New antibiotics for Gram-negative pneumonia

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Thanks to new antibiotics, there is hope in the future regarding treatment of pneumonia caused by Gram-negative bacilli. https://bit.ly/3sl2sVw

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Abstract

Pneumonia is frequently encountered in clinical practice, and Gram-negative bacilli constitute a significant proportion of its aetiology, especially when it is acquired in a hospital setting. With the alarming global rise in multidrug resistance in Gram-negative bacilli, antibiotic therapy for treating patients with pneumonia is challenging and must be guided by *in vitro* susceptibility results. In this review, we provide an overview of antibiotics newly approved for the treatment of pneumonia caused by Gram-negative bacilli. Ceftazidime-avibactam, imipenem-relebactam and meropenem-vaborbactam have potent activity against some of the carbapenem-resistant Enterobacterales, especially *Klebsiella pneumoniae* carbapenemase producers. Several novel antibiotics have potent activity against multidrug-resistant *Pseudomonas aeruginosa*, such as ceftazidime-avibactam, ceftolozane-tazobactam, imipenem-relabactam and cefiderocol. Cefiderocol may also play an important role in the management of pneumonia caused by *Acinetobacter baumannii*, along with plazomicin and eravacycline.

Introduction

Lower respiratory tract infections are among the most common infectious diseases affecting humans [1, 2] and represent an important public health problem, with substantial morbidity and mortality rates [3, 4]. Pneumonia can be classified into community-acquired pneumonia (CAP), hospital-acquired pneumonia (HAP) and ventilator-associated pneumonia (VAP) [5].

HAP and VAP are primarily caused by Gram-negative bacteria, including *Pseudomonas aeruginosa*, Enterobacterales and *Acinetobacter baumannii* [3, 4, 6, 7]. On the other hand, CAP is primarily caused by *Streptococcus pneumoniae* [8]. However, in recent decades, there has been a growing interest in the role of Gram-negative bacteria in patients with CAP, especially those with underlying lung diseases or previous antibiotic therapy [9]. Table 1 summarises the patients at risk for Gram-negative bacilli CAP as well as the risk factors associated with the isolation of multidrug-resistant (MDR) strains.

The rise of resistance limits the options for effective treatment of pneumonia caused by MDR Gram-negative bacteria and makes them a challenge for clinical management and a key global public health concern, associated with higher medical costs, longer hospital stays and increased mortality [10]. It has been recently estimated that if the situation is left unchecked, by 2050 as many as 10 million people could die each year because of antimicrobial resistance [10]. Various mechanisms are responsible for resistance to antibiotics, such as alteration of the drug target, decreased membrane permeability and drug efflux pumps [11], but the hydrolysis mediated by the production of degrading enzymes is the most common mechanism of resistance in clinically important Gram-negative bacteria [12, 13].

TABLE 1 Risk factors associated with community-acquired pneumonia (CAP) caused by Gram-negative bacteria (including multidrug-resistant (MDR) strains)

	Risk factor for MDR strain
Demographics	
Older age [102]	No
Underweight [103]	Yes
Residence in a nursing home or extended care facility [102]	No
Underlying conditions	
Chronic lung disease, mainly COPD and bronchiectasis [104–106]	Yes
Immunodepression [102]	No
Chronic dialysis [102]	No
Cardiovascular disease [103, 105]	Yes
Cerebrovascular disease [105]	No
Diabetes [107]	No
Others	
Smoking [107]	No
Antimicrobial (both oral and intravenous) in the preceding 90 days [104, 106]	Yes
Home wound care [102]	No
Prior infection or colonisation with an MDR Gram-negative pathogen (*e.g. Pseudomonas aeruginosa*) [104, 107]	Yes
Prior hospitalisation [103]	Yes
Enteral tube feeding [105]	No
Clinical presentation	
Severe disease (*e.g.* CAP requiring ICU admission) [103, 106]	No
PSI score III, IV [104]	No

ICU: intensive care unit; PSI: pneumonia severity index.

Traditionally, infections due to MDR Gram-negative bacteria, especially when resistant to carbapenem, have been very difficult to treat, mainly because the available options, such as polymyxins, aminoglycosides and/or glycylcyclines, have significant disadvantages, including nonnegligible toxicity and possible suboptimal pharmacokinetics in some sites of infection [14–16]

During recent years, several new antibiotics with predominant *in vitro* activity against Gram-negative pathogens have been approved, but they show great variability in terms of spectrum of activity, indications, pharmacodynamics/pharmacokinetics and accumulated clinical experience (figure 1 and table 2). All these aspects make it worthwhile to carefully select the best available option for any given patient. In addition, other new agents with activity against Gram-negative bacteria are in clinical development and some of them may provide other interesting options for the treatment of Gram-negative pneumonia in the future [17].

This narrative review aims to discuss the characteristics of the newly available agents for the treatment of Gram-negative pneumonia, specifically focusing on the management of patients with MDR infections.

