New Antibiotics for Hospital-Acquired Pneumonia and Ventilator-Associated Pneumonia

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Abstract

Hospital-acquired pneumonia (HAP) and ventilator-associated pneumonia (VAP) represent one of the most common hospital-acquired infections, carrying a significant morbidity and risk of mortality. Increasing antibiotic resistance among the common bacterial pathogens associated with HAP and VAP, especially *Enterobacterales* and nonfermenting gram-negative bacteria, has made the choice of empiric treatment of these infections increasingly challenging. Moreover, failure of initial empiric therapy to cover the causative agents associated with HAP and VAP has been associated with worse clinical outcomes. This review provides an overview of antibiotics newly approved or in development for the treatment of HAP and VAP. The approved antibiotics include ceftobiprole, ceftolozane–tazobactam, ceftazidime–avibactam, meropenem–vaborbactam, imipenem–relebactam, and cefiderocol. Their major advantages include their high activity against multidrug-resistant gram-negative pathogens.

Keywords
- HAP
- VAP
- nosocomial pneumonia
- new antibiotics
- multidrug resistant
- *Pseudomonas aeruginosa*
- *Klebsiella pneumonia*

Hospital-acquired pneumonia (HAP) and ventilator-associated pneumonia (VAP) are some of the most common and serious infections occurring in hospitalized patients.[1–3] The mortality rate for HAP and VAP ranges between 20 and 50%[4,5] and can reach 75% in some specific settings or when lung infection is caused by multidrug-resistant (MDR) pathogens.[1,6,7]

Because several studies have shown that appropriate initial antibiotic therapy for patients with HAP and VAP significantly improves outcome, an adequate selection of initial treatments represents crucial clinical goals.[1,8–10] However, rates of resistance to "old antibiotics" frequently used to treat HAP and VAP are on the rise,[11,12] and a growing proportion of pathogens isolated from patients with nosocomial pneumonia now display multidrug resistance.[13,14] Evidence suggests that infections caused by MDR pathogens have worse clinical prognosis because of a delay in initiating adequate antibiotic treatment.[15,16]

Reflecting these observations, several novel agents have been developed in recent years to supplement the paucity of agents available for the treatment of MDR pathogens and many of these new antibiotics have been trialed in HAP and VAP (►**Table 1**). This review covers those agents that have reached at least phase 2 or 3 trials or have been recently licensed for the treatment of HAP or VAP.

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Table 1 New molecules FDA and EMA approved for the treatment of hospital-acquired pneumonia and ventilator-associated pneumonia

Drug	Spectrum	Labeled indications	Approved dosage for the treatment of HAP/VAP
Ceftobiprole	Nonextended spectrum β-lactamase, non-AmpC and non-carbapenemases-producing *Enterobacterales*, *P. aeruginosa,* MRSA	EMA: HAP excluding VAP, CAP, ABSSSI	500 mg every 8 h by IV infusion over 2 h
Ceftazidime-avibactam	ESBL, KPC, AmpC, and some OXA (e.g., OXA 48) producing *Enterobacterales*, MDR *P. aeruginosa*, MDR *A. baumannii*	FDA: HAP/VAP, cUTIs, cIAIs EMA: all those infections due to aerobic gram-negative organisms with limited treatment options	2 g of ceftazidime and 0.5 g of avibactam every 8 h by IV infusion over 2 h
Ceftolozane-tazobactam	ESBL-producing *Enterobacterales*, MDR *P. aeruginosa*, some anaerobes, *Streptococcus* spp., MSSA	FDA: HAP/VAP, cUTIs, cIAIs EMA: HAP/VAP, cUTIs, cIAIs	2 g of ceftolozane and 1 g of tazobactam every 8 h by IV infusion over 1 h
Meropenem-vaborbactam	ESBL, KPC, AmpC-producing *Enterobacterales*, non-MDR *P. aeruginosa*, non-MDR *A. baumannii*, *Streptococcus* spp. MSSA	FDA: cUTI, including pyelonephritis. EMA: cUTI (including pyelonephritis), HAP, VAP, cIAI, and infections due to aerobic GNB with limited treatment options	2 g of meropenem and 2 g of vaborbactam every 8 h by IV infusion over 3 h
Imipenem-relebactam cilastatin	ESBL, KPC-producing *Enterobacterales*, MDR *P. aeruginosa*, *Streptococcus* spp., MSSA	FDA: HAP/VAP, cIAI, cUTI; EMA: infections due to aerobic GNB with limited or no other therapeutic options	500 mg of imipenem; 500 mg of cilastatin, and 250 mg of relebactam administered by IV infusion every 6 h over 30 min
Cefiderocol	ESBL, CRE (class A, B, and D enzymes), CR *P. aeruginosa, S. maltophilia, A. baumannii, Streptococcus* spp.	FDA: cUTI, HAP/VAP EMA: infections due to aerobic GNB with limited therapeutic options	2 g every 8 h by IV infusion over 3 h

Abbreviations: ABSSSI, acute bacterial skin and skin structure infections; cIAI, complicated intra-abdominal infection; CRE, carbapenem-resistant *Enterobacterales*; cUTI, complicated urinary tract infection; EMA, European Medicines Agency; ESBLs, extended-spectrum β-lactamases; FDA, Food And Drug Administration; GNB, gram-negative bacteria; HAP, hospital-acquired pneumonia; IV, intravenous; MBL, metallo-β lactamase; MRSA, methicillin-resistant *Staphylococcus aureus*; MSSA, methicillin-susceptible *Staphylococcus aureus*; OXA, oxacillinase; VAP, ventilator-associated pneumonia.

