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# Novelties in the treatment of community-acquired and hospital-acquired pneumonia

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## ABSTRACT

Pneumonia remains a leading cause of morbidity and mortality worldwide, placing a significant burden on healthcare systems due to hospitalizations and the demand for medical resources. In recent years, new drugs have been developed to improve the effectiveness and safety of empirical treatment for community-acquired pneumonia and both empirical and targeted treatments for hospital-acquired and ventilator-associated pneumonia, including those caused by highly antibiotic-resistant pathogens. The aim of this narrative review is to focus on recently approved drugs for pneumonia and provide an overview of promising future therapeutic options.

**Keywords:** Community-acquired pneumonia. Hospital-acquired pneumonia. Novel antibiotics.

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## INTRODUCTION

Pneumonia is a major cause of morbidity and mortality worldwide, with a significant impact on healthcare systems due to hospitalizations and medical resource efforts[1,2]. Pneumonia can be classified into two categories based on its context of onset: community-acquired pneumonia (CAP) and hospital-acquired pneumonia (HAP), the latter including ventilator-associated pneumonia (VAP) (Table 1).

**Table 1.** Definitions of pneumonia

| | |
|---|---|
| CAP | Pneumonia acquired in the community setting |
| HAP | Pneumonia developed ≥ 48 h after hospital admission and was not incubating at the time of admission |
| VAP | Pneumonia developed ≥ 48 h after endotracheal intubation |

CAP: community-acquired pneumonia; HAP: hospital-acquired pneumonia; VAP: ventilator-associated pneumonia.

CAP is a leading cause of emergency department visits and hospitalizations, with an estimated incidence in Europe of 1.07-1.2 cases/1,000 people/year, rising to 14 cases/1,000 among individuals aged over 65 years[3], and it significantly contributes to overall mortality[2]. Although it is necessary for clinicians to make every effort to reach an etiological diagnosis, the initial therapeutic approach in CAP is empirical in most cases. For this reason, antibiotic therapy should include coverage against both typical pathogens (including *Streptococcus pneumoniae, Haemophilus influenzae,* and *Moraxella catarrhalis*) and atypical bacteria (such as *Mycoplasma pneumoniae, Chlamydophila pneumoniae,* and *Legionella* spp.)[3]. Many antibiotics are to date available for the treatment of CAP[4], but the emergence of resistant bacterial strains, such as penicillin-resistant pneumococci (PRP) and macrolide-resistant *M. pneumoniae* deems necessary to continue developing new molecules active against such pathogens. Furthermore, broad-spectrum coverage against multidrug-resistant (MDR) pathogens, such as methicillin-resistant *Staphylococcus aureus* (MRSA) and *Pseudomonas aeruginosa*, which can cause CAP in patients with specific risk factors and may progress to severe disease[5] is often needed. An antibiotic with an appropriate spectrum, favorable safety profile, and good tolerability can optimize treatment. In addition, the possibility of oral therapy may facilitate outpatient treatment or, if hospitalization is required, enable a rapid switch from intravenous (IV) to oral formulation, potentially reducing the length of hospital stay and infusion-related side effects.

HAP represents the second most common nosocomial infection, with an incidence ranging from 5 to over 20 cases/1000 hospital admissions[6]. Among these, VAP represents a significant subset, with an incidence density of 18.3 episodes/1000 ventilator days, as reported in the EU-VAP/CAP study[7]. In recent years, antibiotic resistance among HAP/VAP pathogens has increased significantly, leading to in-hospital mortality rates ranging from 20% to 60% in VAP[8]. The etiology of HAP/VAP often involves MDR Gram-negative bacteria, such as *Klebsiella pneumoniae, P. aeruginosa,* and *Acinetobacter baumannii,* which are resistant to a wide range of antibiotics, including carbapenems, as well as Gram-positive bacteria, such as MRSA, for which treatment

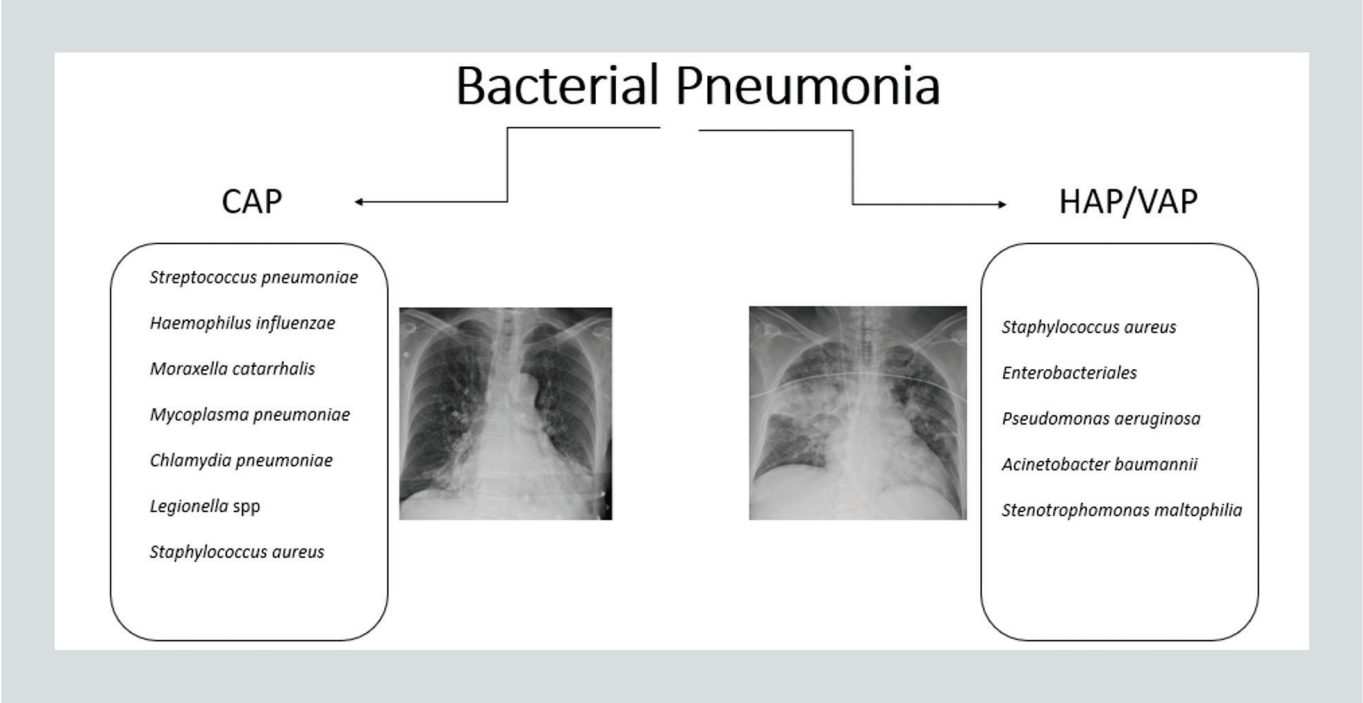


**Figure 1.** Bacterial etiology of CAP and HAP/VAP.
CAP: community-acquired pneumonia; HAP: hospital-acquired pneumonia; VAP: ventilator associated pneumonia.

options, were until recently, largely limited to vancomycin and linezolid[9]. Early identification of the etiological agent and the use of antibiotics with targeted activity against these MDR pathogens are essential for improving clinical outcomes and reducing mortality and complications associated with HAP/VAP.

