rates (16 vs 17%, respectively) and the overall incidence of adverse effects were similar in both groups, even if renal impairment was more frequent with vancomycin (8 vs 18%, respectively).

So, linezolid should also be preferred if patients have renal insufficiency or are receiving other nephrotoxic agents.

The FDA of US warns against the concurrent use of linezolid with serotonergic psychiatric drugs, unless indicated for life-threatening or urgent conditions.

3.2 Pharmacokinetic–pharmacodynamic in the ICU

In clinical practice, this method of antibiotic therapy requires cooperation of experienced clinicians with microbiologists (minimum inhibitory concentration [MIC] determinations) and clinical pharmacologists (determinations of antibiotic concentrations, calculations of selected PK parameters, for example, the AUC, AUC changes during 24 h [AUC24]).

The serum concentration of an antibiotic depends on the dose delivered, its bioavailability and its volume of distribution (Vd). Both Vd and drug clearance (Cl) may be increased in ICU patients. A rise in the Vd, although it reduces drug concentration, might proportionally increase $T_{1/2}$, since $T_{1/2} = Vd/(Cl \times 0.693)$ [25].

On the contrary, a high Cl may reduce the exposure of antibiotics to bacteria [26]. Renal Cl may be increased in septic patients because of increased renal blood flow. Protein binding can also vary dramatically, given that it is an acute-phase reactant, which can affect both CL and Vd.

The strongest effects of physiological abnormalities in critically ill patients on PK parameters are observed during the treatment with hydrophilic antibiotics (aminoglycosides, β-lactams, glycopeptides or colistin). The PK changes result from increased Vd and Cl of the drug, which translates into lower serum concentrations.

To optimize antibiotic dosing in ICU patients, based on theoretical PK–PD modeling, β-lactam antibiotics, as time-dependent antibiotics, should provide better clinical efficacy when administered in prolonged (PI) or continuous infusion (CI). Furthermore, high-dose, extended-interval strategies have been used to optimize the PD profile while minimizing the potential toxicity of the aminoglycosides.

Numerous clinical trials in patients with severe sepsis and septic shock revealed higher clinical efficacy, higher incidence of pathogen eradication, better activity against MDR species (*P. aeruginosa*, *K. pneumoniae*), reduced resistance increases and lower costs when antibiotics were administered in CIs [27-29].

3.3 Monotherapy or combined treatment

The objectives of combined treatment are to search for synergy between different groups of antibiotics, widen the spectrum to ensure appropriate treatment against GNB and avoid the development of resistances [30,31]. But the use of empiric broad-spectrum antibiotics in patients without infection or with an infection caused by susceptible microorganisms is potentially harmful, as it facilitates colonization and superinfection with MDR microorganisms [32,33].

The monotherapy with ciprofloxacin, ceftazidime or imipenem should be avoided, as they are likely to induce resistance potential.

Recent data do not support the combination treatment in the therapy of HAP/VAP [34,35]. In a meta-analysis of 41 RCTs that evaluated empirical antibiotic regimens for 7015 adult patients with clinically suspected VAP, with 13.8% of them infected with *Pseudomonas* spp., it has been reported that monotherapy is not inferior to combination therapy in terms of mortality and treatment failure [34]. Studies such as the latter seem to challenge the recommendation for combined empirical antimicrobial treatment in HAP/VAP.

Moreover, one recent study has shown that with pneumonia and sepsis the use of an appropriate combination therapy is associated with a lower mortality than the use of an appropriate monotherapy, and this may be due to the use of two agents leading to a more rapid killing of the bacteria, a benefit for the more severely ill patient [36].

The potential benefit of using a two-antibiotic regimen to treat severely ill infected patients remains controversial, albeit widely used in many ICUs, especially for certain patient subgroups, including those with neutropenia, *P. aeruginosa* infections and/or VAP [36,37].

Although quinolones can penetrate into the lung better than aminoglycosides and colistin, quinolones have less potential for nephrotoxicity; a trend toward improved survival has been seen with combinations containing aminoglycoside but not containing quinolone [38].

Table 3. Treatment of hospital-acquired pneumonia/ventilator-associated pneumonia according to current guidelines [3,5].