Approved Antibiotics for the Treatment of HAP and VAP

Ceftobiprole

Ceftobiprole is a fifth-generation cephalosporin approved for the treatment of HAP, excluding VAP.[17] Ceftobiprole has a broad-spectrum antibacterial activity, including methicillin-resistant *Staphylococcus aureus* (MRSA), *Moraxella catarrhalis*, *Haemophilus influenzae*, penicillin-resistant pneumococci (PRP), the majority of nonextended spectrum β-lactamase, non-AmpC and non–carbapenemases-producing *Enterobacterales*, and *Pseudomonas aeruginosa*. Ceftobiprole is degraded by extended spectrum β-lactamase (ESBL) and by carbapenemase and is not active against gram-negative anaerobes, *Acinetobacter baumannii*, *Burkholderia cepacia*, *Stenotrophomonas maltophilia*, *Proteus vulgaris*, and *Enterococcus faecium*.[17–21] Ceftobiprole exerts its time-dependent antibacterial activity by binding to different penicillin-binding proteins including PBP2a, making ceftobiprole the only β-lactam (together with ceftaroline) active against MRSA and PBP2x of PRP.[19,22] Ceftobiprole is poorly bound to plasma proteins, has minimal propensity for drug–drug interactions, has a short half-life, and is excreted by the renal filter.[17] Dose adjustment is recommended in patients with moderate to severe kidney failure while it is not necessary in patients with severe obesity.[23] When creatinine clearance (CrCl) is greater than 150 mL/min, extending infusion time to 4 hours is required to keep plasma levels above the minimum inhibitory concentration (MIC).[24,25] Ceftobiprole has demonstrated a good safety profile, and the most common

adverse events (AEs) with ceftobiprole include headache, nausea, diarrhea, vomiting, infusion-site reactions, dysgeusia, and drug-related hypersensitivity.[26] In a 2010 study, no measurable concentrations of ceftobiprole were detected in feces following intravenous (IV) administration in healthy volunteers and no *Clostridioides difficile* strains or toxins were found.[27] A phase 3 noninferiority, double-blind, multicenter, international, randomized study in 781 hospitalized patients has demonstrated safety and efficacy of ceftobiprole[28,29] (500 mg/8 hour infused in 2 hours) versus ceftazidime (2 g/8 hour) plus linezolid (600 mg/12 hour) for the treatment of HAP and VAP. Treatment duration was 7 to a maximum of 14 days. The primary efficacy endpoint was clinical cure at the test-of-cure (TOC) visit, defined as resolution of signs and symptoms of infection, or improvement to such an extent that no further antimicrobial therapy was necessary, in the intent-to-treat (ITT) and clinically evaluable (CE) populations. Ceftobiprole monotherapy was noninferior to comparator arm for patients with HAP. In the VAP group, the study failed to demonstrate noninferiority, possibly due to insufficient sample size; higher heterogeneity in VAP patients according to demographic, clinical, and microbiological characteristics; and to the suboptimal concentration achieved at infection site in critically ill patients in which higher dosage and prolonged infusion might be required.[17,24] In conclusion, due to its safety profile and in vitro activity against most commonly associated HAP pathogens ceftobiprole may be a valuable therapeutic for HAP with the benefit of a monotherapy regimen.

Ceftolozane-Tazobactam

Ceftolozane-tazobactam is a combination of a novel semisynthetic fifth-generation cephalosporin with a well-established β-lactamase inhibitor. Ceftolozane overcomes the most common mechanisms of bacterial resistance including hydrolysis by AmpC β-lactamases[30] and changes in efflux pumps or porin permeability.[31,32] The addition of tazobactam to ceftolozane, in a 2:1 ratio, expands its activity against β-lactamases-producing *Enterobacterales*, including those strains producing ESBLs.[33] However, the combination of ceftolozane–tazobactam is not active against Ambler Class A, B, or D carbapenemases.[34]

As for in vitro studies, ceftolozane–tazobactam exhibits enhanced activity against *P. aeruginosa*, being especially active against MDR or extremely drug-resistant (XDR) strains,[35] including those strains resistant to carbapenems.[32] The MIC of ceftolozane–tazobactam against *P. aeruginosa* is 8- to 16-fold lower than that of ceftazidime, imipenem, or ciprofloxacin.[36] In a recent surveillance study performed in the United States, the susceptibility of *P. aeruginosa* isolates was higher for ceftolozane–tazobactam (97.3%) in comparison to cefepime (86.3%), ceftazidime (85.2%), meropenem, or piperacillin-tazobactam (80.9% each).[37,38] In this study, the only comparator with higher activity than ceftolozane–tazobactam against *P. aeruginosa* was colistin (99.5% susceptible).

Although its efficacy seems to be variable depending on the species, ceftolozane–tazobactam also shows great activity against ESBL-producing *Enterobacterales* (84–94%),[37,39–41] with lower rates of susceptibility reported for ESBL-producing *Klebsiella pneumoniae* (57%) or *Enterobacter cloacae* (64%).[42–44] As for anaerobes, gram-positive cocci, *Acinetobacter* spp., and *Stenotrophomonas maltophilia*,[32,42] the activity of ceftolozane–tazobactam is limited.

Regarding pharmacokinetic, ceftolozane–tazobactam penetrates well in the lung tissue as suggested by studies performed in healthy subject receiving 1 g of ceftolozane and 0.5 g of tazobactam. This study showed an Epithelial Lining Fluid (ELF)/plasma area under the curve (AUC) ratio of 0.48, thus indicating that ELF concentrations of ceftolozane–tazobactam may potentially exceed the MICs of most gram-negative pathogens causing nosocomial pneumonia.[45] However, to ensure therapeutic drug concentration at the site of the infection and to cover pathogen with higher MICs, the drug is currently approved for the treatment of HAP and VAP at the dosage of 2 g of ceftolozane with 1 g of tazobactam every 8 hours.[46] Since both ceftolozane and tazobactam are primarily eliminated through renal excretion, dosage adjustment is required for patients with acute or chronic kidney injury.[47]

The approval of ceftolozane–tazobactam for the treatment of nosocomial pneumonia was based on the ASPECT-NP study, a noninferiority phase 3 trial comparing the efficacy and safety of ceftolozane–tazobactam 3 g every 8 hours with meropenem 1 g every 8 hours for 7 to 14 days of therapy. The primary efficacy was assessed based on all-cause mortality at day 28. Overall, of the 726 randomized patients, 519 (71%) had VAP. Most patients were in the ICU, and half of them had septic shock. The majority of the VAP were caused by *K. pneumoniae*, *Escherichia coli*, and *P. aeruginosa*.