Figure 1 summarizes the main pathogen involved in CAP and HAP/VAP.

Since the existing international guidelines for the antibiotic treatment of CAP and HAP were published several years ago[4,6,10], this narrative review seeks to offer an updated perspective on approved therapies and emerging agents that may represent current or future therapeutic options for the management of this syndrome.

## RECENTLY APPROVED ANTIBIOTICS FOR CAP

### Ceftaroline

Ceftaroline fosamil, the pro-drug of active ceftaroline, is a fifth-generation cephalosporin currently approved for the treatment of adults and children with CAP and complicated skin and skin structure infections (cSSTIs). The standard recommended dose of ceftaroline for adult patients with CAP is 600 mg every 12 h over 1 h IV infusion[11].

Ceftaroline exerts its activity by binding to penicillin-binding proteins (PBPs), particularly PBP-2a, and is effective against a wide range of pathogens, including methicillin-resistant MRSA, PRP, and some Gram-negative bacteria such as *Haemophilus* spp. and *M. catarrhalis*[12].

FOCUS 1 and FOCUS 2 are the phase 3 randomized controlled trials (RCTs) that demonstrated non-inferiority of ceftaroline compared to ceftriaxone plus a macrolide for the treatment of moderate-to-severe CAP. In these trials, ceftaroline showed better clinical cure rates at the test-of-cure visit, suggesting its efficacy for treating CAP. Another phase 3 trial showed superiority of ceftaroline over ceftriaxone for PORT class 3-4 CAP[13,14]. Despite these RCTs did not include MRSA as an etiological agent of pneumonia, real-world studies, such as the CAPTURE registry, support the use of ceftaroline in severe MRSA-related CAP, with clinical success reported in up to 62% of patients[15].

In a systematic review on the use of ceftaroline in MRSA pneumonia, a clinical success rate of 54-76% was reported for patients with MRSA CAP and of 57-60% for patients with MRSA HAP/VAP[16].

Pharmacoeconomic studies suggest that ceftaroline leads to earlier discharge and lower rates of initial antibiotic failure compared to ceftriaxone. Ceftaroline was also found to be cost-saving in the case of pneumococcal pneumonia[17].

Moreover, its favorable drug-drug interaction profile (for example, when compared to linezolid) makes it an interesting treatment option in case of comorbid patients with potential drug-drug interaction issues[5].

In conclusion, ceftaroline is a key novel antibiotic to treat severe CAP (sCAP), especially when MRSA is confirmed or suspected, such as in the case of CAP due to influenza or coronavirus disease 2019. Its efficacy, safety, and cost-effectiveness make it a valuable option in both empiric and targeted therapy for severe infections.

## Ceftobiprole

Ceftobiprole is a fifth-generation cephalosporin that exerts its antibacterial activity through the inhibition of transpeptidase activity and binding to penicillin-binding proteins (PBPs). It was approved in Europe at a dosage of 500 mg every 8 h over 2 h for the treatment of CAP and HAP[18]. It is effective against a variety of Gram-positive and Gram-negative pathogens, including MRSA, *M. catarrhalis*, *H. influenzae*, PRP, the majority of non-extended spectrum β-lactamase (ESBL), non-AmpC and non-carbapenemases-producing *Enterobacterales*, and *P. aeruginosa*[19]. A large antimicrobial surveillance program found that ceftobiprole retained bactericidal activity against 99.3% of *S. pneumoniae* isolates and 100% of *S. aureus*[20]. Its activity against *P. aeruginosa* was comparable to that of ceftazidime and 2-fold higher than that of cefepime. The antimicrobial activity against *Enterobacterales* was comparable to that of third- and fourth-generation cephalosporins[20]. In phase 3 trials, ceftobiprole has demonstrated non-inferiority to ceftriaxone plus linezolid for patients with sCAP[21]. Overall, ceftobiprole has a good safety profile, with minimal drug-drug interactions and low potential for toxicity[21].

In conclusion, ceftobiprole is a valid option for treatment of sCAP and HAP, especially in patients with MRSA or *Pseudomonas aeruginosa* infections, particularly in those with respiratory comorbidities or the elderly. Like ceftaroline, ceftobiprole could be considered for empirical MRSA coverage in the case of viral pneumonia.

## Lefamulin

Lefamulin is a pleuromutilin-class antibiotic, approved by the Food and Drug Administration (FDA) and European Medicines Agency (EMA) for the treatment of CAP. It is available in both IV and oral formulations and works by inhibiting protein synthesis through binding to the 50S bacterial ribosome at the peptidyl transferase center, preventing tRNA binding and peptide transfer[22]. In 2019, it was approved by the FDA for the treatment of CAP in both IV and oral forms with different dosages due to incomplete oral absorption (IV dosage: 150 mg every 12 h; oral dosage: 600 mg every 12 h)[23].

Lefamulin has broad-spectrum activity against Gram-positive bacteria like *S. pneumoniae,* MRSA, and *Enterococcus faecium* (including vancomycin-resistant enterococci VRE), Gram-negative pathogens like *H. influenzae, M. catarrhalis,* and *Neisseria spp.,* and also against atypical bacteria such as *M. pneumoniae, Legionella pneumophila,* and *Chlamydia pneumoniae*[22]. Lefamulin penetrates rapidly and extensively in the lungs. The epithelial lining fluid (ELF) concentration of lefamulin is almost six-fold higher than in plasma, and high drug concentrations are achieved in the alveolar macrophages as well[24].

Efficacy of lefamulin in patients with CAP was evaluated in two multicenter, double-blind, randomized, phase 3 trials called LEAP1 and LEAP2. In the LEAP 1 trial, IV lefamulin was compared to moxifloxacin (with or without linezolid) in patients with moderate-to-severe CAP and reached non-inferiority in clinical response[25]. The same favorable result was demonstrated in LEAP2 with the comparison of the oral formulation of lefamulin and moxifloxacin in patients with moderate CAP[26].