Ceftobiprole

Ceftobiprole is a fifth-generation cephalosporin approved for the treatment of CAP and HAP, excluding VAP. As reported in table 2, ceftobiprole shows a potent activity against several Gram-negative pathogens, such as *Haemophilus influenzae*, *Moraxella catarrhalis*, *P. aeruginosa* and depressed AmpC producers, but not against extended-spectrum β-lactamases (ESBL)-, carbapenemases- or metallo-β-lactamases (MBL)-producing Enterobacterales [18]. In addition, it shows no activity against *A. baumannii*, *Burkholderia cepacia* and *Stenotrophomonas maltophilia*. Ceftobiprole also provides pronounced bactericidal activity against Gram-positive bacteria, such as *S. pneumoniae* and methicillin-resistant *Staphylococcus aureus* (MRSA) [18].

There were two pivotal clinical trials for ceptobiprole conducted in patients with CAP and HAP (table 3) [19, 20]. Regarding CAP, hospitalised patients were randomised to receive ceftobiprole 500 mg every 8 h in 2 h infusions *versus* ceftriaxone 2 g every 24 h in 30 min infusions. Patients were stratified according to their Pneumonia Severity Index and, if MRSA was suspected, placebo or linezolid was added in both the ceftobiprole and ceftriaxone arm [19]. Overall, noninferiority was achieved in terms of primary efficacy end-point (clinical cure rate at the test of cure (TOC)) in both intention-to-treat (ITT) and clinically

	Enterobacterales					
	Class A Carbapenemase (*e.g.* KPC)	**Class B Carbapenemase (*e.g.* NDM)**	**Class D Carbapenemase (*e.g.* OXA-48)**	***Pseudomonas aeruginosa***	***Acinetobacter baumannii***	***Stenotrophomonas maltophilia***
Ceftobiprole						
Ceftolozane-tazobactam						
Ceftazidime-avibactam						
Cefiderecol						
Meropenem-vaborbactam						
Imipenem-relebactam						
Aztreonam-avibactam						
Plazomicin						
Eravacycline						

FIGURE 1 Activity of new agents against Gram-negative pathogens. Grey shading: variable activity; red shading: non-activity; green shading: activity. KPC: *Klebsiella pneumoniae* carbapenemases; OXA: OXA-β-lactamases; NDM: New Delhi metallo-β-lactamase.

evaluable (CE) populations [20]. In the other phase 3, double-blind, multicentre, international, randomised study, ceftobiprole was compared to ceftazidime plus linezolid for the treatment of HAP and VAP, with a planned treatment duration of 7 days and up to a maximum of 14 days [19]. The primary efficacy end-point was clinical cure at the TOC visit, defined as resolution of signs and symptoms of infection, or improvement to such an extent that no further antimicrobial therapy was needed. Ceftobiprole monotherapy was noninferior to the comparator arm for patients with HAP, both in the ITT and CE populations. However, this study failed to demonstrate the noninferiority of ceftobiprole in patients with VAP [19]. The substantial heterogeneity in baseline characteristics of VAP patients and the suboptimal concentration achieved at the infection site in critically ill patients are the most likely explanations for the differential outcome in VAP patients [21, 22]. Overall, ceftobiprole is generally well tolerated with a low rate of adverse events. The most common ones are dysgeusia, nausea, vomiting and diarrhoea followed by hypertransaminasemia and infusion site reactions [19, 20, 23]

In conclusion, due to its safety profile and spectrum of activity, ceftobiprole may be a viable single therapeutic option for the treatment of CAP and HAP caused by Gram-negative bacteria, especially when concomitant MRSA is suspected (table 2).

Ceftolozane-tazobactam

Ceftolozane-tazobactam is the combination of a modified cephalosporin (ceftolozane) with a well-established β-lactamase inhibitor (tazobactam). Ceftolozane is stable against multiple resistance mechanisms of Gram-negative bacteria, including overexpression of AmpC, porin loss or drug efflux pumps [24, 25]. Ceftolozane currently represents the most active β-lactam against *P. aeruginosa*, including MDR or extremely drug resistant (XDR) isolates [24, 25]. The combination of ceftolozane and tazobactam shows activity against ESBL-producing Enterobacterales (figure 1) [24]. However, it lacks activity against all carbapenemases-producing strains (*e.g.* MBL or serine carbapenemases), including *P. aeruginosa* and Enterobacterales. The combination also lacks efficacy against *A. baumannii* or *S. maltophilia* [24].