Ceftolozane–tazobactam met the prespecified noninferiority criterion based on the 28-day mortality rate (24.0% in the ceftolozane–tazobactam group and 25.3% in the meropenem group; weighted proportional difference: 1.1% [95% confidence interval (CI): −5.1 to 7.4]). Of importance, in patients with ventilated HAP and in those in whom previous antibacterial therapy was unsuccessful before study entry, the 95% CI for the between-group difference did not cross zero, with lower mortality in the ceftolozane–tazobactam group than in the meropenem group.[48]

Regarding experiences coming from daily clinical practice, a recent meta-analysis including 33 real-world studies on respiratory tract infections reported similar outcomes (clinical and microbiological success) with ceftolozane–tazobactam as those observed in pivotal clinical trials. These results were observed despite including a greater proportion of MDR pathogens as well as patients with serious underlying diseases, which may have been excluded from pivotal trials.[49]

A retrospective, multicenter, observational cohort study compared patients treated with ceftolozane-tazobactam with those treated with either polymyxin or aminoglycoside-based regimens for infections due to drug-resistant *P. aeruginosa* (half of the patients had VAP with 7% of them being bacteremic). Patients receiving ceftolozane–tazobactam had a better clinical cure (adjusted odds ratio [aOR]: 2.63; 95% CI, 1.31–5.30) and lower acute kidney injury (aOR: 0.08; 95% CI: 0.03–0.22).[50]

Promising results have been also obtained in a multicenter Italian cohort study including 101 patients treated with ceftolozane–tazobactam for severe infections caused by *P. aeruginosa*. Overall, 32% of the patients had HAP/VAP, and in 61% of the cases the drug was administered as second-line therapy because of failure or previous antimicrobial therapy. Overall, clinical success was observed in 84 of 101 patients (83.2%) at the end of the treatment. Regarding the subgroup of nosocomial pneumonia, the clinical success rate was 75%.[51] Bassetti et al also provided real-world clinical data regarding the role of ceftolozane–tazobactam in the treatment of 153 patients with ESBL-producing *Enterobacterales*.[52] Almost half (48.3%) of the patients were admitted to the ICU at the time of their infection and 30.0% of them had HAP or VAP. Pathogens most commonly included were *E. coli* and *K. pneumoniae*. Clinical success was observed in 78.3% of the patients, whereas 30-day mortality was reported for 9.8% of them. In multivariate analysis, receiving ceftolozane–tazobactam as empiric therapy (OR, 0.12; 95% CI, 0.01–0.34; $p < 0.001$) was the only factor associated with clinical success,[52] together with an adequate source control of the infection (OR, 0.42; 95% CI, 0.14–0.55; $p < 0.001$). In our opinion, ceftolozane–tazobactam represents an attractive option for the treatment of VAP or HAP due to MDR or XDR *P. aeruginosa*. The drug can also be a valuable alternative to carbapenems for the treatment of nosocomial pneumonia due to ESBL-producing *Enterobacterales*.

Meropenem–Vaborbactam

Meropenem–vaborbactam is a novel non-β-lactam cyclic boronic acid β-lactamase inhibitor combined with a well-known carbapenem, specifically designed to exert high activity against MDR *Enterobacterales*, including those strains producing Ambler class A, and C β lactamases.[53] However, vaborbactam does not expand the activity of meropenem against glucose nonfermenting gram-negative bacilli[54] and it has no activity against class B and class D carbapenemases.[55,56]

The in vitro activity of meropenem–vaborbactam has been investigated against more than 10,000 gram-negative isolates from hospitalized patients with pneumonia, including VAP. Among tested agents, meropenem–vaborbactam showed the highest susceptibility rates against *Enterobacterales* isolates (98.0%). In addition, against *P. aeruginosa* isolates, meropenem–vaborbactam was the most active β-lactam tested (82.1% susceptible), with amikacin (86.0%) and colistin (99.4%) showing higher susceptibility rates.[57] Similar results were also observed in another U.S. study including gram-negative isolates from respiratory tract.[58]

In a phase 1 study, plasma clearance of meropenem and vaborbactam was similar, suggesting that concomitant administration does not impact plasma pharmacokinetics of either drugs, regardless of the dosage or schedule.[59,60] Both drugs were excreted by the kidneys, thus requiring proportional dose reduction in patients with renal impairment.[59] Regarding its use in respiratory tract infection, meropenem–vaborbactam showed a good pulmonary penetration as suggested by the AUC values of 63 and 53%, respectively, detected in ELF and total plasma concentration of healthy volunteers receiving three doses of meropenem–vaborbactam.[61]

The efficacy and safety of meropenem–vaborbactam for HAP and VAP has been evaluated in the Targeting Antibiotic Non-susceptible Gram-Negative Organisms (TANGO)-2 trial, a multicenter, randomized open-label phase 3 study comparing meropenem–vaborbactam versus best available treatment (BAT) for the treatment of confirmed or suspected serious infections due to carbapenem-resistant *Enterobacterales* (CRE).[62] Overall, 43 out of 77 eligible patients had confirmed CRE infections and were randomized 2:1 to receive either 7 to 14 days of meropenem 2 g plus vaborbactam 2 g every 8 hours as monotherapy or 7 to 14 days of BAT. As there is no standard of care for CRE infections, a wide variety of mono and combination therapies were administered in the BAT group. Of importance, a greater proportion of patients with previous treatment failure randomly received meropenem–vaborbactam (28.1 vs. 0% in BAT). Primary efficacy endpoints for each infection type were based on FDA guidelines in the microbiological CRE-MITT population and included the proportion of patients who achieved overall success (composite endpoint of clinical cure and microbiologic eradication) at TOC in the complicated urinary tract infection (cUTI)/AP subgroup; all-cause mortality in the combined HAP/VAP and bacteremia subgroups; and the proportion of patients with clinical cure at TOC in the complicated intra-abdominal infection (cIAI) subgroup.