Lefamulin would be a valid alternative to fluoroquinolones (FQ) and other typical frontline antimicrobials for the treatment of CAP and is particularly appealing for its possibility of being administered IV or orally, depending on the patient's needs. More consistent post-marketing clinical data is needed to better define lefamulin's efficacy and safety in real-life clinical settings, including outpatient use and its use in critically ill patients[5].

## Omadacycline

Omadacycline is a semisynthetic aminomethylcycline, structurally related to tetracycline[27]. It binds specifically to the primary tetracycline binding site on the bacterial 30S ribosomal subunit and overcomes common tetracycline resistance mechanisms, such as efflux pumps and ribosomal protection[28].

At present, the FDA has approved omadacycline for the treatment of CAP and acute bacterial skin and skin structure infections[29]. The recommended dosage is a 200 mg IV loading dose, followed by a daily dose of 100 mg IV or 300 mg orally. Omadacycline has high plasma, ELF, and alveolar macrophage penetration, making it an effective option in treating pneumonia[30]. Omadacycline is effective against a broad range of pathogens causing CAP, including *S. pneumoniae, H. influenzae,* MRSA, Gram-negative bacilli, and atypical bacteria[31].

The efficacy of omadacycline was demonstrated in a phase 3, randomized, double-blind trial named the OPTIC trial, which compared omadacycline to moxifloxacin for treating CAP in adults[32]. Omadacycline was non-inferior to moxifloxacin in terms of early clinical response and post-treatment clinical response. Of note, patients with sCAP or septic shock were excluded from the study. Omadacycline had a safety profile similar to moxifloxacin but showed a lower incidence of diarrhea, with no reported cases of *Clostridioides difficile* infections[32].

In conclusion, omadacycline is an effective, once-daily treatment option for treating CAP, with a favorable pharmacological, safety, and efficacy profile. However, additional studies are needed in certain settings that were excluded from registration trials, such as in patients with sCAP and in outpatient settings.

## Delafloxacin

Delafloxacin is a next-generation fluoroquinolone with a distinct chemical structure that allows better penetration of bacterial membranes and enhances bactericidal activity under acidic conditions. It targets both DNA gyrase and topoisomerase IV, offering a broader spectrum of activity than older fluoroquinolones[33].

Delafloxacin was approved by the FDA and EMA in 2019 for the treatment of CAP in adults. The recommended dose is 300 mg IV every 12 h, with an option to switch to 450 mg orally every 12 h after initial IV treatment[34,35].

Delafloxacin has strong efficacy against a wide range of pathogens, including *S. pneumoniae* (including PRP), MRSA, *P. aeruginosa*, *Enterobacterales*, and intracellular pathogens[36]. To note, it also exhibits a significantly 64-fold higher activity against MRSA compared to levofloxacin[37]. In the phase 3 DEFINE-CAPB trial, delafloxacin was compared to moxifloxacin for the treatment of CAP. Delafloxacin showed non-inferiority to moxifloxacin in achieving the primary endpoint of early clinical response. The study included patients with a quite wide range of clinical severity (PORT risk classes II-V), including those with chronic obstructive pulmonary disease (COPD) and asthma[38]. Delafloxacin was generally well tolerated, without reports of common side effects reported with older FQ, such as cardiotoxicity, phototoxicity, or neurologic effects[39].

In conclusion, delafloxacin represents a valuable therapeutic option in the treatment of CAP, with a broad spectrum of activity, good lung penetration, and a favorable safety profile compared to older FQs. However, real-world data on its use are still limited.

## Nemonoxacin

Nemonoxacin is a novel, non-fluorinated quinolone antibiotic with a broader spectrum of activity and a reduced resistance profile compared to other FQs. It targets both DNA topoisomerase II and IV, making it effective against Gram-positive cocci, Gram-negative bacilli, and atypical bacteria, including the most common pathogens in CAP[40]. Nemonoxacin has shown potent *in vitro* activity against resistant pathogens

such as MRSA, PRP, and ertapenem-non-susceptible *Enterobacterales*[41]. The oral formulation of nemonoxacin has been approved in Taiwan and China for the treatment of CAP at a dose of 500 mg once daily[42]. Nemonoxacin has not received official approval from the FDA, which has required further phase 3 studies to document its safety and efficacy, although granting the drug the label of "Qualified Infectious Disease Product".

Clinical trials, including phase 2 and 3 studies, have demonstrated that oral nemonoxacin is non-inferior to oral levofloxacin in treating mild to moderate CAP, with similar clinical cure and microbiological success rates[43,44]. The safety profile of nemonoxacin is also comparable to that of levofloxacin, with a meta-analysis suggesting that nemonoxacin might be safer than other FQ with regard to cardiotoxicity[45]. Another recent randomized, double-blind phase 3 clinical trial demonstrated non-inferiority of nemonoxacin to levofloxacin both administered IV in treating CAP in adult patients[46].

Table 2 summarizes antibiotics available for CAP.

Figure 2 presents a flowchart for the empirical therapy of CAP.

## NEW ANTIBIOTICS FOR CAP UNDER INVESTIGATION

### Phase 3 studies for CAP

#### *Solithromycin*

Solithromycin is a fourth-generation macrolide and the first of the fluoroketolide class; it binds to distinct sites on the 50S ribosomal subunit, providing strong antibacterial activity also against macrolide-resistant pathogens[47]. Solithromycin has strong activity against common pathogens causing CAP, including resistant strains of *S. pneumoniae*, *H. influenzae*, MRSA, and atypical bacteria[48]. The efficacy of solithromycin in the treatment of CAP has been evaluated in two phase 3 trials called SOLITAIRE-ORAL and SOLITAIRE-IV[49,50]. Both trials showed non-inferiority to moxifloxacin for the early clinical response to CAP, but solithromycin has shown a higher incidence of adverse events, especially in the IV form, for which infusion site reactions and hepatotoxicity were common. For this reason, the FDA declined approval due to safety concerns and requested larger studies to better define the safety profile of solithromycin.