	Therapy	
	Early-onset HAP/VAP	**Late-onset HAP/VAP**
ATS/IDSA (2005)	Ceftriaxone or Levofloxacin, moxifloxacin, ciprofloxacin or Ampicillin/sulbactam or Ertapenem	Cefepime or ceftazidime or Imipenem/cilastatin, meropenem or Piperacillin/tazobactam PLUS Ciprofloxacin or levofloxacin or Amikacin, gentamicin, tobramycin
MRSA		Vancomycin, linezolid
ERS/ECCMID/ESICM (2009)	Ampicillin/sulbactam or amoxicillin/clavulanate or Cefuroxime, cefotaxime, ceftriaxone or Moxifloxacin, levofloxacin	Ceftazidime or Imipenem/cilastatin, meropenem or Piperacillin/tazobactam PLUS Ciprofloxacin or levofloxacin
MRSA		Vancomycin, linezolid
Fungi		Fluconazole, caspofungin, voriconazole

ATS/IDSA: American Thoracic Society/Infectious Diseases Society of America; ERS/ECCMID/ESICM: European Respiratory Society/European Society for Clinical Microbiology and Infectious Diseases; HAP: Hospital-acquired pneumonia; MRSA: Methicillin-resistant *Staphylococcus aureus;* VAP: Ventilator-associated pneumonia.

In the ATS/IDSA guidelines, the recommendation was to continue the aminoglycoside in combination with other agents for 5 days when the infection is due to *P. aeruginosa* and for 3 days when a more susceptible pathogen was the cause [5].

3.4 Downscaling of treatment

The responding patient should have de-escalation of antibiotics, narrowing therapy to the most focused regimen possible on the basis of culture data.

Combination therapy can be de-escalated to monotherapy once culture data are available, completing therapy with a single agent to whom the pathogen is sensitive.

De-escalation of initial broad-spectrum therapy may prevent the emergence of resistant organisms, minimize the risk of drug toxicity and reduce costs. The de-escalating approach to antibiotic therapy (i.e., culture-guided treatment) could benefit the ICU as a whole by reducing the selection pressure for resistance. In a study of Eachambati *et al.* [39], with 1596 patients in surgical ICUs, de-escalation therapy did not lead to recurrent pneumonia or increased mortality in critically ill surgical patients with VAP, even in patients with septic shock.

Kollef and coworkers evaluated 398 patients with VAP [40]. The mean duration of treatment was 11.8 ± 5.9 days, in most cases (61.6%), and downscaling was possible in 22.1% of the patients. The mortality rate was lower in patients who underwent downscaling (17%) than in those undergoing escalation of therapy (42.6%) or in whom neither reduction nor downscaling was performed (23.7%, p = 0.001).

Another study of Singh *et al.* [41] evaluated the role of downscaling strategy according to initial Clinical Pulmonary Infection Score (CPIS). With this strategy, only 11 of these 39 patients required antibiotics for > 3 days (increase in CPIS < 6). The two groups showed the same clinical course and mortality.

The standard duration of therapy that is listed in the guidelines is 7 – 8 days for most pathogens and longer (usually 14 days) for nonfermenting (NF) GNB, *S. aureus* bacteremia, some fungal or viral infections and inmunological deficiencies (neutropenia). Prolonged therapy in patients with HAP simply leads to colonization with resistant bacteria, which may precede a recurrent episode of VAP [42].

A Cochrane meta-analysis [43], including 1703 ICU patients, supports this statement, which concluded that for patients with VAP not due to NF GNB, a short fixed-course (7 or 8 days) antibiotic therapy may be more appropriate than a prolonged course (10 – 15 days).

3.5 Aerolized antibiotics

Aerosolized therapy is frequently administered during mechanical ventilation, but strategies are not standardized and therefore probably not ideal [44]. Aerosolized delivery into lungs is a method of improving antibiotic delivery to

the lung epithelial lining fluid , which offers the potential for lower systemic concentrations resulting in fewer side effects, as nephrotoxicity.

Colistin, aminoglycosides, b-lactams, monobactams, carbapenems and fosfomycin have been studied or proposed as aerosolized agents, and each has problems. A well-tolerated aerosolized formulation should be preservative free and not hyperosmolar, and have near-neutral pH and at least 30 mEq of permeant anion. Additionally, there are a number of technical issues in delivery of aerosolized medications in mechanically ventilated patients.

