# Respiratory infection. Approach to SARS-CoV-2 infection in transplant patients

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# Nosocomial pneumonia: Current etiology and impact on antimicrobial therapy

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## ABSTRACT

Nosocomial pneumonia is an infection with high clinical impact and high morbimortality in which *Pseudomonas aeruginosa* plays a priority role, especially in the critically ill patient. Conventional antipseudomonal treatments, historically considered as standard, are currently facing important challenges due to the increase of antimicrobial resistance. In recent years, new antimicrobials have been developed with attractive sensitivity profiles and remarkable efficacy in clinical scenarios of nosocomial pneumonia including bacteremia, mechanical ventilation, infections with multidrug-resistant organisms or situations of therapeutic failure. This new evidence underscores the need to update current clinical guidelines for the antimicrobial treatment of nosocomial pneumonia, especially in the most critically ill patients.

Keywords: Hospital-acquired pneumonia, *Pseudomonas aeruginosa*, Enterobacterales, Ceftolozane-tazobactam, Ceftazidime-avibactam

## INTRODUCTION

Hospital-acquired pneumonia, in addition to vascular catheter-associated infections, urinary tract infections, and surgical site infections, stands as one of the most common healthcare-associated infections and, in addition, represents a noteworthy cause of mortality.

Hospital-acquired pneumonia is the leading cause of healthcare-associated infection in intensive care units (ICU) [1] in Spain. More specifically, ventilator-associated pneumonia accounts for 41.06% of infections in ICU with an incidence rate of 13.83 per 100 mechanically ventilated patients

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[2]. The mortality rate of nosocomial pneumonia, regardless of mechanical ventilation, is in the range of 20-50%, and can reach up to 75% when there is structural or functional alteration of the respiratory tract or when the infection is caused by a multidrug-resistant microorganism [3,4].

To date and until the implementation of molecular techniques to optimize treatment, the choice of antimicrobial agent in hospital-acquired pneumonia in the early stages is usually empirical. This decision is usually based on the severity of the clinical picture, the results of previous cultures, knowledge of the local epidemiology and an assessment of the risk factors for multidrug-resistant microorganisms. Appropriate antimicrobial treatment therefore remains a challenge.

As recommended in the 2016 guidelines from the American Thoracic Society (ATS) and the Infectious Diseases Society of America (IDSA), empirical antimicrobial treatment for healthcare-associated pneumonia should comprise piperacillin-tazobactam, an anti-pseudomonal cephalosporin, levofloxacin, or an anti-pseudomonal carbapenem. Additionally, coverage against methicillin-resistant *Staphylococcus aureus* (MRSA) should be considered if the patient has risk factors. In cases of respiratory distress, high mortality risk, or recent receipt of intravenous antibiotics within the prior 90 days, double anti-pseudomonal coverage is advisable [5].

When determining the antimicrobial treatment for patients with hospital-acquired pneumonia, it is crucial to consider the following factors: (i) Etiology and resistance patterns: understand the causative agent and its resistance profile; (ii) Pharmacokinetics and pharmacodynamics: with special attention to how the drug distributes and its concentration within the infection site to ensure its effectiveness and (iii) Clinical trials experience: consider insights gained from relevant clinical trials in making treatment decisions.
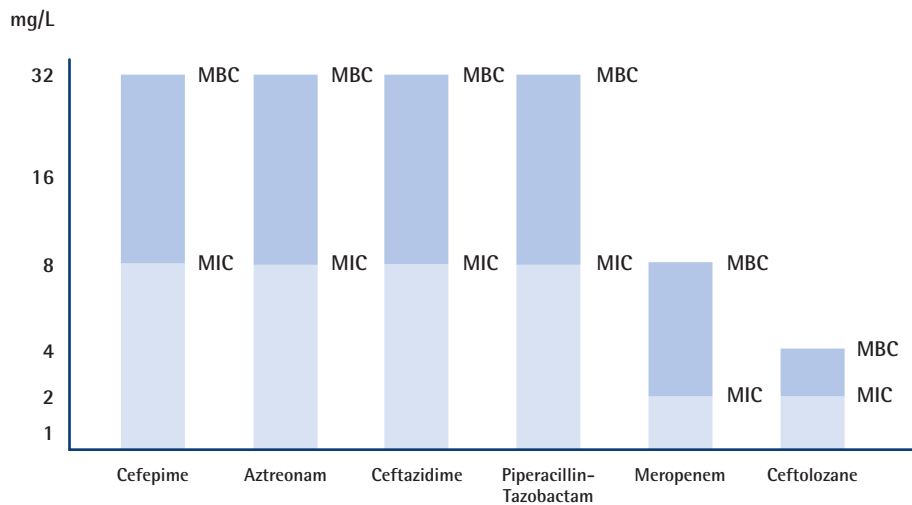
**Figura 1** | **MIC–MBC difference, impact on clinical efficacy and selection window for resistant pathogens (intra-treatment resistance) [12].**