### Phase 2 studies for CAP

#### *Zabofloxacin*

A novel oral FQ has been approved in South Korea, the Middle East, and North African countries for the treatment of acute bacterial exacerbation of COPD[51]. Its mechanism of action involves dual targeting of DNA gyrase and topoisomerase IV, exerting a bactericidal effect[52]. Its spectrum of activity is primarily directed against community-acquired respiratory pathogens, including *S. pneumoniae, S. aureus* (including FQ-resistant strains), *H. influenzae, M. catarrhalis*, and *K. pneumoniae*[53]. However, it is ineffective against difficult-to-treat (DTR) Gram-negative bacteria, such as *P. aeruginosa* and *A. baumannii*[52,53]. A phase 2 study was conducted to evaluate the safety and efficacy of zabofloxacin. However, the results of

**Table 2.** Novel antibiotics for community-acquired pneumonia

| Drug | Drug class | Spectrum | Formulation | Labeled indication | Approved dosage for treatment of CAP |
|---|---|---|---|---|---|
| Ceftaroline | Fifth-generation cephalosporin | PR *S. pneumoniae*, MSSA, MRSA, hVISA, VISA, and VRSA, daptomycin non-susceptible *S. aureus*, linezolid resistant *S. aureus*, non-ESBL or AmpC-producing *Enterobacterales*, *Haemophilus* spp., and *Moraxella catarrhalis* | Only IV | ABSSSI CAP | 600 mg every 12 h IV |
| Ceftobiprole | Fifth-generation cephalosporin | PR *S. pneumoniae*, MSSA, MRSA, non-ESBL, non-AmpC and non-carbapenemases-producing *Enterobacterales*, *P. aeruginosa* | Only IV | ABSSI CAP HAP (excluding VAP) | 500 mg every 8 h IV |
| Lefamulin | Pleuromutilin | Gram-positive, Gram-negative, and atypical respiratory pathogens, including PR and macrolide-resistant *S. pneumoniae*, *H. influenzae*, *S. aureus*, *Mycoplasma pneumoniae*, *Legionella*, and *Chlamydophila pneumoniae* | IV and Oral | CAP | 150 mg every 12 h IV or 600 mg every 12 h orally |
| Omadacycline | Aminomethylcycline | PR and macrolide-resistant streptococci, MRSA, some Gram-negative bacilli, both aerobes and anaerobes, and atypical bacteria | IV and Oral | ABSSSI CAP | 100 mg every 24 h IV or 150 mg every 24 h orally |
| Delafloxacin | Fluoroquinolone | Streptococci, *S. aureus* including MRSA, *Enterobacterales*, *P. aeruginosa*, and intracellular pathogens, including fluoroquinolone-resistant isolates | IV and Oral | ABSSSI CAP | 300 mg every 12 h IV or 450 mg every 12 h orally |
| Nemonoxacin | Non-fluorinated quinolone | Gram-positive, Gram-negative bacteria, and atypical pathogens, including MRSA, VRE, and *A. baumannii* | IV and Oral | CAP (only in China and Taiwan) | 500 mg every 24 h orally |

*A. baumannii: Acinetobacter baumannii*; ABSSSI: acute bacterial skin and skin structure infections; CAP community-acquired pneumonia; ESBL: extended spectrum β-lactamase; HAP: hospital-acquired pneumonia; hVISA: VISA: and VRSA: vancomycin heterogeneous, intermediate, and resistant *S. aureus*; IV: intravenous; MRSA: methicillin-resistant *S. aureus*; MSSA: methicillin-sensible *S. aureus*; PR: penicillin- resistant; VAP: ventilator-associated pneumonia; VRE vancomycin resistant *Enterococcus* spp.; *S. pneumonia: Streptococcus pneumonia*; *S. pneumoniae: Streptococcus pneumoniae*; *S. aureus: Staphylococcus aureus*; *P. aeruginosa: Pseudomonas aeruginosa*.

this trial have not yet been made available (NCT01081964). The drug is well tolerated, with gastrointestinal adverse effects being the most commonly reported ones. A key advantage is that it is not associated with QTc prolongation[54]. Future studies may explore its potential role in the treatment of CAP.

## Aravofloxacin (JNJ-Q2)

A fifth-generation FQ, available in both oral and IV formulations, appears promising, demonstrating more than 16-fold greater potency than moxifloxacin and levofloxacin against *S. pneumoniae*. Its mechanism of action