The ceftolozane-tazobactam minimum inhibitory concentration (MIC) against *P. aeruginosa* is 8–16-fold lower than those of ceftazidime, imipenem or ciprofloxacin [26]. Recently, a surveillance study was carried out in the US to assess the effectiveness of ceftolozane-tazobactam compared with other antimicrobials. The results showed that *P. aeruginosa* strains had an overall susceptibility rate for ceftolozane-tazobactam (97.5%) higher than that for cefepime (83.6%), ceftazidime (82.6%), meropenem (76%) or piperacillin-tazobactam (77.7%) [27]. The only comparator that showed a greater activity was colistin, which showed a 99.9% susceptibility rate in the same isolates [27]. These results were in line with data from a recent Spanish study in which the most active antipseudomonals against the 1445 isolates studied

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TABLE 2 Dosage, pros and author's perspective of the new antibiotics currently approved for the treatment of pneumonia due to Gram-negative pathogens

	Ceftobiprole	Ceftolozane-tazobactam	Ceftazidime-avibactam	Cefiderocol	Meropenem-vaborbactam	Imipenem-relebactam
Antimicrobial activity	*Moraxella catarrhalis, Haemophilus influenza,* non-ESBL-, non-AmpC- and noncarbapenemases-producing Enterobacterales; *Pseudomonas aeruginosa*	ESBL-producing Enterobacterales; MDR *P. aeruginosa*	ESBL-, KPC-, AmpC- and OXA-48-producing Enterobacterales; MDR *P. aeruginosa*	ESBL- and CRE (class A, B, and D enzymes)-producing Enterobacterales; MDR *P. aeruginosa, S. maltophilia* and *A. baumannii*	ESBL-, KPC- and AmpC-producing *Enterobacterales*; non-MDR *P. aeruginosa*; non-MDR *A. baumannii*	ESBL- and KPC-producing *Enterobacterales*; MDR *P. aeruginosa*
Approved dosage for the treatment of pneumonia	2 h *i.v.* infusion 500 mg every 8 h	2 g of ceftolozane and 1 g of tazobactam every 8 h by *i.v.* infusion over 1 h	2 g of ceftazidime and 0.5 g of avibactam every 8 h by *i.v.* infusion over 2 h	2 g every 8 h by *i.v.* infusion over 3 h	2 g of meropenem and 2 g of vaborbactam every 8 h by *i.v.* infusion over 3 h	500 mg of imipenem and 250 mg of relebactam by *i.v.* infusion every 6 h over 30 min
Pros	Approved for CAP and HAP, but not for VAP	Best β-lactam with activity against *P. aeruginosa* Carbapenem-sparing agent Lower mortality observed in patients with ventilated HAP	Good clinical experience for treatment of KPC infection Carbapenem-sparing agent Good activity OXA-48-producing Enterobacterales Can be combined with aztreonam for the treatment of MBL-producing Enterobacterales	Wide spectrum of activity Unique drug with activity against MBL-producing Enterobacterales	Potent activity against KPC Low-propensity for developing *in vivo* resistance	Potent activity against KPC Potent activity against MDR *P. aeruginosa*

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TABLE 2 Continued

	Ceftobiprole	Ceftolozane-tazobactam	Ceftazidime-avibactam	Cefiderocol	Meropenem-vaborbactam	Imipenem-relebactam
Authors' perspective	Ceftobiprole could be a viable single therapeutic option for the treatment of CAP and HAP caused by Gram-negatives, especially when concomitant MRSA is suspected.	We believe that ceftolozane-tazobactam represents the first option as a backbone for the treatment of MDR *P. aeruginosa* as well as a carbapenem-sparing regimen for the treatment of pneumonia in clinical settings with a high rate of ESBL-producing strains.	Ceftazidime–avibactam currently represents one of the drugs of choice for the treatment of CRE infections. When treating patients with MDR Gram-negative bacteria pneumonia, ceftazidime-avibactam can be used in association with a second drug such as gentamycin, fosfomycin or colistin (or, in the future, with plazomycin). Moreover, it may have a role as a potential alternative to carbapenems in patients with nosocomial pneumonia with high rates (>20–25%) of infections caused by ESBL-producing or OXA-48-producing Gram-negative bacteria.	We believe that cefiderocol represents an interesting choice for empirical and definitive treatment of HAP and VAP when a carbapenem-resistant Gram-negative bacteria, including CRE, MDR *P. aeruginosa*, and MDR *A. baumannii* is suspected or confirmed. Whether or not it should be used as part of a combination treatment is still an unresolved issue.	In our opinion, meropenem-vaborbactam should be considered the first treatment option for CRE pneumonia, especially in consideration of its lower mortality rates, as recently documented in the TANGO II trial.	Imipenem-relebactam could offer an important new treatment option as part of an empirical or targeted therapy for HAP or VAP due to MDR Gram-negative bacteria. We believe that further studies coming from real-life experiences are needed.

A.: *Acinetobacter*; CAP: community-acquired pneumonia; CRE: carbapenem-resistant Enterobacterales; ESBL: extended-spectrum β-lactamases; HAP: hospital-acquired pneumonia; KPC: *Klebsiella pneumoniae* carbapenemases; MBL: metallo-β-lactamases; MDR: multidrug resistant; MRSA: methicillin-resistant *Staphylococcus aureus*; OXA: OXA-β-lactamases; *S.*: *Stenotrophomonas*; VAP: ventilator-associated pneumonia.