The use of a nebulizer model with median mass aerodynamic diameter of 1 – 5 μm (optimal = 2.8 – 4.5 μm) and the optimal site for placement in 30 cm from the endotracheal tube in the inspiratory loop are recommended.

The Society of Infectious Diseases Pharmacists recommends that the typical dose for tobramycin is 300 mg every 12 h and colistin 150 mg every 12 h, and for colistin a dose of 150 mg every 12 h.

Two meta-analyses of clinical trials of aerolized antibiotics in VAP patients have been published recently [45,46].

Colistimethate (colistin methanosulfate) is a chemically derived inactive prodrug of the antibiotic colistin. Florescu *et al.* [47], in a recent review, suggest that colistin (i.v. or aerolized) can be a safe and effective alternative therapy for VAP caused by MDR-GNB. By the route of administration, microbiological cure rate was 46% for the i.v. form (5 studies; 95 patients) and 73% for the aerosolized form (3 studies; 121 patients).

Lu *et al.* [46] in a prospective, observational, comparative trial reported that aerosolized colistin was noninferior to i.v. β-lactams plus aminoglycosides or quinolones in patients with VAP because of *P. aeruginosa* or *A. baumannii*.

On the other hand, nebulized ceftazidime/amikacin combination does not improve the course of clinical *P. aeruginosa* VAP when compared with i.v. administration [45].

There are a number of studies that suggest that the aerolized antibiotics may have a benefit in patients who have failed i.v. therapy alone or have MDR organisms [48]. Michalopoulos *et al.* [49] in a retrospective study with 60 ICU patients with MDR *P. aeruginosa* or *A. baumanii or Klembsiella pneumoniae.* VAP reported a clinical cure rate of 83% when aerolized colistin was added to i.v. therapy. Small and uncontrolled series have shown that when patients have VAP due to MDR *P. aeruginosa* or *Acinetobacter* spp., aerosolized aminoglycosides, polymyxin or colistin may be helpful as adjunctive therapy to systemic antibiotics [50].

Bronchospasm is the more severe, possible life-threatening event, although a less-common side effect was described in patients receiving nebulized antibiotics, especially when the i.v. formulation was used. The prolonged use of broad-spectrum antibiotics is known to lead to the emergence of MDR strains of microorganisms and nebulization is not an exception to the rule. However, in the studies included in a meta-analysis [51], there was no evidence of emergence of resistance in the aerosolized antibiotic treatment arm, with treatment duration ranging from 4 to 15 days. In fact, the selection of resistant pathogens has been reported by studies evaluating aerosolized antimicrobials as a long-term prophylactic measure against pneumonia.

4. Adjunctive therapy

4.1 Corticosteroids

Nowadays, while the antimicrobial therapy is not completely enough to significantly reduce mortality number in severe pneumonia, additional therapy such as glucocorticosteroids (GCs) may constitute an important portion for better resolution of pneumonia. GCs inhibit the expression and action of many cytokines involved in the inflammatory response associated with pneumonia. Innovative treatments of GCs in severe pneumonia have emerged from the septic shock field.

ln a pilot study by Monton *et al.* [52], in patients with severe pneumonia requiring mechanical ventilation, they detected a possible immunosuppressive effect of GCs in pneumonia. A decrease in levels of proinflammatory cytokines, such as IL-6 and TNF-α, was observed in both serum and BALF from patients who had received GCs as a coadjuvant treatment. Results from multiple controlled clinical trials clearly demonstrate that low-dose corticosteroid replacement therapy in septic shock is associated with improved blood pressure and shorter duration of vasopressor support in patients with septic shock, but not a benefit in mortality [53-55].

The undesirable effects of the use of corticoids in nosocomial pneumonia are first the prolonged use of GCs, which can alter the phagocytic action of macrophages and alveolar granulocytes, which can facilitate the acquisition of severe bacterial and opportunistic infections. Second, another adverse effect of corticosteroid administration is the potential contribution to critical illness polymyoneuropathy (neuromuscular weakness) [56].