In the microbiological CRE-MITT population, meropenem–vaborbactam was associated with higher rates of clinical cure than BAT at both EOT (65.6% [21/32] vs. 33.3% [5/15]; difference, 32.3%; 95% CI: 3.3–61.3%, $p = 0.03$) and TOC (59.4% [19/32] vs. 26.7% [4/15]; difference, 32.7%; 95% CI: 4.6–60.8%; $p = 0.02$). Microbiologic cure was also higher in patients receiving meropenem–vaborbactam in comparison to those receiving BAT (65.6 vs. 40.0%; difference, 25.6%; $p = 0.09$ at EOT).[62] Of importance, on subgroup of patients with HAP/VAP or bacteremia, day-28 all-cause mortality was numerically lower in the meropenem–vaborbactam group (22.2 vs. 44.4% $p = 0.25$).[62]

Evidences regarding clinical experiences with meropenem–vaborbactam for the treatment of HAP/VAP are growing.[63,64] Recently, Alosaimy et al[63] described the clinical characteristics and outcomes of 40 patients treated with meropenem–vaborbactam for a variety of gram-negative infections, primarily including CRE. Seventy percent of them were critically ill. The most frequent diagnosis was pneumonia in 32.5% (13/40 patients). Clinical success was achieved in 70% of patients (28/40), with pneumonia being the most common infection type among patients experiencing clinical success (9/28).

The much-awaited post-approval experience regarding meropenem–vaborbactam has been recently reported.[65] A multicenter, retrospective, cohort study of 131 patients with CRE infections (49 respiratory infection) compared meropenem–vaborbactam ($n = 26$) to ceftazidime–avibactam ($n = 105$). Despite ceftazidime–avibactam was administered as a combination therapy more often, clinical success was

similar between groups (69.2 vs. 62%, $p = 0.49$). Likewise, 30-day and 90-day mortality and rates of AEs did not differ between groups. However, development of resistance was more common with ceftazidime–avibactam monotherapy (3 vs. 0 patients).[65]

In conclusion, meropenem–vaborbactam represents one of the best therapeutic options currently available for treating patients with HAP or VAP due to CRE pathogens.

Imipenem–Relebactam

Relebactam is a novel bicyclic diazabicyclooctane β-lactamase inhibitor structurally related to avibactam.[66] It shows potent activity against classes A[67] and C β-lactamases. However, it does not impede hydrolysis mediated by class B carbapenemases and shows minimal activity against class D oxacillinases (e.g., OXA-48 enzymes).[68]

The addition of relebactam to imipenem potentiates the activity of the carbapenem against gram-negative bacteria, including imipenem nonsusceptible strains, *P. aeruginosa* and some β-lactamase-producing *Enterobacterales* such as ESBL or KPC producers. However, the combination showed irrelevant activity against *A. baumannii* or *S. maltophilia*.[69,70] As for in vitro studies, relebactam improves the activity of imipenem against Ambler class A ESBL-producing (2- to 16-fold reduction) or KPC-producing *Enterobacterales* (32- to 128-fold MIC reduction),[71] with imipenem–relebactam showing activity against 100% of KPC-producing *K. pneumoniae* isolates.[67,72,73] Regarding *P. aeruginosa*, the rate of sensitivity to imipenem–relebactam was approximately 90%.[74] Of importance, 80% of imipenem-resistant isolates displayed recovered susceptibility to imipenem when relebactam was added, especially with strain of *P. aeruginosa* with AmpC production or OprD porin loss.[71,75]

The standard dosage of imipenem–relebactam is 500 to 250 mg every 6 hours, over 30 minutes of infusion. Dose reduction is recommended if CrCl is lower than 90 mL/min.[76] Both imipenem and relebactam have good lung tissue penetration, with studies reporting similar relative exposure levels in both the pulmonary epithelial lining and the plasma.[77,78] Safety and efficacy of imipenem-relebactam for the treatment of HAP/VAP has been investigated in two Phase 3 noninferiority trial. RESTORE-IMI 1 was a multicenter, double-blind phase 3 trial comparing the efficacy and tolerability of imipenem–relebactam to imipenem plus colistin combination in different types of infections (including HAP/VAP) caused by imipenem nonsusceptible pathogen. Patients were randomized 2:1 to 5 to 21 days of imipenem–relebactam or colistin plus imipenem. The primary endpoint in efficacy differed according to each infection type, but for patients with HAP/VAP it was 28-day all-cause mortality. Overall, 47 patients were included in the study (31 in imipenem–relebactam vs. 16 in colistin + imipenem). The most common diagnosis was pneumonia, with VAP being diagnosed in 29% of the patients; the qualifying baseline pathogens were *P. aeruginosa* (77%), followed by *Klebsiella* species (16%) and *Enterobacterales* (6%).[79] Favorable overall response was observed in 71% imipenem–relebactam and 70% colistin plus imipenem patients (90% CI, –27.5%, 21.4%), day-28 favorable clinical response in 71 and 40% (90% CI, 1.3, 51.5), and 28-day mortality in 10 and 30% (90% CI, −46.4, 6.7), respectively. In the subgroup of patients with HAP/VAP, 7 of 8 patients achieved an overall clinical response in the imipenem–relebactam group (87.5%) versus 2 out of 3 in the colistin plus imipenem group (66.7%; 95% CI: 50.8–99.9%). Moreover, patients receiving imipenem–relebactam showed a 20% reduction in terms of 28-day mortality in comparison to those treated with colistin plus imipenem (95%, CI, 10.3–60.8%).[79]

RESTORE IMI-2 was the other phase 3 randomized clinical trial specifically evaluating the noninferiority of imipenem–relebactam in comparison to piperacillin-tazobactam for the treatment of hospitalized adult patient with HAP/VAP. A 7-day course of linezolid was also allowed if MRSA was isolated in the baseline respiratory sample. The most common isolated pathogens were *K. pneumoniae* (25.6%) and *P. aeruginosa* (18.9%).[80] Imipenem-relebactam was found noninferior to piperacillin-tazobactam in the MITT population with respect to the primary outcome of 28-day all-cause mortality (adjusted treatment difference: – 5.3%; 95% CI: – 11.9 to 1.2%).[80] Notably, in the predefined subgroup of mechanically ventilated patients or those with an APACHE II score greater than 15, day-28 mortality rate was found significantly lower in patients receiving imipenem–relebactam in comparison to piperacillin/tazobactam.[80]

In our opinion, imipenem–relebactam should always be considered for the treatment of suspected or confirmed HAP/VAP caused by gram-negative bacilli with resistance to carbapenem.