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TABLE 3 Efficacy data from large, randomised clinical trials investigating the use of novel agents with anti-Gram-negative activity in patients with community-acquired pneumonia (CAP) or hospital-acquired pneumonia (HAP)/ventilator-associated pneumonia (VAP)

Reference, trial	Drugs (dosage)	Comparators (dosage)	Primary end-point	Disease and study population for the primary analysis	Cured/total (rates, %)	Percent difference (95% CI)
Nicholson *et al.* [19]	Ceftobiprole (500 mg every 8 h for 7–14 days)	Ceftriaxone (2 g every 24 h for 7–14 days) ± linezolid (600 mg every 12 h if MRSA suspected)	Clinical cure rate at the TOC visit	CAP severe enough to require hospitalisation *ITT population* Ceftobiprole Ceftriaxone±linezolid *CE population* Ceftobiprole Ceftriaxone±linezolid	 ITT 240/314 (76.4) ITT 257/324 (79.3) CE 200/231 (86.6) CE 208/238 (87.4)	 – –
Awad *et al.* [20]	Ceftobiprole (500 mg every 8 h for 7–14 days)	Ceftazidime (2 g every 8 h) plus linezolid (600 mg every 12 h) for 7–14 days	Clinical cure rate at the TOC visit	HAP including VAP *ITT population* Ceftobiprole Ceftriaxone plus linezolid *CE population* Ceftobiprole Ceftriaxone plus linezolid	 ITT 195/391 (49.9) ITT 206/390 (52.8) CE 174/251 (69.3) CE 174/244 (71.3)	 −2.9 (−10.0–4.1) −2.0 (−10.0–6.1)
Kollef *et al.*[34], ASPECT-NP	Ceftolozane-tazobactam (3 g every 8 h for 8–14 days)	Meropenem (1 g every 8 h for 8–14 days)	28-day all-cause mortality	Ventilated nosocomial pneumonia *ITT population* Ceftolozane-tazobactam Meropenem	 87/362 (24.0) 92/364 (25.3)	 1.1 (−5.1–7.4)
Torres *et al.* [48], REPROVE	Ceftazidime-avibactam (2 g/0.5 g every 8 h for 7–14 days)	Meropenem (1 g every 8 h for 7–14 days)	Clinical cure at TOC visit	Nosocomial pneumonia including VAP *cMITT population* Ceftazidime-avibactam Meropenem *CE population* Ceftazidime-avibactam Meropenem	 245/356 (68.8) 270/370 (73.0) 199/257 (77.4) 211/270 (77.1)	 −4.2 (−10.76–2.46) −0.7 (−7.9–6.4)
Wunderink *et al.* [62], APEKS-NP	Cefiderecol (2 g every 8 h for 7–14 days)	Meropenem (2 g every 8 h for 7–4 days)	All-cause 14-day mortality	HAP, VAP or HCAP *ITT population* Cefiderocol Meropenem	 18/145 (12.4) 17/146 (11.6)	 0.8 (−6.6–8.2)
Bassetti *et al.* [63], CREDIBLE-CR	Cefiderecol (2 g every 8 h for 7–14 days)	Best available therapy	Clinical cure at TOC	Nosocomial pneumonia *CR-mITT population* Cefiderocol Best available therapy	 20/40 (50.0) 10/19 (52.6)	 –

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TABLE 3 Continued

Reference, trial	Drugs (dosage)	Comparators (dosage)	Primary end-point	Disease and study population for the primary analysis	Cured/total (rates, %)	Percent difference (95% CI)
Wunderink *et al.*[73], **TANGO II**	Meropenem-vaborbactam (2 g/2 g every 8 h for 7–14 days)	Best available therapy	Day 28 all-cause mortality	Carbapenem-resistant Enterobacterales HABP/VABP *mCRE-MITT population* Meropenem-vaborbactam Best available therapy	 4/20 (22.2) 4/9 (44.4)	 −22.2[#]
Motsch *et al.* [85], **STORE IMI-1**	Imipenem-relebactam (500 mg/250 mg every 6 h for 5–21 days)	Imipenem (500 mg every 6 h) plus colistin (loading dose 300 mg then 150 mg every 12 h)	Favourable overall response	HAP/VAP *mMITT population* Imipenem-relebactam Imipenem plus colistin	 7/8 (87.5) 2/3 (66.6)	 –
Titov *et al.* [86], **RESTORE-IMI 2**	Imipenem-relebactam (500 mg/250 mg every 6 h for 7–14 days)	Piperacillin/tazobactam (4 g/0.5 g every 6 h for 7–14 days)	Day 28 all-cause mortality	HABP/VABP *mITT population* Imipenem-relebactam Piperacillin/tazobactam	 42/264 (15.9) 57/267 (21.3)	 −5.3 (−11.9–1.2)
McKinnel *et al.* [96], **CARE**	Plazomicin (15 mg·kg^{-1} every 24 h for 7–14 days) plus meropenem or tigecycline	Colistin 5 mg·kg^{-1} every 24 h plus meropenem or tigecycline	Composite of death from any cause at 28 days or clinically significant disease-related complications	HAP or VAP caused by suspected or confirmed CRE *mMITT population* Plazomicin-based regimen Colistin-based regimen	 2/3 (67) 2/5 (40)	 27 (−48–82)