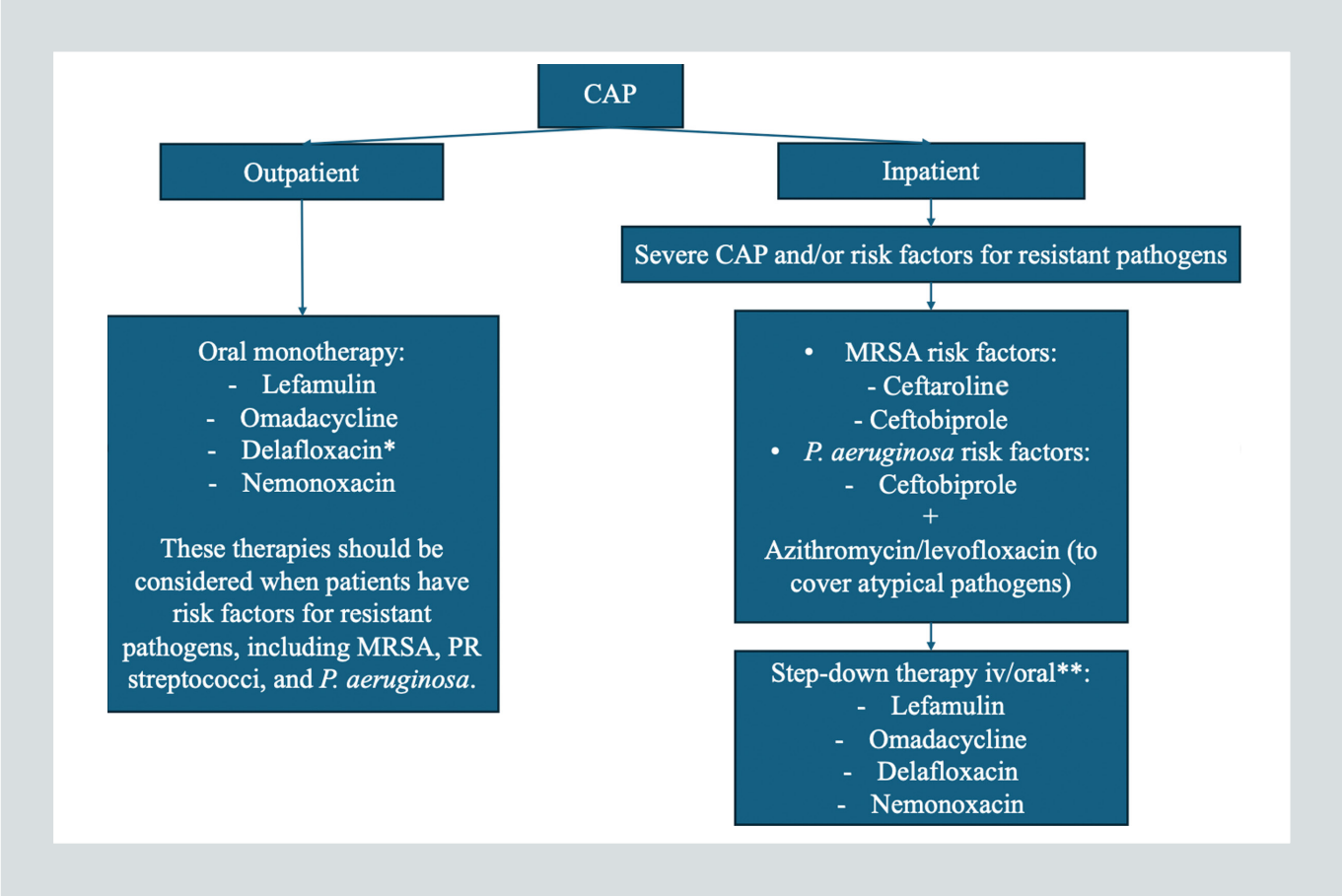


**Figure 2.** Empirical therapy for community-acquired pneumonia.
*Of the proposed therapies, only delafloxacin is active against *Pseudomonas aeruginosa*.
**Step-down therapy should be considered for patients who are clinically improving and hemodynamically stable. If oral therapy is chosen, the patient must be able to take oral medication and have a normally functioning gastrointestinal tract.
CAP: community-acquired pneumonia; IV: intravenous; MRSA: methicillin-resistant *Staphylococcus aureus*; PR: penicillin-resistant.

involves dual targeting of DNA gyrase and topoisomerase IV, covering a broad spectrum of pathogens, including *S. pneumoniae, MRSA, Enterococcus* spp., *Escherichia coli, Klebsiella* spp., *H. influenzae,* and *P. aeruginosa*[55,56]. Among the studies conducted, a phase 2 trial evaluated the efficacy of aravofloxacin versus moxifloxacin for the treatment of CAP. However, it failed to demonstrate non-inferiority, likely due to the small sample size[57]. The drug has received "Qualified Infectious Disease Product and Fast Track" designations from the FDA.

## Nafithromycin

Nafithromycin is a novel oral lactone ketolide that inhibits the 50S ribosomal subunit and exhibits *in vitro* activity against *S. pneumoniae* (including macrolide-resistant strains), *H. influenzae, M. catarrhalis,* methicillin-susceptible *S. aureus* (MSSA), and *C. pneumoniae*[58,59]. A phase 2 randomized, placebo-controlled study compared nafithromycin with moxifloxacin for the treatment of CAP in adults. Preliminary results demonstrated clinical non-inferiority; however, no microbiological data were reported

(NCT02903836). Its good penetration into the ELF and its activity against macrolide-resistant pathogens make it a potential candidate for the future treatment of pneumonia[60].

### *Radezolid*

It is the first biaryloxazolidinone that demonstrates activity against typical bacterial pathogens while also exhibiting enhanced efficacy against intracellular organisms such as *Chlamydia* and *Legionella* species. Interestingly, it retains activity against linezolid-resistant strains[61]. To date, only two phase 2 studies have been completed. Notably, a phase 2 clinical trial evaluating its efficacy in mild-to-moderate CAP at three different dosages demonstrated comparable efficacy across all dose groups (NCT00640926).

Table 3 shows new antibiotics for CAP under investigation.

**Table 3.** New antibiotics for community-acquired pneumonia under investigation

| Drug name | Drug class | Development phase | Formulation |
|---|---|---|---|
| Solithromycin | Fluoroketolide | Phase 3 | Oral and IV |
| Zabofloxacin | Fluoroquinolone | Phase 2 | Oral |
| Aravofloxacin | Fluoroquinolone | Phase 2 | Oral and IV |
| Nafithromycin | Lactone ketolide | Phase 2 | Oral |
| Radezolid | Biaryloxazolidinone | Phase 2 | Oral |

IV: intravenous.

## RECENTLY APPROVED ANTIBIOTICS FOR HAP AND VAP

Since these diseases are often associated with MDR Gram-negative pathogens, the drug development pipeline has been enriched with molecules specifically targeting this spectrum of activity, and approval studies are increasingly pathogen-focused rather than syndrome-based.

## Ceftobiprole

In the setting of HAP, the efficacy of ceftobiprole was investigated in a phase 3 RCT, in which ceftobiprole was compared to ceftazidime plus linezolid[62]. However, ceftobiprole did not reach non-inferiority in the subgroup of patients with VAP, and thus this indication was excluded[62]. Complete information regarding ceftobiprole mechanism of action, spectrum of activity, and further clinical indications are already summarized in the Ceftobiprole section, at the beginning of this study.

## Ceftolozane/Tazobactam

Ceftolozane/tazobactam is a combination of ceftolozane, a semisynthetic fifth-generation cephalosporin, and tazobactam, a β-lactamase inhibitor. It exerts bactericidal activity by binding to PBPs and inhibiting bacterial cell wall biosynthesis. Notably, it is highly active against *P. aeruginosa*, maintaining efficacy despite non-enzymatic resistance mechanisms such as porin loss and efflux pumps[63]. The addition of tazobactam extends its spectrum to include ESBL-producing *Enterobacterales*; however, it remains ineffective against carbapenemase-producing strains, including Ambler class A, class D, and class B β-lactamases. Its spectrum of activity does not include anaerobic bacteria, Gram-positive

cocci, *Acinetobacter baumannii*, or *Stenotrophomonas maltophilia*[63-65].

Ceftolozane/tazobactam is currently approved for the treatment of HAP/VAP at the dosage of 2 g ceftolozane/1 g tazobactam every 8 h to overcome higher MICs of pathogens and to ensure appropriate concentrations in the ELF[66].

Its approval for the treatment of HAP and VAP was based on the phase 3 ASPECT-NP trial, comparing the safety and efficacy of ceftolozane/tazobactam with meropenem for 7 to 14 days of therapy. Ceftolozane/tazobactam demonstrated a similar microbiological eradication rate and non-inferiority in clinical cure and all-cause mortality. Of note, in the subgroup of patients with ESBL-producing *Enterobacterales*, the 28-day mortality was lower in the ceftolozane/tazobactam treatment group[67].

Real-world studies have confirmed the findings of registration trials, demonstrating the effectiveness and safety of ceftolozane/tazobactam in the treatment of HAP/VAP caused by Gram-negative bacteria, including ESBL-producing *Enterobacterales* and MDR *P. aeruginosa*. These results support its role as a valuable carbapenem-sparing option[68-70].