## THE ETIOLOGY OF NOSOCOMIAL PNEUMONIA AND RESISTANCE PATTERNS

In contrast to other healthcare-associated infection models, where *Escherichia coli* is typically the most common pathogen, hospital-acquired pneumonia presents a different pattern. *P. aeruginosa* stands out as the most frequent etiological agent, accounting for up to 17.73% of isolates in cases of ventilator-associated pneumonia. Among enterobacteria, *Klebsiella pneumoniae* is the most prevalent, found in 8.72% of isolates (which is half as common as *P. aeruginosa*). *E. coli* is isolated in 6.59% of cases of ventilator-associated pneumonia [2].

In Spain, the most common mechanism of antimicrobial resistance in *P. aeruginosa* is the combination of *ampC* and alterations in permeability, which can be attributed to porin deficiency or increased expression of efflux pumps [6].

According to the prevalence study of healthcare-associated infections in Spain, roughly 20-40% of enterobacterial isolates exhibit resistance to third-generation cephalosporins, including ESBL or *ampC* resistance mechanisms. Additionally, 2-16% of isolates demonstrate resistance to carbapenems. These figures are notably higher in the case of non-fermenting microorganisms, with approximately 25-30% of *P. aeruginosa* isolates exhibiting resistance to carbapenems) [1].

When considering only isolates from respiratory tract samples, the resistance rates for meropenem and piperacillin-tazobactam, which are considered the standard therapies [5], are as follows: 34.26% and 38.94%, respectively, for *P. aeruginosa*, and 11.32% and 30.88% for *K. pneumoniae* [2]. These figures align with other studies, indicating resistance rates of 25-30% for the pathogens typically associated with healthcare-associated pneumonia to these antimicrobials, which are commonly recommended in clinical practice guide-

lines [7]. Finally, the count of *P. aeruginosa* strains posing significant treatment challenges - defined as those showing resistance to multiple classes of antimicrobials, such as piperacillin-tazobactam, carbapenems, antipseudomonal cephalosporins, aminoglycosides and quinolones - has been increasing, reaching 13.8% in 2022 [8].

## MICROBIOLOGICAL AND PHARMACODYNAMIC ADVANTAGES OF NEW ANTIPSEUDOMONAL DRUGS

Fortunately, following the release of the aforementioned antimicrobial therapy recommendations [5], new antimicrobial drugs with improved microbiological profiles have been developed. These drugs have undergone favorable assessments by regulatory agencies and have received therapeutic approval for the treatment of healthcare-associated pneumonia. Most important advantages of these new antimicrobial drugs is their more favorable resistance profile. In our country, the susceptibility of *P. aeruginosa* isolates to ceftazidime-avibactam and ceftolozane-tazobactam is 94.2-94.6%, respectively [9]. In a more recent study, in vitro sensitivity of isolates from respiratory samples, including *P. aeruginosa*, *K. pneumoniae*, and *E. coli*, exceeded 87%. Susceptibility was slightly lower in isolates with elevated carbapenem minimum inhibitory concentrations (MIC) [10].

In addition to the benefit in the spectrum, the new antibiotics provide advantages in the management of nosocomial pneumonia. The first is the stability in the sensitivity they maintain against isolation. Specifically, ceftazidime-avibactam and ceftolozane-tazobactam maintain MICs of 8 and 2mg/L respectively in carbapenem-resistant *P. aeruginosa* strains when MICs of cefepime, ceftazidime or piperacillin-tazobactam are ≥

| Table 1 | New antimicrobial drugs studies in hospital-acquired pneumonia. | | |
|---|---|---|---|
| | REPROVE [23] | APEKS-NP [24] | ASPECT-NP [25] |
| Study drugs | Ceftazidime-Avibactam vs Meropenem | Cefiderocol vs Meropenem | Ceftolozane-Tazobactam vs Meropenem |
| Patients | 726 | 292 | 726 |
| APACHE II [(Mean (SD)] | 14,5% (4.01) vs 14.9% (4.05) | 16.0% (6.1) vs 16,4% (6.9) | 17.5% (5.2) vs 17.4% (5.7) |
| Bacteremia | 4,68 % | 9,59% (32) | 6,06%*** |
| Mechanical ventilation at baseline | 43,11 % | 59,93% | 100% |
| Clinical cure rate | 68,8% vs 73,0% (difference –4.2 [95% CI –10.76 to 2.46])* 77·4% vs 78·1% (difference –0.7 [95% CI –7.86 to 6.39])** | 65% vs 67% (difference -2.0 [95% CI – 12.5 to 8.5])* | 54.4% vs 53.3% (difference 1.1 [95% CI -6.2 to 8.3])* 63.8% vs 64.7 (difference -1.3 [95% CI -10.2 to 7.7])** |
| Microbiological eradication | 55.6% vs 64.1% (difference -8.6 [95% CI –18.65 to 1.64]) | 48% vs 48% (difference -1.4 [95% CI -13.5 to 10.7]) | 73.1% vs 68.0% (difference 4.5 [95% CI -3.4 to 12.5]) |
| Mortality at day 28 | 8.1% vs 6.8% (difference 1.4 [95% CI –2.48 to 5.35])* | 20.0% vs 22.0% (difference -1.2 [95% CI -12.1 to 10.0])* [32] | 24.0% vs 25.3% (difference 1.1 [95% CI -5.1 to 7.4])* |