CE: clinically evaluable; cMITT: clinically modified intention-to-treat (population); CR: carbapenem resistant; CR-MITT: carbapenem-resistant microbiological ITT (population); HABP: hospital-acquired bacterial pneumonia; HCAP: healthcare-associated pneumonia; ITT: intent-to-treat (population); mCRE-MITT: microbiologic carbapenem resistant Enterobacterales-modified intent-to-treat (population); mITT: modified intent-to-treat (population); mMITT: modified microbiological intent to treat (population); MRSA: methicillin-resistant *Staphylococcus aureus*; TOC: test of cure; VABP: ventilator-associated bacterial pneumonia. [#]Data represent the difference in percentages for meropenem-vaborbactam and best available therapy.

were colistin and ceftolozane-tazobactam (both 94.6% susceptible, MIC required to inhibit growth of 50%/90% ($MIC_{50/90}$) = 1/2 $mg \cdot L^{-1}$) [28]. Regarding ceftolozane-tazobactam activity against Enterobacterales, recent studies reported that ceftolozane-tazobactam was highly active against *Escherichia coli*, including AmpC- or ESBL-producing isolates. On the other hand, the activity of ceftolozane-tazobactam decreased against ESBL-producing *K. pneumoniae* strains [24, 29, 30] and *Proteus* spp. [31].

The drug achieves good penetration in the lung parenchyma, as suggested by a recent study carried out on healthy subjects receiving ceftolozane-tazobactam (1.0–0.5 g), in which ceftolozane-tazobactam epithelial lung fluid (ELF)/plasma area under the curve (AUC) ratio reached 0.48 [32]. This finding indicates that ELF concentrations of ceftolozane-tazobactam may reach and exceed the MIC of most Gram-negative pathogens causing nosocomial pneumonia [32]. However, ceftolozane-tazobactam is currently approved for the treatment of nosocomial pneumonia (both HAP and VAP) at a higher dosage (2 g of ceftolozane and 1 g of tazobactam every 8 h) [33].

The ASPECT-NP study was a randomised, double-blind trial performed to compare ceftolozane-tazobactam (at a dosage of 3 g every 8 h) with meropenem (1 g every 8 h) for the treatment of patients presenting nosocomial pneumonia (table 3). A total of 726 patients were enrolled and 519 (71%) of them had VAP. Most patients were in the intensive care unit (ICU) and half of them had septic shock. *K. pneumoniae*, *E. coli* and *P. aeruginosa* were the most frequent isolates in patients with VAP. The primary end-point was 28-day all-cause mortality [34]. Ceftolozane-tazobactam was noninferior to meropenem in terms of both 28-day all-cause mortality (24.0% in the ceftolozane-tazobactam group and 25.3% in the meropenem group, weighted treatment difference 1.1%, 95% CI −5.1–7.4) and clinical cure at TOC (54.0% in the ceftolozane-tazobactam, group and 53% in the meropenem group, weighted treatment difference 1.1%, 95% CI −6.2–8.3) [34]. Of importance, prior studies had generally reported a higher mortality rate in patients with ventilated HAP than in those with VAP [35]. In the ASPECT-NP study, a difference in terms of mortality between these two conditions was only observed for patients receiving meropenem [34, 35]. Indeed, among patients with ventilated HAP, the odds of dying at day 28 from any cause were 2.3 times higher in the meropenem group compared to those in the ceftolozane-tazobactam group [36].

As for studies coming from real-life experience, a recent meta-analysis including 33 real-world studies including 658 patients with lower respiratory tract infections reported similar outcomes (clinical success, microbiological success and 30-day mortality) with ceftolozane-tazobactam as those observed in the ASPECT-NP trial [37]. These results were observed despite that the real-life experience data included a greater proportion of MDR pathogens as well as patients with different comorbidities [37, 38] that were excluded in the pivotal trials [34]. In another retrospective, observational cohort study, patients who were treated with ceftolozane-tazobactam were compared with those who received polymyxin- or aminoglycoside-based regimens for the treatment of infections caused by drug-resistant *P. aeruginosa*. This study enrolled a total of 200 patients (100 patients per arm). At the time of *P. aeruginosa* infection, 69% of the patients were in the ICU, 63% were receiving mechanical ventilation and 42% had septic shock. The most frequent infection was VAP (52%) and 7% of patients with this infection had concomitant positive blood cultures. In this study, after adjusting for differences between groups, patients treated with ceftolozane-tazobactam had a better clinical cure (adjusted OR (aOR) 2.63, 95% CI 1.31–5.30) and lower acute kidney injury (aOR 0.08, 95% CI 0.03–0.22) [39]. Concordant results were also reported in two similar case control studies, in which compared to “old antibiotics”, ceftolozane-tazobactam was more effective in the treatment of MDR/XDR *P. aeruginosa* VAP [40] and HAP [16], while reporting a better safety profile in terms of acute kidney injury.