Annane and colleagues [55] recently evaluated patients with septic shock (60% of them pneumonia-related) and showed that low doses of GCs were associated with better outcomes in sepsis-associated acute respiratory distress syndrome diagnosed with critical illness-related corticosteroid insufficiency. The results from the Corticosteroid Therapy of Septic Shock (CORTICUS) trial [54] showed no survival benefit with a relatively long corticosteroid course (11 days) and challenged this observation. In addition, the steroid-treated patients had a significantly increased frequency of hyperglycemia, hypernatremia and superinfections, including new episodes of sepsis. There was a reduced risk of infection in the Annane and colleagues trial, but in the CORTICUS study there was an increase in infection. The usefulness of GCs seems to have been demonstrated in pneumonia caused by *Pneumocystis jiroveci* and in septic shock, which responds poorly to fluid resuscitation and vasopressor therapy.

Current Surviving Sepsis Campaign guidelines recommend hydrocortisone in doses not to exceed 300 mg/day for patients

with vasopressor-dependent septic shock for up to 7 days or until vasopressor support is no longer required.

5. New antibiotic choices

A number of new therapeutic agents have become available, either in clinical trials or have been approved for clinical use; these include doripenem, cefobiprole, telavancin and avibactam.

5.1 Doripenem

It is a new carbapenem antibiotic with a very broad spectrum of antimicrobial activity including *P. aeruginosa, A. baumannii* and ESBL-producing isolates. The *in vitro* data indicate that doripenem has the intrinsic activity of imipenem against gram-positive organisms and of meropenem against gram-negative organisms [57]. It has generally lower MICs against gram-negative organisms [58].

Emerging results from *post hoc* analyses of data from the HAP and VAP studies show that clinical cure rates with doripenem among certain populations at high risk of infection, such as those with high Acute Physiology and Chronic Health Evaluation II scores and those infected with *P. aeruginosa*, are noninferior to the cure rates among comparator populations in two large Phase III clinical studies [59].

In a study of Kollef *et al.*, in 2012 [60], they demonstrated that among patients with microbiologically confirmed VAP, a fixed 7-day course of doripenem (1 g as a 4-h infusion every 8 h) had nonsignificant higher rates of clinical failure and mortality compared to a fixed 10-day course of imipenem-cilastatin (1 g as a 1-h infusion every 8 h). But, VAP attributed to *P. aeruginosa* had a statistically greater risk of 28-day all-cause mortality when treated with doripenem compared to imipenem-cilastatin with an increased separation in the survival curves after completion of 8 days.

Interestingly, in a recent Phase III clinical trial, Roberts *et al.* [61], describing the population PK of doripenem in critically ill patients with nosocomial pneumonia and then using Monte Carlo dosing simulations to procure clinically relevant dosing recommendations for that population, suggest higher doses of the drug than those provided until now.

5.2 Telavancin

Telavancin is a antibiotic-semisynthetic lipoglycopeptide rapidly bactericidal against gram-positive bacteria, such as *Staphylococci* (MRSA), Vancomycin-intermediate *Staphylococcus aureus* (VISA) and heterogeneous (h) VISA [62]. Initial data from the two prospective randomized studies of patients with HAP (ATTAIN) were published by Rubinstein *et al.*, indicating that telavancin is noninferior to vancomycin on the basis of clinical response in the treatment of HAP due to gram-positive pathogens, mainly MRSA [63].

In Europe, European Medicines Agency accepted telavancin for the treatment for adults with nosocomial pneumonia, including VAP known or suspected to be caused by MRSA, in patients without renal insufficiency. In 2013, telavancin was approved by FDA for the treatment of HAP and VAP caused by *S. aureus*, but not for other bacterial causes of HAP or VAP; it is recommended only when alternative agents cannot be used [64].

5.3 Ceftobiprole

Ceftobiprole is a new member of the pyrrolidinone-3-ylidenemethyl cephem series of cephalosporins. Ceftobiprole is active against *S. aureus,* including MRSA and VISA, *Enterococcus* species (including vancomycin-resistant but not ampicillin-resistant enterococci), pneumococci, some anaerobes, and gram-negative bacilli – especially has anti-pseudomonal activity similar to cefepime.

A Phase III clinical trial for nosocomial pneumonia has been completed and demonstrated the noninferiority of ceftobiprole plus placebo compared with linezolid plus ceftazidime with respect to the clinical cure (77% for ceftobiprole and 76% for combination therapy), but was inferior for the treatment of ventilated patients [65].