*Clinically modified intention-to-treat population, ** Clinically evaluable population, *** Gram-negative respiratory pathogen only.

32 or 128 mg/L [11]. The second is the lower cross-resistance, compared to classical antipseudomonal antibiotics (piperacillin-tazobactam, ceftazidime, cefepime), which after having been previously used in the patient, more easily induce resistance to the antibiotic used or to any of the others. This generally occurs due to overexpression of ampC or of the Mex AB/XY expulsion pump [12]. However, this cross-resistance is exceptional among the new antipseudomonal antibiotics, which are stable against ampC de-repression and are not affected by either loss of porins or hyperactivity of efflux pumps [13].

Ceftazidime-avibactam also includes the important addition of coverage against *Enterobacteriaceae*, including strains carrying high resistance (ESBL, ampC, OXA-48, KPC). The main added advantage of ceftolozane-tazobactam lies in its proximity between MIC and MBC (Minimal bactericidal concentration). This particularity is useful to reduce or avoid the selection window that facilitates the emergence of resistant strains. For example, the difference between MIC and MBC in ceftazidime, aztreonam, cefepime or piperacillin-tazobactam ranges between 8 and 32mg/L, with high and maintained concentrations of the antibiotic being necessary to avoid the selection of resistant strains. In the case of meropenem the difference between MIC and MBC is 2 to 8mg/L, however, in ceftolozane-tazobactam it is 2 to 4mg/L [12] (Figure 1). First consequence of this proximity between MIC-MBC are the lower likelihood of intra-treatment antimicrobial resistance (recorded in the ceftolozane-treated group with respect to the meropenem-treated group in the ASPECT-NN study) [14]. Second, it is ability to achieve a lung and plasma epithelial linning fluid (ELF) concentration that ensures a 86-95% probability of target attachment (PTA) at the approved and marketed dose of 3g/8h [15,16]. Therefore, this proximity between MIC and

MBC favors microbiological eradication, especially in situations where achieving optimal drug concentrations at the site of infection is challenging, such as cases involving capillary leakage, alterations in the ventilation/perfusion (V/Q) ratio, respiratory distress and severe pneumonia.

The distribution and concentration of antimicrobial drugs within the infection site are crucial factors of paramount importance. The diffusion of ceftazidime-avibactam and cefiderocol to the ELF is approximately 30-35% of the plasma concentration [17,18]. This percentage can be increased reaching of up to 60% the plasma concentration by extending the infusion time, ensuring that drug concentrations remain above the MIC throughout the dosing interval [18]. On the other hand, meropenem-vaborbactam has slightly lower sensitivity figures [19]; however, it manages to reach concentrations in the ELF of up to 60% of the plasma concentration. This characteristic can be particularly valuable in the treatment of critically ill patients [20]. Diffusion of ceftolozane-tazobactam to the ELF, it is approximately 30-40% of the plasma concentration.

Even more effective treatment could be achieved with these new drugs, using the same dose, but extending the infusion time. Ceftazidime-avibactam is stable at room temperature (22-25°C) for up to 4 hours after reconstitution [21] and ceftolozane-tazobactam for up to 24 hours [22], and can be administered as a continuous infusion. In both drugs, the pharmacodynamic ratio of posological effectiveness (T>MIC 50%) is above 99%, extending the infusion to the limit of its molecular stability.