Cefiderocol

Cefiderocol is a novel siderophore cephalosporin active against gram-negative bacilli, including *Enterobacterales* and nonfermenters exhibiting difficult-to-treat resistance phenotype. This wide spectrum of activity is dependent on its unique properties that enable cefiderocol to remain stable in the presence of all classes of β-lactamases including Ambler Class A, B, C, and D β-lactamases. The chemical structure of cefiderocol is similar to that of cefepime and ceftazidime, with the addition of a catechol moiety at the C-3 position of the side chain that forms a chelating complex with ferric iron. This process facilitates high concentration of the antibiotic in the periplasmatic space ("Trojan horse" strategy),[81,82] allowing cefiderocol to efficiently inhibit the synthesis of peptidoglycans.[83] The in vitro activity of cefiderocol against several multidrug-resistant pathogens has been investigated in a large surveillance program (SIDERO-WT).[84–86] Overall, more than 28,000 gram-negative isolates from various sources (including VAP) were randomly collected and tested. More than 99% of the tested strains showed low MIC values against cefiderocol (MIC_{90} between 0.25 and 1 μg/mL for *E. coli*, *Klebsiella* spp., *Citrobacter* spp., *Enterobacter* spp., and *Serratia* spp., from 0.03 to 1 μg/mL against *P. aeruginosa*, *B. cepacia*, and *S. maltophilia*, 1 to 4 μg/mL against *A. baumannii*).[86,87]

Cefiderocol has a linear pharmacokinetic curve. It is excreted nonmetabolized into urine for 60 to 70%; dosage

adjustments are required for patients with severe impairment of renal function.[88] The pulmonary exposition to cefiderocol in healthy individuals is similar to ceftazidime (ELF/plasma AUC ratio of 0.239 for cefiderocol vs. 0.229 for ceftazidime).[89] A dose of 2 g every 8 hours is suggested on the basis of pharmacokinetic/pharmacodynamic modeling and simulation.[88]

The efficacy of cefiderocol in patients with HAP and VAP caused by gram-negative bacilli was evaluated in the APEKS-NP study, a phase 3 double-blind, randomized, noninferiority trial. The patients were randomized to cefiderocol 2 g every 8 hours or to meropenem 2 g every 8 hours, both as 3-hour infusion. In this study, linezolid was administered for at least 5 days, while cefiderocol or meropenem was administered for 7 to 14 days. The primary endpoint was all-cause mortality at 14 days for the microbiological ITT population, with a preestablished noninferiority margin of 12.5%. In this study, 123 out of 292 patients (42%) of the ITT population were diagnosed with VAP with *K. pneumoniae*, *P. aeruginosa*, and *A. baumannii* being the most commonly isolated pathogens.[90] Cefiderocol was found noninferior to meropenem with respect to all-cause mortality at day 14 (12.4% in cefiderocol arm vs. 11.6% in meropenem arm, adjusted treatment difference in ITT population of 0.8%, 95% CI: –6·6 to 8·2; $p = 0{\cdot}002$). All-cause mortality on day 28 and safety endpoints were similar between the two treatment arms.[90]

Another significant contribution of cefiderocol to modern antimicrobial chemotherapy has also been treating serious carbapenem-resistant infections, including HAP and VAP.[91,92] The CREDIBLE-CR study was an open-label, international, multicenter, pathogen-oriented phase 3 trial in which cefiderocol 2 g every 8 hours was compared with the BAT for treating HAP, VAP, cUTI, or bloodstream infections due to carbapenem-resistant gram-negative bacilli. Patients were randomized 2:1 to receive cefiderocol or BAT. Nosocomial pneumonia was present in 45% of the patients and about one quarter of them had VAP. The most common isolates were *A. baumannii* (46%, 54 patients), *K. pneumoniae* (33%, 39 patients), and *P. aeruginosa* (19%, 22 patients). In the modified intention-to-treat (mITT) population, clinical cure rates at TOC were comparable between the two arms (50%, 95% CI: 33.8–66.2 in the cefiderocol arm vs. 53%, 28.9–75.6 in the BAT arm). Similar results were also observed in the carbapenem-resistant microbiological ITT subgroup of patients with HAP and VAP, in which the primary outcome of clinical cure at 7 ± 2 days following the end of treatment was met in 50 and 53% of patients. However, regarding patients with HAP and VAP, the mortality at the end of the study was higher in the cefiderocol group (42%) versus BAT (18%), mainly when the infecting pathogen was *A. baumannii*.[92] On the basis of these results, a warning of increased all-cause mortality for patients with carbapenem-resistant *A. baumannii* infections treated with cefiderocol monotherapy has been released.[93] A further RCT (the open-label GAME CHANGER trial) evaluating the efficacy of cefiderocol in comparison to BAT for the treatment of bloodstream infections caused by MDR gram-negative pathogens is currently ongoing (NCT 03869437).

Case reports of patients with HAP or VAP treated with cefiderocol in compassionate use have highlighted unique challenges in managing infections due to MDR gram-negative bacilli.[94–96] Recently, an Italian case series investigated 10 cefiderocol-treated critically ill patients who suffered serious carbapenem-resistant infections (40% of them had VAP). Thirty-day clinical success and survival rates were 70 and 90%, respectively. Only 2 out of 10 patients had a microbiological failure.[97] Of note, half of the patients included in this study were ICU admitted because of COVID-19 pneumonia.[97]

In conclusion, we believe that cefiderocol is a promising cephalosporin with an important potential for the treatment of HAP and VAP, thanks to the very broad spectrum of activity against carbapenem-resistant gram-negative bacteria, including MBL-producing *Enterobacterales* and MDR *P. aeruginosa*.