The results of these studies lead us to consider ceftolozane-tazobactam as the first choice for the treatment of VAP or HAP caused by MDR or XDR *P. aeruginosa*. Ceftolozane-tazobactam should also be considered as a valuable alternative to carbapenems for the treatment of nosocomial pneumonia caused by ESBL-producing Enterobacterales (table 2) [41].

Ceftazidime-avibactam

Ceftazidime-avibactam is a combination agent containing a semi-synthetic third-generation cephalosporin and a novel non β-lactam/β-lactamases inhibitor. Avibactam protects ceftazidime from the hydrolytic activity of a wide range of class A (*e.g.* ESBL and *K. pneumoniae* carbapenemases (KPC)), C (*e.g.* AmpC) and D β-lactamases (*e.g.* OXA-48 enzymes). However, it lacks activity against class B β-lactamases [37] and has low activity against *A. baumannii* or anaerobic Gram-negative bacteria and Gram-positive cocci (figure 1) [38]. In a recent surveillance study, >99% of Enterobacterales strains were susceptible to ceftazidime-avibactam with an MIC_{90} of 0.5 $\mu L \cdot mL^{-1}$, seven doubling dilutions lower than

the MIC_{90} for ceftazidime-alone (64 μL·mL^{-1}) [42]. Ceftazidime-avibactam also retains activity against carbapenem-resistant (CR) Enterobacterales strains, with 80% of isolates showing *in vitro* susceptibility [42]. As for *P. aeruginosa*, a significant proportion of isolates show susceptibility to ceftazidime-avibactam (90%) [43], including two-thirds of ceftazidime nonsusceptible strains and three-fourths of CR *P. aeruginosa* isolates [43, 44].

Although resistance to ceftazidime-avibactam is emerging, it appears to be low. In a recent surveillance study, nonsusceptibility to ceftazidime-avibactam was found in 0.5% and 8% of Enterobacterales and *P. aeruginosa* isolates, respectively [43, 44]. The most common mechanism of resistance includes the presence of β-lactamases that are not efficiently inhibited by avibactam because of punctiform mutations [45]. Lung penetration of ceftazidime-avibactam has been studied in a phase 1 trial performed in healthy subjects. This study found that ELF and plasma concentrations of ceftazidime and avibactam increase in a dose-dependent manner for both molecules, with a plasma/ELF ratio of 40% [46].

Ceftazidime-avibactam is currently US Food and Drug Administration (FDA) and European Medicine Agency approved [47] for the treatment of HAP and VAP based on the results of a randomised, controlled double-blind, phase 3 noninferiority trial comparing ceftazidime-avibactam (2.0–0.5 g infused over 2 h, every 8 h, for 7–14 days) to meropenem (1 g infused over 30 min, every 8 h, for 7–14 days) (REPROVE study) [48] (table 3). The primary end-point of the study was the proportion of patients clinically cured at the TOC visit in the coprimary clinically modified ITT and CE populations. Overall, 879 patients (290, 33.3% with VAP) were included in the ITT population. Baseline pathogens were similar between groups and, as expected for patients with nosocomial pneumonia, the prominent Gram-negative pathogens were *K. pneumoniae* and *P. aeruginosa*. Ceftazidime-avibactam was noninferior to meropenem in the coprimary analysis population. In the clinically modified ITT population, 245 out of 356 patients (68.8%) in the ceftazidime-avibactam group were clinically cured at TOC visit, in comparison with 270 out of 370 (73.0%) in the meropenem group (difference −4.2, 95% CI −10.76–2.46; p=0.0066). Overall, 199 out of 257 (77.4%) in the ceftazidime-avibactam group and 211 out of 270 (78.1%) in the meropenem group were cured in the CE population (difference −0.7, 95% CI −7.86–6.39; p=0.0007) [48].

Several real-world experiences with ceftazidime-avibactam for the treatment of HAP and VAP have been published, and all of them confirmed the excellent efficacy and tolerability of the drug in daily clinical practice [49–54]. As for the economic implications, the cost of ceftazidime-avibactam has been recently compared to that of meropenem for empirical treatment of hospitalised patients with HAP/VAP. According to a base-case analysis, patients treated with ceftazidime-avibactam experienced higher clinical cure rates, shorter hospitalisation and a higher number of life years and quality-adjusted life-years (QALYs). In comparison to meropenem, ceftazidime-avibactam had an estimated incremental cost of €1254 per patient, although the higher costs were offset by reduction in hospitalisation costs and gain in QALYs [55].