## CLINICAL TRIALS EXPERIENCE

To the best of our knowledge, three studies have been

| Table 2 | Antipseudomonal recommendation against multi-drug resistant *P. aeruginosa* in the main guidelines for the treatment of antimicrobial-resistant gram-negative infection |
|---|---|
| Guideline | Antipseudomonal recommendation against multi-drug resistant *P. aeruginosa* |
| Mensa J. et al. Antibiotic selection in the treatment of acute invasive infections by *Pseudomonas aeruginosa*: Guidelines by the Spanish Society of Chemotherapy. (2018) [12]) | In order of preference: Ceftolozane-tazobactam > Ceftazidime-avibactam > Meropenem > Ceftazidime or Piperacillin-tazobactam ± Amikacin or Colistin |
| Paul M. et al. European Society of Clinical Microbiology and Infectious Diseases (ESCMID) guidelines for the treatment of infections caused by multidrug-resistant Gram-negative bacilli. (2022) [28]) | Ceftolozane-tazobactam Insufficient evidence available for: Imipenem-relebactam, Cefiderocol or Ceftazidime-avibactam |
| Pintado V. 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. (2023) [29]) | Ceftolozane-Tazobactam Alternatives: Ceftazidime-avibactam, Imipenem-relebactam, Colistin, Cefiderocol, Fosfomycin |
| Tamma PD et al. Infectious Diseases Society of America 2023 Guidance on the Treatment of Antimicrobial Resistant Gram-Negative Infections. (2023) [30]) | In order or preference: Ceftolozane-tazobactam > Ceftazidime-avibactam > Imipenem-relebactam Alternative: Cefiderocol |

conducted to evaluate the outcomes of these new drugs in the treatment of hospital-acquired pneumonia. When comparing the use of ceftazidime-avibactam (REPROVE) [23], cefiderocol (APEKS-NP) [24], or ceftolozane-tazobactam (ASPECT-NP) [25] to meropenem, no significant differences were observed in terms of clinical cure, microbiological eradication, or 28-day mortality. This information is summarized in Table 1.

A more in-depth analysis of the patient characteristics in these studies reveals that the patients included in the ASPECT-NP study [25] are clinically more critical. They exhibit higher APACHE II scores, experience bacteremia more frequently, and importantly, all of them are under mechanical ventilation therapy. This heightened severity of patient conditions enhances the significance of the study's results.

Ceftolozane–tazobactam also demonstrated non-inferiority to meropenem in terms of clinical cure rates among patients who had previously received unsuccessful antibacterial therapy (such as piperacillin-tazobactam, anti-pseudomonal third-generation cephalosporins, or quinolones) for the current episode of hospital-acquired pneumonia before entering the study [24]. Interestingly, high clinical success rates were achieved in patients who received ceftolozane-tazobactam as secondary therapy (84.8%) or salvage therapy (86.2%), as well as in those with life-threatening *P. aeruginosa* infections (80.7%), including 31.7% with hospital-acquired pneumonia, over one-half of *P. aeruginosa* strains being extensively drug-resistant (XDR), and with 78.2% of isolates displaying resistance to at least one carbapenem [26]. Moreover, in a post-hoc analysis of ASPECT-NP, focused on ventilated patients with hospital-acquired bacterial pneumonia and confirmed

microbiological isolation in a respiratory samples [27], the likelihood of death by day 28 was 2.3 times higher in participants treated with meropenem as opposed to ceftolozane-tazobactam (with a 95% confidence interval ranging from 1.2 to 4.5). This observation was made after accounting for other clinically relevant factors.

While it is accurate that the clinical practice guidelines for hospital-acquired pneumonia have not been revised since 2016, in recent years, several scientific societies have formulated antimicrobial treatment recommendations for addressing infections caused by resistant gram-negative bacteria, particularly for invasive infections involving *P. aeruginosa* [12,28-30]. These recommendations take into account the use of these new antimicrobial drugs, and valuable advice and treatment suggestions for hospital-acquired pneumonia can be derived from them. These recommendations are summarized in Table 2.

Therapeutic appropriateness significantly influences patient outcomes. The choice of medication has an impact on mortality rates, even when early diagnosis and intervention are in place. Data from 2021 year's ENVIN report underscores that appropriate antibiotic treatment for hospital-acquired pneumonia is currently at 76,34% [2], echoing the gap previously discussed concerning both microbiological and clinical aspects.

In cases where patients lack risk factors for multi-resistant microorganisms or signs of respiratory distress, following the 2016 guidelines [5] is a suitable approach during the initial stages. However, when patients present these risk factors, exhibit respiratory distress or have progressed beyond the seventh day of illness, it's advisable to consider a transition to

newer antibiotics such as ceftolozane-tazobactam or ceftazidime-avibactam [31]. These alternatives may offer a more effective and appropriate treatment in such specific cases.

In summary, hospital-acquired pneumonia is a prevalent and life-threatening medical condition, often caused by *P. aeruginosa* as the primary pathogen, along with less frequent occurrences of other enterobacteria. Conventional antimicrobial agents, historically considered as the standard treatment, now face significant resistance challenges. Fortunately, newer antimicrobial drugs with improved sensitivity profiles and additional advantages have emerged, proving highly effective even in the most critical clinical scenarios, including cases involving bacteremia, respiratory distress, mechanical ventilation, infections with multidrug-resistant organisms, and instances of therapeutic failure. These developments underscore the need for an update to the existing clinical practice guidelines for antimicrobial treatment of hospital-acquired pneumonia.

## CONFLICT OF INTEREST

The authors declare no conflict of interest.

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