## Ceftazidime/Avibactam

Ceftazidime/avibactam is a combination of ceftazidime, a third-generation cephalosporin, and avibactam, a non-β-lactam semisynthetic β-lactamase inhibitor. It is approved for the treatment of HAP/VAP, both as an empiric and targeted therapy[71]. Its main characteristic is its activity against Gram-negative bacteria, including *P. aeruginosa* strains with various resistance mechanisms, such as ESBLs, Ambler class A, class C, and certain class D β-lactamases (e.g., OXA-48). However, it lacks efficacy against strains producing metallo-β-lactamases and against *Acinetobacter* spp. producing OXA-type carbapenemases[72,73]. The current dosage of 2 g ceftazidime/0.5 g avibactam every 8 h has been shown to achieve PK/PD targets in patients with pneumonia, including critically ill individuals. The phase 3 REPROVE trial demonstrated non-inferiority compared to meropenem[71].

Although no randomized clinical trials have specifically evaluated the use of ceftazidime/avibactam for carbapenem-resistant *Enterobacterales* (CRE) infections, real-world data suggest a high success rate and a favorable safety profile. These findings support its use as a preferred, first-line treatment for suspected or proven CRE infections[74-76].

## Meropenem/Vaborbactam

The combination of meropenem with vaborbactam, a novel cyclic boronic acid β-lactamase inhibitor characterized by high affinity for the active sites of serine-based β-lactamase enzymes[77], exhibits strong activity against *Enterobacterales* producing Ambler class A and C β-lactamases. However, vaborbactam does not protect meropenem from strains producing class B and D β-lactamases and does not enhance meropenem activity against glucose-non-fermenting Gram-negative bacilli[78,79]. Meropenem/vaborbactam is administered at a dosage of 2g/2g every 8 h as a prolonged 3-h infusion.

The phase 3 trial TANGO-II was a pathogen-oriented trial, demonstrating the efficacy of meropenem/vaborbactam versus the best available therapy in patients with serious CRE infections, including HAP/VAP. It showed a higher clinical cure and microbiological eradication rates in the meropenem/vaborbactam group and also a lower mortality rate[80].

Real-world data are increasing in the use of meropenem/vaborbactam in the clinical practice, showing optimal results of efficacy in CRE infections, including critically ill patients and cases of ceftazidime/avibactam resistance[81-83], making it one of the treatments of choice in case of proven/probable CRE infections, including lung infections[76].

## Imipenem/Relebactam

Imipenem/relebactam is a novel combination of the carbapenem imipenem-cilastatin and relebactam, a new bicyclic diazabicyclooctane β-lactamase inhibitor[84]. Its spectrum includes Gram-negative bacteria producing Ambler Class A and C β-lactamases, with relebactam restoring imipenem activity against *P. aeruginosa* strains whose resistance is mediated by OprD porin loss or AmpC overproduction. However, imipenem/relebactam is still hydrolyzed by bacteria producing class B and D β-lactamases, and it shows no activity against *A. baumannii* or *S. maltophilia*[85,86]. Moreover, *Proteus* spp., *Providencia* spp., and *Morganella* spp. exhibit lower susceptibility to imipenem, and relebactam does not alter this intrinsic characteristic[87].

The approved dosage for imipenem/(cilastatin)/relebactam is 500/(500)/250 mg every 6 h, infused over 30 min.

Imipenem/relebactam reached the approvement for HAP/VAP treatment after two phase 3 clinical trials (RESTORE-IMI 1 and RESTORE-IMI 2), in which this new combination was found to be non-inferior to the comparator (colistin plus imipenem and piperacillin/tazobactam, respectively), with a lower 28-day mortality and a higher overall clinical response. In particular, in the RESTORE-IMI 2 study, imipenem/relebactam demonstrated a significantly lower mortality rate compared to the comparator, even in a subgroup of patients requiring mechanical ventilation and having an APACHE II score above 15[88,89].

Although few studies on the real-life use of imipenem/relebactam are available, the results are promising, particularly in cases of DTR *P. aeruginosa*, making it a valuable option when carbapenem-resistant Gram-negative bacilli are suspected[90-92].

## Cefiderocol

Cefiderocol represents a new generation cephalosporin with a unique mechanism of action, binding to ferric iron and using iron channel transporters through the cell wall to enter the bacteria and reach a high concentration in the periplasmic space, employing a so-called "Trojan horse" strategy[93].

Its spectrum of action is very wide, covering both Gram-negatives harboring all classes of carbapenemases (from Ambler class A to D) and non-fermenting bacteria such as *P. aeruginosa*, *S. maltophilia*, and *A. baumannii* (including meropenem-resistant strains)[94].

Cefiderocol is administered IV at a dosage of 2 g every 8 h. The phase 3 double-blind, randomized trial APEKS-NP showed the non-inferiority of cefiderocol compared to meropenem in the case of HAP and VAP, including VAP caused by *K. pneumoniae*, *P. aeruginosa*, and *A. baumannii*. In particular, in the case of meropenem-resistant *A. baumannii* strains, all-cause observed mortality was 0%[95].

However, in the CREDIBLE-CR open-label trial, the all-cause mortality rate at the end of the study was higher in the cefiderocol group (42%) versus best available therapy (18%), particularly when the infecting pathogen was *A. baumannii.* This observation led to a warning regarding its use in this setting[96,97], even though certain patients characteristics in this group could explain the results and a subsequent analysis of the trial demonstrated a good efficacy of cefiderocol treatment against MBL producing Gram-negative bacteria, including *P. aeruginosa*[98].

Real-life experience reports also confirmed a role for cefiderocol, compared to colistin-based regimens, in case of infections due to DTR Gram-negative bacteria with limited treatment options. However, further data are needed to better define its optimal place in clinical practice[99-101].

## Aztreonam/Avibactam

This antibiotic represents the combination of aztreonam (a monobactam with activity against MBL) and avibactam (a non-β-lactam semisynthetic with β-lactamase inhibitor activity), which protects aztreonam from the hydrolysis by other β-lactamases often present in Gram-negative bacteria together with MBL. For this reason, aztreonam/avibactam retains activity against all Ambler class carbapenemases and also against *P. aeruginosa* strains[102,103]. Moreover, a recent study from the United States showed that aztreonam-avibactam also retains activity against *Enterobacterales* non-susceptible to ceftazidime-avibactam and/or meropenem/vaborbactam[104].

In the phase 3 clinical trial REVISIT, aztreonam/avibactam (with metronidazole in cases of complicated intra-abdominal infection) was compared to meropenem, showing efficacy and safety in Gram-negative bacterial infections. Of note, 24% of isolates tested for possible carbapenemases expression were positive (MBL or serine carbapenemases, or both)[105].

While awaiting the data from the clinical trial, real-life experience with the combination of ceftazidime/avibactam plus aztreonam demonstrated a lower 30-day mortality rate compared to the best available therapy in patients with infections due to bacteria expressing New Delhi MBL enzymes[106].

Nowadays, aztreonam/avibactam is approved by the EMA at a dosage of 1.5 g/0.5 g every 8 h, with a loading dose of 2 g/0.67 g[107]. It represents an interesting option for infections due to MBL-producing bacteria.