In our opinion, ceftazidime-avibactam currently represents the drug of choice for the treatment of HAP or VAP due to OXA-48- or KPC-producing Enterobacterales. It may also have a role in nosocomial pneumonia caused by ESBL-producing Enterobacterales or CR *P. aeruginosa* (table 2).

Cefiderocol

Cefiderocol is a new modified cephalosporin with a cathecol side chain that forms a chelated complex with ferric iron. This mechanism facilitates its penetration into bacterial cells, where cefiderocol inhibits cell-wall synthesis by binding to penicillin-binding proteins and inhibiting peptidoglycan synthesis [56]. This novel cephalosporin retains activity even in the presence of β-lactamases such as Ambler class A, B, C and D β-lactamases (figure 1) [57, 58]. SIDERO-WT, a large surveillance programme carried out in various centres between 2014 and 2015, was performed to assess the *in vitro* activity of cefiderecol against various MDR bacteria. Overall, more than 28 000 Gram-negative isolates were randomly collected, including isolates from patients with VAP. Among the tested strains, more than 99% of Enterobacterales (*E. coli*, *Klebsiella* spp., *Citrobacter* spp., *Enterobacter* spp. and *Serratia* spp.) showed susceptibility to cefiderecol with an MIC_{90} ranging from 0.25 to 1 μg·mL^{-1}. As for *P. aeruginosa*, *B. cepacia* and *Stenotrophomonas maltophilia*, the MIC_{90} ranged from 0.03 to 1 μg·mL^{-1}, whereas for *A. baumannii* the MIC_{90} ranged from 1 to 4 μg·mL^{-1} [59, 60].

As for pharmacokinetics, when compared to ceftazidime, cefiderecol showed a similar lung tissue concentration (ELF/plasma AUC ratio 0.239 for cefiderocol compared to 0.229 for ceftazidime) [61].

Regarding clinical data, cefiderocol was compared to meropenem in the APEKS-NP study, a multicentre double-blinded phase 3, noninferiority trial. In this study, patients received either cefiderocol or

meropenem (1:1 proportion) plus linezolid (for at least 5 days) (table 3). The primary end-point of the study was 14 days all-cause mortality in the modified ITT population. Of the 292 patients, 123 were diagnosed with VAP. The most frequently isolated pathogens were *K. pneumoniae* followed by *P. aeruginosa* and *A. baumannii* [62]. Regarding the primary end-point, cefiderocol was found to be comparable to meropenem (12.4% for cefiderocol compared to 11.6% for meropenem, adjusted treatment difference in ITT population of 0.8%, 95% CI −6.6–8.2; p=0.002). The two therapeutic arms also showed similar results in terms of all-cause 28-day mortality and safety end-points [62]. Of importance, among 16 patients with *A. baumannii* strains with a meropenem MIC >64 $\mu L \cdot mL^{-1}$, all-cause mortality at day 14 was 0% in the cefiderocol group and 47% in the meropenem group.

CREDIBLE-CR was a randomised controlled trial that tested the efficacy and safety of cefiderecol in a population with infections caused by CR pathogens (table 3). This pathogen-specific trial compared cefiderocol 2 g every 8 h with the best available therapy (BAT) (2:1 ratio), usually administered as a combination of multiple antibiotics [63], in 152 patients including nosocomial pneumonia in 45% of them. The most common isolates were *A. baumannii* (46%, 54 patients), *K. pneumoniae* (33%, 39 patients) and *P. aeruginosa* (19%, 22 patients). In the modified ITT (mITT) population, clinical cure rates at TOC were comparable between the two arms (50%, 95% CI 33.8–66.2 in the cefiderocol arm *versus* 53%, 95% CI 28.9–75.6 in the BAT arm). Similar results were also observed in the CR-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 the treatment was met in 50% and 53% of the patients, respectively. Unfortunately, when analysing mortality, it was found that patients with HAP and VAP treated with cefiderocol (42%) had a higher 28-day mortality (cefiderocol 42% *versus* 18% in the BAT), mainly when the infecting pathogen was *A. baumannii* [63]. According to these results, a warning of increased all-cause mortality for patients with CR *A. baumannii* infections treated with cefiderocol monotherapy has been released [64].

As for clinical experience, Falcone *et al.* [65] recently compared the 30-day mortality among 124 patients treated with either cefiderocol- (47, 37.9%) or colistin-containing regimens (77, 62.1%) for different nosocomial infections caused by *A. baumannii* (bloodstream infections and VAP). 30-day mortality was higher in patients receiving colistin compared to those who received cefiderocol-containing regimens (55.8% *versus* 34%, p=0.018). This difference was confirmed in patients with a bloodstream infection, but not in those with VAP. On multivariable analysis, septic shock, Sequential Organ Failure Assessment score and age were independently associated with 30-day mortality, while cefiderocol therapy was protective in an inverse probability of treatment weighting analysis (hazard ratio 0.44, 95% CI 0.22–0.66, p<0.001). Moreover, patients treated with colistin-containing regimens experienced a higher probability of developing acute kidney injury.