Other Antibiotics

Tedizolid

Tedizolid phosphate is an oxazolidinone prodrug that is rapidly converted by endogenous phosphatases to the active moiety tedizolid.[98] Similar to linezolid, tedizolid works by binding to the 23S rRNA of the 50S subunit preventing the formation of the 70S initiation complex and inhibiting protein synthesis.[99] The oral bioavailability of tedizolid is more than 90%. Tedizolid does not need to be modified in patients with renal impairment, hepatic impairment, or on hemodialysis.[100,101] Its half-life is approximately 12 hours and steady-state concentrations are achieved within 3 days. Peak plasma tedizolid concentrations are achieved at the end of the 1-hour IV infusion of tedizolid phosphate.[101,102] The majority of elimination occurs via the liver, with 82% of the dose recovered in feces and 18% in urine. There is no effect on cytochrome P450 (CYP) enzymes and no potential drug interactions with tedizolid were identified by in vitro CYP inhibition or induction studies.[101,103] Compared with linezolid, tedizolid seems to present a lower incidence of gastrointestinal AEs and bone marrow suppression.[103] Tedizolid is a reversible inhibitor of monoamine oxidase (MAO) in vitro, but interactions with MAO inhibitors could not be evaluated in phase 2 and 3 trials, as subjects taking such medications were excluded. Drug interaction studies to determine effects of 200 mg oral tedizolid phosphate at steady state on pseudoephedrine and tyramine pressor effects were conducted in healthy volunteers. No meaningful changes in blood pressure or heart rate with pseudoephedrine were observed in the healthy volunteers, and no clinically relevant increase in tyramine sensitivity was observed.[101,104] Tolerability in clinically important subpopulations (obese, elderly, renal impairment, hepatic disease/impairment) appears to be comparable to the overall population.[105] Tedizolid is approved by the FDA and the European Medicines Agency (EMA) for treating acute bacterial skin and skin structure infections (ABSSSIs) as an oral or IV 200-mg dose administered once daily for 6 days.[98] Tedizolid exhibits activity against a broad spectrum of gram-positive pathogens, including PRP, vancomycin-resistant *Enterococcus*

spp., MRSA, vancomycin-resistant *S. aureus*; in vitro potency of tedizolid was 4- to 8-fold greater than linezolid across a range of gram-positive pathogens.[106–110] The incorporation of a D-ring substituent and a hydroxymethyl group in place of acetamide gives tedizolid activity against some linezolid-resistant pathogens.[101] The Surveillance of Tedizolid Activity and Resistance program tested more than 11,000 gram-positive clinical isolates from the United States and Europe, including respiratory tract specimens, and found that tedizolid inhibited 99.7% of isolates at a MIC of $\leq$0.5 mg/L.[111] An international study across 96 international medical centers showed a high potency of tedizolid against *S. aureus* and *S. pneumoniae* tested for susceptibility by reference broth microdilution.[112] Tedizolid demonstrates excellent pulmonary penetration in adult healthy volunteers, with ELF concentrations higher than free plasma concentrations for the entire dosing interval and an approximately 40-fold ELF-to-plasma penetration ratio.[113] Recently, a phase 3, randomized, double-blind study conducted at 122 study sites in 32 countries from 2014 to 2018 compared tedizolid to linezolid for ventilated gram-positive HAP or VAP (vHAP/VAP).[114] Patients were randomized 1:1 to tedizolid phosphate 200 mg once daily as a 60-minute IV infusion for 7 days or linezolid 600 mg twice daily as a 60-minute IV infusion for 10 days (patients with concurrent gram-positive bacteremia received 14-day treatment). The primary efficacy end points were day-28 all-cause mortality and investigator-assessed clinical response at the TOC visit (7–14 days after last study drug infusion or time of failure) in the ITT population. Overall, 726 patients were randomized (tedizolid, $n = 366$; linezolid, $n = 360$). Tedizolid was noninferior to linezolid for day-28 all-cause mortality rate: 28.1 and 26.4%, respectively. Noninferiority of tedizolid was not demonstrated for investigator-assessed clinical cure at TOC. In post hoc analyses, no single factor accounted for the difference in clinical response between treatment groups. Both drugs were well tolerated with drug-related AEs occurrence being 8.1 and 11.9% of patients who received tedizolid and linezolid, respectively.[114] A recently published study suggests tedizolid as a promising therapeutic option for the treatment of cystic fibrosis–associated MRSA/methicillin-susceptible *S. aureus* infections, having potent in vivo activity and low resistance potential.[115]

Ceftaroline–Avibactam

Ceftaroline is a fifth-generation cephalosporin providing high activity against common respiratory pathogens, including MRSA, PRP, and non-ESBL-producing *Enterobacterales*. Limited or no activity has been observed against anaerobes, ESBL and AmpC producing strains, *A. baumannii*, and *P. aeruginosa*.[116]

When combined with avibactam, ceftaroline resists the hydrolysis from class A (including ESBLs, KPC), class C (AmpC), and some class D β-lactamases, while preserving its gram-positive activity.

Although the in vitro activity of ceftaroline-avibactam support furthers the evaluation of this drug as an effective treatment option for HAP and VAP, there are no studies performed so far regarding the use of this new drug for nosocomial pneumonia. If future studies will show positive results, this drug could represent an attractive single-agent option for the treatment of VAP or HAP due to mixed gram-positive and gram-negative pathogens.

Plazomicin

Plazomicin is a new semisynthetic aminoglycoside resistant to inactivation by aminoglycoside-modifying enzymes. Therefore, it is active against a larger proportion of CRE than those with amikacin, tobramycin, or gentamycin.[117] However, similar to other aminoglycosides, it is affected by 16s ribosomal ribonucleic acid (rRNA) methyltransferase.[118]

In vitro, plazomicin was active against more than 95% of *Enterobacterales* strains ($MIC_{50/90}$, 0.5/1 mg/L) with susceptibility breakpoint lower than 2 mg/L.[119] Regarding *P. aeruginosa* and *Acinetobacter* spp., plazomicin exhibited $MIC_{50/90}$ comparable to amikacin. Likewise, $MIC_{50/90}$ against gram-positive bacteria, including MRSA, was similar to gentamicin ($\leq$2 mg/L). However, no activity has been found against anaerobes, *Enterococcus*, *Streptococcus*, and *Stenotrophomonas*.[120]

Plazomicin is currently FDA approved at a dosage of 15 mg/kg IV for the treatment of cUTI including AP caused by aerobic gram negative. The pharmacokinetics is similar to that of other aminoglycosides with low plasma protein binding (20%)[121] and low lung penetration (13%).[122]

Clinically, the CARE trial evaluated the efficacy and safety of plazomicin compared with colistin for the treatment of BSI, HAP/VAP, and cUTI caused by CRE. The most common microbiologic isolate was carbapenem-resistant *K. pneumoniae* in both arms. Among patients with HAP/VAP, the primary end point (a composite endpoint of death from any cause at 28 days or clinically significant disease-related complications in the microbiologic mMITT) occurred in 67% in the plazomicin arm (two out of three patients) and in 40% (two out of five patients) in the colistin arm (difference, 27%; 95% CI, −48 to 82). Additionally, Serious Adverse Events (SAEs) were significantly lower in the plazomicin group than in the colistin one (50% plazomicin vs. 81% colistin).[123]