## Sulbactam/Durlobactam

Sulbactam/durlobactam combines sulbactam, a β-lactam with intrinsic activity against *Acinetobacter* spp., and durlobactam, a new diazabicyclooctane β-lactamase inhibitor, which protects sulbactam in case of Ambler

class A, C, and D carbapenemases expression. The drug was studied specifically for infections caused by *Acinetobcater baumannii-calcoaceticus complex*, with very promising *in vitro* data, also against strains resistant to colistin and cefiderocol[108,109].

Sulbactam/durlobactam was approved by the FDA at a dosage of 1 g/1 g every 6 h, infused over 3 h, for HAP and VAP caused by the *Acinetobacter baumannii-calcoaceticus complex*. Sulbactam/durlobactam was compared to colistin in the phase 3 trial, ATTACK trial, demonstrating non-inferiority in terms of 28-day mortality, with evidence of lower nephrotoxicity compared to colistin[110].

To date, some case reports have described the efficacy of sulbactam/durlobactam in clinical practice[111,112], so more data will be added in the future to guide its best use in clinical practice.

Table 4 summarizes the new antibiotics for HAP/VAP.

Figure 3 presents a flowchart for the empirical and targeted therapy of HAP and VAP.

## ANTIBIOTICS THAT COULD BE CONSIDERED IN THE FUTURE

### Plazomicin

Plazomicin is a new semisynthetic aminoglycoside effective against MRSA as well as Gram-negative bacteria that produce carbapenemases or have aminoglycoside resistance due to modifying enzymes. The FDA approved it for the treatment of complicated urinary tract infections, including pyelonephritis. It is not yet approved for the treatment of HAP/VAP, but in the randomized CARE trial, the efficacy and safety of plazomicin were compared with colistin (both in combination with meropenem or tigecycline) also in patients with pneumonia. However, the number of patients was very small, so the FDA has not yet approved plazomicin for the treatment of HAP and VAP[113].

### Eravacycline

Eravacycline is a synthetic fluorocycline structurally similar to tigecycline, with a broad spectrum of activity against Gram-positive and Gram-negative bacteria, including *A. baumannii* and anaerobes, but not *P. aeruginosa*[114,115]. To date, no RCTs have evaluated its use for the treatment of HAP or VAP; however, in healthy volunteers, eravacycline concentrations in the ELF were six times higher than in plasma[116]. Only one retrospective study has assessed eravacycline for *A. baumannii* pneumonia, compared to the best available therapy (BAT). Patients treated with eravacycline had higher 30-day mortality rates and lower microbiological cure rates. However, after excluding patients with SARS-CoV-2 infection, no statistically significant difference was observed compared to BAT. This exclusion, however, reduced the sample size, thereby decreasing the statistical power of the analysis[117]. Further data are needed to clarify its potential role in the treatment of nosocomial pneumonia, possibly in combination with other agents.

### Aerosolized antibiotics

Up to now, no antibiotics have been specifically approved for HAP/VAP via the

**Table 4.** Novel antibiotics for hospital-acquired/ventilator associated pneumonia

| Drug | Drug class | Spectrum | Formulation | Labeled indication | Approved dosage for treatment of HAP/VAP |
|---|---|---|---|---|---|
| Ceftolozane/ Tazobactam | Cephalosporin/β-lactamase inhibitor | ESBL-producing *Enterobacterales*, MDR *P. aeruginosa*, some anaerobes | IV | FDA and EMA: HAP/VAP, cIAI, cUTI | 2 g/1 g every 8 h |
| Ceftazidime/ Avibactam | Cephalosporin/β-lactamase inhibitor | ESBL, KPC, AmpC, and some OXA (e.g., OXA 48) producing *Enterobacterales*, MDR *P. aeruginosa* | IV | FDA and EMA: HAP/VAP, cIAI, cUTI<br>EMA: associated bacteremia with limited treatment options | 2 g/0.5 g every 8 h |
| Meropenem/ Vaborbactam | Carbapenem/Novel β-lactamase inhibitor | ESBL, KPC, AmpC-pro- ducing *Enterobacterales*, non-MDR *P. aeruginosa*, non-MDR *A. baumannii* | IV | FDA: cUTI<br>EMA: HAP/VAP, cIAI, cUTI, associated bacteremia with limited treatment options | 2 g/2 g every 8 h |
| Imipenem/ Relebactam | Carbapenem/Novel β-lactamase inhibitor | ESBL, KPC-producing *Entero- bacterales*, MDR *P. aeruginosa* | IV | FDA: HAP/VAP, cIAI, cUTI<br>EMA: HAP/VAP also with associated bacteremia with limited treatment options, Gram negative infections with limited treatment options | 500 mg/250 mg every 6 h |
| Cefiderocol | Cephalosporin | ESBL, CRE (class A, B, and D enzymes), CR *P. aeruginosa, S. maltophilia, A. baumannii* | IV | FDA: HAP/VAP, cUTI<br>EMA: aerobic Gram-negative infections with limited treatment options | 2 g every 8 h |
| Aztreonam/ Avibactam | Monobactam/β-lactamase inhibitor | ESBL, CRE (class A, B, and D enzyme)<br>Limited activity against *A. baumannii* and *P. aeruginosa* | IV | FDA and EMA: HAP/VAP, cIAI, cUTI<br>EMA: aerobic Gram-negative infections with limited treatment options | 1.5 g/0.5 g every 8 h |
| Sulbactam/ Durlobactam | β-lactam/β-lactamase inhibitor | ESBL, CRE, OXA producing *A. baumannii* | IV | FDA: HAP/VAP caused by susceptible *Acinetobacter baumannii–calcoace- ticus complex* | 1 g/1 g every 6 h |

cIAI: complicated intra-abdominal infections; CR: carbapenem-resistant; CRE: carbapenem-resistant *Enterobacterales*; cUTI: complicated urinary tract infections; EMA: European Medicines Agency; ESBL: extended-spectrum β-lactamases; FDA: Food and Drug Administration; HAP: hospitalized-acquired pneumonia; IV: intravenous; KPC: *Klebsiella pneumoniae* carbapenemase; MDR: multi-drug resistant; OXA: oxacillinases; VAP: ventilator-associated pneumonia; *P. aeruginosa: Pseudomonas aeruginosa, S. maltophilia: Stenotrophomonas maltophilia; A. baumannii: Acinetobacter baumannii*.

inhalation route, partly due to the inconclusive results of previous randomized trials, which failed to demonstrate a clear clinical benefit, as for adjunctive inhaled amikacin alongside IV standard-of-care antibiotics and inhaled tobramycin[118-120]. However, the