But the recommended dose of ceftobiprole is not fixed yet. In a more recent review about ceftobiprole [66], it was reported that in patients with normal PK and non-VAP, ceftobiprole is effective for the treatment of HAP in the recommended doses, but it is unlikely to achieve the desired PD targets when PK parameters are altered in VAP (e.g., increased Vd and Cl). In these settings, off-label use at higher doses may overcome these limitations; but in the presence of alternative therapies, it cannot be currently recommended.

5.4 Avibactam

Avibactam is a novel non-β-lactam broad-spectrum β-lactamase inhibitor with potent inhibitory activity against Ambler class A and class C serine β-lactamases, including ESBLs, chromosomal cephalosporinases (AmpC), serine carbapenemases (e.g., KPC) and cephamycinases, and it is being evaluated clinically in combination with ceftazidime and ceftaroline [67].

A Phase III, randomized, multicenter, double-blind, comparative study has taken place, to compare the efficacy, safety and tolerability of ceftazidime/avibactam versus meropenem in the treatment of nosocomial pneumonias (including VAP) in hospitalized adults [68].

6. New approaches

6.1 Macrolides

Despite an inappropriate bacterial spectrum, macrolides have immunomodulatory and anti-inflammatory effects that may be of interest in HAP/VAP. They also inhibit gene expression of proteins participating in quorum sensing of *P. aeruginosa*. In a multicenter, double-blind study, including 200 ICU patients with sepsis and VAP, Giamarellos *et al.* [69] concluded that clarithromycin in a dose of 1 g for 3 days accelerated the resolution of VAP and weaning from mechanical ventilation

Table 4. Hospital-acquired pneumonia/ventilator-associated pneumonia antibiotic dosing.

Early onset (< 5 days since admission) and no MDR risk factors	Dosing
Ceftriaxone	2 g i.v. or i.m. every 24 h
Levofloxacin	750 mg i.v. or PO every 24 h
Moxifloxacin	400 mg i.v. or PO every 24 h
Ciprofloxacin	400 mg i.v.every 8 h
Ampicillin-sulbactam	3 g i.v. or i.m. every 6 h
Ertapenem	1 g i.v. or i.m. every 24 h
Late onset (≥ 5 days since admission), with MDR risk factors	
Cefepime	2 g i.v. every 8 h
Ceftazidime	2 g i.v. every 8 h
Imipenem	500 mg i.v. every 6 h or 1 g i.v. every 8 h
Meropenem	2 g every 8 h
Piperacillin-tazobactam	4.5 g every 8 h
Vancomycin	15 mg/kg every 12 h
Linezolid	600 mg every 12 h
Ciprofloxacin	400 mg every 8 h
Levofloxacin	750 mg every 24 h
Fluconazole	800 mg every 12 h
Caspofungin	50 mg every 24 h
Voriconazole	4 mg/kg every 12 h

i.v.: Intravenous; MDR: Multidrug-resistant; PO: Per oral administration.

in surviving patients and delayed death in those who died of sepsis.

6.2 Monoclonal antibody

Based on a murine model of pneumonia, the data suggest that type 3 secretion system and elastase are the most important virulence factors in clinically relevant *P. aeruginosa* strains. Antibody-mediated inhibition of the PcrV protein, an essential component of this system, might abrogate the ability of *P. aeruginosa* to damage epithelial cells, neutrophils and macrophages, thereby limiting its pathogenicity.

A new tool for VAP therapy is a recombinant, PEGylated, engineered, human Fab' fragment that specifically binds to a *P. aeruginosa* PcrV epitope and blocks its function. In a recent RCT, monoclonal antibodies targeting the type 3 secretion system reduced the incidence of VAP in patients with *P. aeruginosa* tracheal colonization [70].

7. Conclusion

Considering the dramatic increase in the rates of MDR VAP, clinicians must be aware of current MDR pathogens, and their appropriate management. Optimal treatment of MRSA pneumonia involves vancomycin, linezolid and the new agent telavancin. Polymixins, especially colistin, should be reserved for highly resistant GNB that are not sensitive to other agents.

PK and PD optimization strategies are recommended for MDR VAP due to highly resistant organisms in patients with normal renal function or severe illness.

Aerosolized antibiotics, aminoglycosides, are suitable as adjuncts to systemic antibiotic therapy, especially in patients with MDR pathogens or nonresponding VAP. However, RCTs dealing with the administration of anti-infective agents via the respiratory tract are necessary in order to validate the efficacy, safety, advantages and disadvantages of this therapeutic approach for the treatment of nosocomial pneumonia.