Although plazomicin has emerged as a valuable option in the treatment of HAP/VAP caused by CRE, the FDA denied the approval for this indication, mainly due to the small sample size of the HAP subgroup in the CARE trial (five VAPs in the colistin group and three in the plazomicin group).[124] In our opinion, because plazomicin shows a wide spectrum of activity including MRSA and MDR gram negatives, it could offer an important new treatment option as part of a combination regimen for patients with HAP and VAP.[125]

Aztreonam–Avibactam

Aztreonam is the only β-lactam-providing activity against metallo-β-lactamases (MBL), but it is hydrolyzed by most ESBLs or AmpC enzymes, which are often coproduced in carbapenem-resistant strains.[126] The association with avibactam confers aztreonam stability with respect to most of MDR pathogens, including those co-harboring class A, C, and D β-lactamases.[127,128] Antimicrobial activity of aztreonam–avibactam against gram-negative bacteria collected from patients hospitalized with pneumonia has been recently

investigated.[129] Overall, 99.9% of the *Enterobacterales* were inhibited by aztreonam–avibactam, even when isolates were NDM, KPC, or OXA-48 producers.[129–131] As for *P. aeruginosa*, more than 75% of tested isolates were in vitro susceptible to aztreonam–avibactam, showing an MIC value lower than 8 mg/L.[129]

To the best of our knowledge, there are no studies evaluating lung distribution of aztreonam–avibactam in healthy subject. However, a good lung penetration of aztreonam–avibactam could be presumed, as pharmacokinetics parameters are similar when aztreonam is given alone or in combination with avibactam.[132,133]

The drug has not been FDA or EMA approved, as the pivotal trials evaluating aztreonam–avibactam for the treatment of serious gram-negative infections are currently ongoing.[134] However, waiting for more robust data, aztreonam has been used in combination with ceftazidime–avibactam for the treatment of serious infections caused by MBL-producing strains.[135–137]

In a prospective multicenter study performed in Italy and Greece, and including 82 patients with bloodstream infections due to NDM-producing *Enterobacterales* (source of the infection was the respiratory tract in 10% of the cases), ceftazidime–avibactam plus aztreonam was associated with lower 30-day mortality rate, lower clinical failure at 14 days, and shorter length of hospital stay when compared with regimens using other active agents. In another retrospective study including 10 patients with serious CRE infections (2 out of 10 were HAP) treated with ceftazidime–avibactam plus aztreonam, clinical success was achieved in 60% (6/10) of the cases. When only patients with HAP were analyzed, one experienced clinical success and the other died, although death was not considered as infection related.[138]

Cefoperazone–Sulbactam

Cefoperazone–sulbactam is a combination of a third-generation cephamycin and an old β-lactamase inhibitors. It is active against *Enterobacterales* and *Pseudomonas* spp. Sulbactam confers to the combination activity against *Acinetobacter* and anaerobes and provides to cefoperazone more stability to some β-lactamases and mitigates the high inoculum effect.[139] In a RCT from Taiwan enrolling 166 patients, cefoperazone–sulbactam was administered at the dosage of 2 g every 12 hours versus cefepime for the treatment of HAP and healthcare-associated pneumonia. No difference was found between the two groups in the ITT and safety analysis. The correct evaluation of the microbiological analysis was limited by the small number ($n = 16$) of bacterial isolates.[140] The same group from Taiwan enrolled 410 patients in a retrospective study comparing the use of cefoperazone–sulbactam versus piperacillin/tazobactam for the treatment of HAP and VAP. The primary outcome was clinical cure defined as the proportion of patients not needing adjunctive antibiotic therapy and with improved or resolved symptoms or signs 7 days after the end of treatment. Cefoperazone–sulbactam was found to be as clinically effective as piperacillin/tazobactam, although in cefoperazone–sulbactam group the Charlson Comorbidity Index and APACHE II scores were higher (Charlson's score: 6.5 ± 2.9 vs. 5.7 ± 2.7, $p < 0.001$; APACHE II score: 21.4 ± 6.2 vs. 19.3 ± 6.0, $p = 0.002$).[141]

Eravacycline

Eravacycline is a novel fluorocycline, structurally similar to tigecycline. It is available in oral and IV formulation. Its spectrum of activity ranges from gram-positive to gram-negative and anaerobic bacteria with the exception of *P. aeruginosa* .[142] Notably, eravacycline exerts its activity against *A. baumannii* isolates resistant to sulbactam.[143] A low rate of *C. difficile* infection is reported during the therapy with eravacycline.[144] For intra-abdominal infections, robust data come from the IGNITE 1 and IGNITE4 phase 3 clinical trials where eravacycline was found noninferior to ertapenem and meropenem.[145] ELF concentrations of eravacycline were found to be greater than plasma levels by six- and fifty-fold in healthy adult volunteers receiving the IV formulation in a phase 1 study.[146] Further investigations are needed to support the use of eravacycline in respiratory infections.

Murepavadin

Formerly known as POL7080, murepavadin is the first molecule of a novel class of pathogen-specific antibiotic with a nonlytic mechanism of action called "outer membrane protein targeting antibiotics." Murepavadin inhibits the formation of the lipopolysaccharide causing cell death.[147] Several studies have assessed the high activity against *P. aeruginosa* in vitro,[148] also in MDR strains.[149] In vitro activity of murepavadin against colistin-resistant *P. aeruginosa* showed MIC_{50} and MIC_{90} 0.125 and 0.5 mg/L, respectively. MIC distributions for colistin-resistant and colistin-susceptible were similar, indicating no cross-resistance.[150] Murepavadin was well tolerated at doses up to 4.5 mg/kg of body weight in a phase 1 study. The most common AE was paresthesia. In animal models, murepavadin showed good penetration into ELF (ELF/plasma ratio of 24.4% for total drug and 108.9% for free drug) with ELF concentration similar to free plasma concentration.[151] In a phase 2 trial, murepavadin was coadministered to the standard of care treatment for VAP caused by *P. aeruginosa* and high rate of clinical cure and low rate of mortality at day 28 was observed.[152] Dose adjustment is warranted in impaired renal function, but safety was confirmed in patients with different degree of renal function.[147] Results from two phase 3 trials (NCT03409679 and NCT03582007) for the treatment of HAP and VAP are expected.