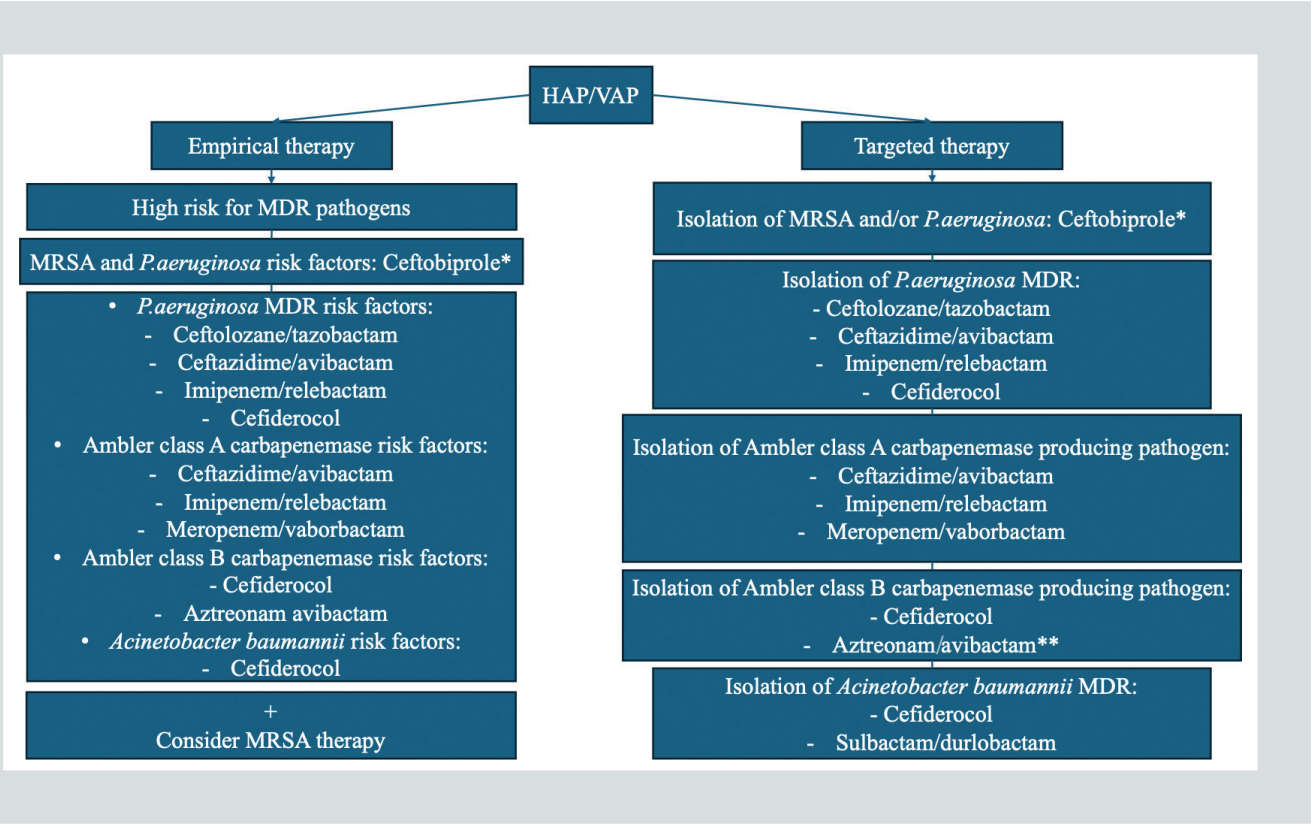


**Figure 3.** Empirical and targeted therapy for hospital-acquired and ventilator-associated pneumonia.
*Ceftobiprole is approved only for HAP, not for VAP.
**Aztreonam/avibactam has a limited activity against *A. baumannii* and *Pseudomonas aeruginosa*.
HAP: hospital-acquired pneumonia; MDR: multi-drug resistant; MRSA: methicillin-resistant *Staphylococcus aureus*; VAP: ventilator-associated pneumonia.

administration of antibiotic therapy through aerosolization could be a promising strategy, particularly for nosocomial pneumonia caused by MDR pathogens, where achieving adequate drug concentrations in the ELF is crucial[121].

Alongside nosocomial lung infections, some studies have explored aerosolized antibiotic use in bronchiectasis patients, with or without cystic fibrosis, mainly as a preventive approach against recurrent exacerbations.

In the setting of bronchiectasis, liposomal ciprofloxacin was studied in both a rapid-release formulation (Lipoquin, ARD-3100) and a slow-release formulation (Pulmaquin, ARD-3150). A phase 2 study (ORBIT-2 trial) demonstrated a reduction in *P. aeruginosa* bacterial load in mucus and a prolonged time to exacerbation in patients with *P. aeruginosa*-associated bronchiectasis without cystic fibrosis[122]. These findings were confirmed in the phase 3 ORBIT-4 trial, but not in ORBIT-3, both of which evaluated the safety and efficacy of the slow-release formulation for *P. aeruginosa* in non-cystic fibrosis bronchiectasis[123]. Given these conflicting results, further research is warranted to better identify patients who may derive the greatest benefit from using inhaled liposomal ciprofloxacin. Another interesting inhaled drug is

arbekacin, an aminoglycoside antibiotic active against drug-resistant Gram-negative bacteria, including *Enterobacterales*, *P. aeruginosa*, *Acinetobacter* species, and MRSA[124]. Its IV formulation is approved in Japan for the treatment of bacteremia and pneumonia caused by MRSA[124]. However, its limited penetration into the ELF has led to the development of an inhaled formulation, ME1100[125]. A randomized, open-label phase 1b study (NCT02459158) recently evaluated the ME1100 inhalation solution in combination with the best available therapy for the treatment of mechanically ventilated patients with bacterial pneumonia, assessing its pharmacokinetics, safety, and tolerability. This formulation requires further studies but could represent a new therapeutic option for the treatment of nosocomial pneumonia caused by DTR pathogens.

## CONCLUSION

Several antibiotics have been approved in recent years for the treatment of CAP and HAP/VAP allowing a patient-oriented and a pathogen-oriented treatment. This is especially important in the context of growing antibiotic resistance and the increasing need for antimicrobial stewardship.

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## CONFLICTS OF INTEREST

None.

## ETHICAL DISCLOSURES

**Protection of humans and animals.** The authors declare that no experiments involving humans or animals were conducted for this research.

**Confidentiality, informed consent, and ethical approval.** The study does not involve patient personal data nor requires ethical approval. The SAGER guidelines do not apply.

**Declaration on the use of artificial intelligence**. The authors declare that no generative artificial intelligence was used in the writing of this manuscript.

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