Management of VAP in the future may be based on a combination of: i) optimizing dosing, and considering PK and PD of antibiotics; ii) newer antibiotics; and iii) immunotherapy. Rapid diagnostics may ultimately facilitate a more rapid evaluation of new drugs and perhaps better detect subgroups that may benefit most.

The prevention of VAP, using bundles, a collection of clinical standards, has been promoted as an effective method for reducing VAP [71]. The measures included are pharmacological and nonpharmacological (procedures). Regarding infection control, issues are the use of selective digestive decontamination, the oropharyngeal decontamination with chlorhexidine solution, the prophylactic treatment of patients with neutropenia (granulocyte colony-stimulating factor), administration of probiotics and downescalation of therapy.

8. Expert opinion

This article provides a detailed overview of current pharmacotherapy for nosocomial pneumonia. However, there are some issues affecting the management of HAP needing further consideration and reevaluation.

First, the microorganism prediction in VAP according to the time of onset of pneumonia (early and late onset) and the presence of risk factors for MDR microorganisms [5]. Recent studies are challenging such conclusions and demonstrate no association between MDR pathogens and time of onset of pneumonia. In the study of my group [72], consisting of 276 patients with VAP, microbial prediction by 2005 ATS/IDSA guidelines was lower in the group with early-onset VAP than in the group with late-onset VAP (12 [50%] of 24 vs 119 [92%] of 129; $p < 0.001$) mainly because of MDR in 10 patients (26%) from group with early-onset VAP.

In a secondary analysis of a multicenter study in 29 European ICUs, Martin-Loeches *et al.* [73] reported that pneumonia developed in centers with greater than 25% prevalence of MDR (odds ratio = 11.3, 95% CI 2.1 – 59.3) were independently associated with MDR in group 1 patients. This classification of ATS is no longer helpful for empirical antibiotic therapy, since the pathogens are the same for both groups. Moreover, an interesting study by Kett *et al.* [74], including 304 patients with nosocomial pneumonia with risk factors for MDR pathogens, demonstrated that adherence with guidelines empirical treatment was associated with increased mortality (34 vs 20%, $p = 0.0042$). These studies

suggest the need for extensive research to accurately identify risk factors for harboring MDR pathogens. It is very important to know the most common organisms responsible for these infections in each hospital and each ICU, as well as their antimicrobial susceptibility patterns, in order to reduce the incidence of inappropriate antibiotic therapy and improve the prognosis of patients.

Second, in the delivery of adequate antimicrobial therapy it is important to ensure that patients receive the correct dose of antibiotic and, in the case of MDR, pathogens and considering PK–PD and the AUIC (**Table 4**) [75]. A classic study by Paladino *et al.* [76] showed better survival among patients with VAP caused by *P. aeruginosa* when the AUC/MIC ratios for ciprofloxacin were optimized.

Particularly in MDR microorganisms, dosages and intervals of administration are important. The loading dose is probably the most important dose and is a function of the volume of distribution of the drug and the desired plasma concentration but independent of renal function. The research has been focused on maximizing the existing therapies by optimizing the dosing and PK of drug delivery, that is, the use of PI and CI of selected agents. CI of β-lactam antibiotics commonly increases the time that the antibiotic concentration exceeds its MIC and may therefore increase efficacy. On the other hand, concentration-dependent antibiotics like aminoglycosides are best administered as a single daily dose or as intermittent doses.

Regarding antibiotic therapy the use of colistin has been increasing in the recent past to treat VAP and bacteremia caused by MDR bacteria such as *P. aeruginosa*, *K. pneumoniae* and *A. baumannii* and newer studies have shown lesser toxicity and good efficacy.

Lastly, in relation to the future, we believe that inhaled antibiotics will become standard of care. Compared with i.v. administration, aerosolization has the advantage of high local concentrations and fast clearance, which in turn may yield improved efficacy and decreased risk of microbial resistance. Interestingly, recent data suggest that outcomes in patients with MDR GNB are comparable when high-dose colistin (5 MU/8 h) is nebulized, either alone or in combination with parenteral therapy. Large multicenter trials are needed to determine whether preliminary findings will translate to improved clinical activity and decreased microbial resistance in VAP patients, and to optimize the use of aerosolized antibiotics.

Declaration of interest

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