Iclaprim

Iclaprim is a dihydrofolate reductase (DR) inhibitor antibiotic with a 20-fold greater ability to inhibit DR compared with trimethoprim and as such not needing the combination with a sulfonamide. Iclaprim exhibits in vitro bactericidal activity against gram-positive bacteria including MRSA and some gram-negative (*H. influenzae* and *M. catarrhalis*). A phase 1 study showed a rapid diffusion of iclaprim into the pulmonary compartments and an ELF drug concentration 20- to 40-

fold greater than in serum.[153,154] Iclaprim was studied in five clinical studies for treating serious skin infections (one phase 2 and four phase 3 trials) where it showed noninferiority versus vancomycin. Efficacy and safety of iclaprim in the treatment of HAP and VAP were investigated in a phase 2 study in which iclaprim was found noninferior to vancomycin in terms of clinical cure rates and safety profile.[155] A phase 3 clinical trial is needed to further support its safety and efficacy in this indication.

New Investigational Agents

Aerosol administration of antibiotics in HAP and VAP offers the advantage of achieving high concentration in the site of the infection, especially in infections caused by pathogens susceptible only to antibiotics with a weak lung penetration, and to mitigate AEs of systemic toxicity.[156] Inhaled molecules may be delivered through liposomes allowing a slow release of the molecule with a constant high concentration.[157] Aerosol therapy may be performed with new molecules or with optimized inhalation formulation of known antibiotics. While some antibiotics have long time been used in this formulation, new ones are under study evaluation due to the increasing incidence of bacterial resistance and the utility of combination regimens for MDR pathogens. A promising molecule is liposomal ciprofloxacin, available in the rapid-release formulation (Lipoquin, ARD-3100) and in the slow-release formulations (Pulmaquin, ARD-3150). In the ORBIT-2 trial, the rapid-release formulation showed a good safety and tolerability profile in 22 cystic fibrosis patients.[158] The ORBIT-3 and ORBIT-4 international phase 3 randomized, double-blind, placebo-controlled trials assessed the safety and efficacy of the slow-release formulation for the treatment of *P. aeruginosa* in non–cystic fibrosis bronchiectasis patients. While in the ORBIT-4 there was a significant longer time to exacerbation, ORBIT-3 did not yield the same result.[159] Further researches are needed to establish the place in therapy of liposomal ciprofloxacin. A phase 2 double-blind placebo-controlled trial assessed the safety and efficacy of the amikacin-fosfomycin inhalation system (AFIS) as adjunctive therapy to IV therapy in the treatment of VAP caused by gram-negative bacteria including *A. baumannii*, *P. aeruginosa*, *S. maltophilia*, and *Enterobacterales*. AFIS significantly reduced bacterial burden (tracheal culture at day 3 positive in 19% of patients in the AFIS group vs. 40% in the placebo group, $p < 0.001$), but clinical outcome between the two groups was not superior in the AFIS group.[160] Arbekacin is a broad-spectrum aminoglycoside with activity against MRSA and *P. aeruginosa*. In an animal comparative study versus amikacin for the treatment of *P. aeruginosa* VAP, nebulized arbekacin (ME1100) showed superiority in the survival rate compared with placebo and amikacin groups.[161] Some positive experiences from Japan report the use of arbekacin, used in the nebulized formulation for the treatment of MRSA and MDR gram-negative pulmonary infections.[162] The fixed-dose combination of aztreonam and tobramycin has shown good stability and synergistic antibacterial effect in in vitro simulation against MDR *P. aeruginosa* and *A. baumannii*.[163] A new frontier in the management of difficult-to-treat infections and pathogens is the use of bacteriophages. The use of phage-cocktail or the phage–antibiotic combination have been proposed to overcome the growing issue of phage and antibiotic resistance.[164] In an in vitro study comparing inhaled combination of phage PEV20 with different antibiotics against *P. aeruginosa*, ciprofloxacin and, to a less extent, amikacin exhibited synergistic action.[165] Bacterial load in mechanically ventilated porcine model and mouse lungs infected by *P. aeruginosa* was reduced from 1.5-log ($p < 0.001$) to 5.9 log-10 ($p < 0.005$) after the inhalation of phage cocktail and phage–ciprofloxacin combination, respectively.[166,167] Phages have also been successfully used in animal models in the prophylaxis of MRSA pneumonia. Derivatives of phages such as endolysins have been used in mouse models in *Streptococcus pneumoniae* infections with different results depending on the nebulizer.[168]

Conclusion

Management of patients with HAP and VAP requires prompt and adequate antibiotic administration and exposure. During the last decade, the progressive increase of nosocomial respiratory tract infections caused by MDR organisms has been associated with delays in the prescription of an adequate antibiotic treatment and increased mortality, representing a major concern. New approved and investigational agents for the treatment of respiratory tract infections represent promising options to preserve and enhance our antibiotic armamentarium. The most attractive characteristic of new drugs is the broad-spectrum activity against MDR organisms, particularly gram negatives, which still represent a major challenge in clinical practice. The efficacy of these agents in real life should be further investigated. In particular, studies regarding the potential opportunity for a monotherapy in patients with infections by MDR gram-negative pathogens are needed. Positioning and differentiation of new treatment options, along with the optimization of available therapeutic options, are needed to incorporate these drugs in daily clinical use to face the challenge of antimicrobial resistance in patients with HAP and VAP.

In conclusion, several newly approved agents hold promise for the treatment of HAP and VAP and hopefully new agents will enrich our antimicrobial arsenal in the next years. Targeted pharmacokinetic and clinical studies in real-life scenario of HAP and VAP are important to position these new agents in clinical practice, whereas vigilant use will ensure their longevity in our armamentarium.

Conflict of Interest
Outside the submitted work, D.N.G. reports investigator-initiated grants by Pfizer Inc. and Gilead Italia. Outside the submitted work, M.B. has received funding for scientific advisory boards, travel and speaker honoraria from Angelini, Astellas, Bayer, BioMérieux, Cidara, Cipla, Gilead, Menarini, MSD, Pfizer, Shionogi, Tetraphase, Nabriva. The other authors did not report conflicts of interest relevant to this paper.

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