To conclude, we believe that cefiderocol currently represents an interesting therapeutic choice for the treatment of HAP and VAP due to MBL-producing Enterobacterales, MDR *P. aeruginosa* and other CR Gram-negative bacteria. Being one of the most recently released antibiotics, there is still a need for studies aiming to address in depth the effectiveness of this drug. However, the currently available evidence shows its potential role in the treatment of these infections, also thanks to the wide spectrum that includes every type of β-lactamases class (table 2).

Meropenem-vaborbactam

Meropenem-vaborbactam is the combination of 1) a well-established carbapenem, meropenem, with 2) vaborbactam, a new non-β-lactam β-lactamase inhibitor derived from boric acid. Vaborbactam protects meropenem from the degradation by class A and C β lactamases [66]. However, no activity was observed against class B and D β-lactamases. Similarly, vaborbactam does not grant more *in vitro* activity, compared to meropenem alone, against glucose-nonfermenting Gram-negative bacilli [67] (figure 1) [68, 69]. In a comparative analysis including clinical isolates of KPC-positive Enterobacterales, meropenem-vaborbactam showed more potent *in vitro* activity compared to meropenem alone, ceftazidime-avibactam, tigecycline, ceftazidime alone, minocycline, polymyxin B and gentamycin [70]. These results were confirmed in a surveillance study including more than 10 000 Gram-negative isolates from hospitalised patients with nosocomial pneumonia. In this study, meropenem-vaborbactam was the β-lactam with the highest susceptibility rates not only against Enterobacterales isolates (98.0%) but also against *P. aeruginosa* ones (82.1% susceptible) [71].

As for pharmacokinetics, meropenem-vaborbactam distribution in the lungs was assessed by administering three doses of the drug in volunteers without any comorbidity. The lung penetration of meropenem-vaborbactam was considerable, with AUC values of 63% and 53% in the ELF and total plasma, respectively [72].

In the TANGO II trial (safety and efficacy of meropenem-vaborbactam monotherapy compared to the BAT in adults with serious infections caused by CR Enterobacterales) [73], 43 out of 77 eligible patients had a confirmed CR Enterobacterales infections and were randomised in a 2:1 ratio to receive either 7–14 days of meropenem 2 g plus vaborbactam 2 g every 8 h as monotherapy or 7–14 days of the BAT (table 3). In this study, all-cause mortality was the primary efficacy end-point in patients with HAP and VAP. As the management of CR pathogens does not have a standard regimen and its quite challenging, a variety of different mono and combination therapies were used in the BAT arm. The study results showed meropenem-vaborbactam to be associated with higher rates of clinical cure than the BAT at both end of trial (65.6% (21/ 32) *versus* 33.3% (5/15); difference, 32.3%; 95% CI 3.3–61.3%; p=0.03) and TOC (59.4% (19/32) *versus* 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 the BAT (65.6% *versus* 40.0%; difference, 25.6%; p=0.09 at end of trial) [73]. Another aspect that needs to be highlighted is the lower 28-day all-cause mortality in patients with nosocomial pneumonia or bacteraemia who received meropenem-vaborbactam than in those who received BAT (22.2% *versus* 44.4% p=0.25) [73].

Alosaimy *et al.* [74], in a recent multicentre, real-world study, reported the safety and clinical outcomes of 126 patients with different hospital-acquired infections. The most common sources were the respiratory tract (38.1%) and intra-abdominal region (19.0%), while the most common isolated pathogens were CR Enterobacterales (78.6%). 30-day mortality and recurrence occurred in 18.3% and 11.9% of infections, respectively. Of importance, receiving early treatment with meropenem-vaborbactam (<48 h from symptoms onset) was independently associated with a better clinical outcome at multivariable analysis (aOR, 0.277; 95% CI 0.081–0.941)

A much-awaited post-approval experience regarding meropenem-vaborbactam has been recently reported [75]. This study aimed to compare meropenem-vaborbactam efficacy in comparison to ceftazidime-avibactam in serious CR Enterobacterales infections. A total of 131 patients satisfied the criteria to be enrolled in the study and 49 of them had a respiratory tract infection. Clinical success was the primary end-point and was found to be comparable in the two arms (69.2% *versus* 62.0%, p=0.49). The same results were obtained looking at the 30-day mortality, 90-day mortality and also looking at the percentage of adverse events in the two arms. One significant difference was found in terms of development of resistance, with ceftazidime-avibactam monotherapy leading to three patients developing resistant strains *versus* no patients for meropenem-vaborbactam [75].

In our opinion, meropenem-vaborbactam should be considered as one of the best therapeutic options currently available for the treatment of patients with HAP or VAP due to CR Enterobacterales pathogens (table 2).

Imipenem-relebactam

Relebactam is a recently synthetised β-lactamase inhibitor developed to restore the activity of imipenem against Gram-negative isolates producing class A [76] and C β-lactamases, but not class B and class D [77]. The addition of relebactam to imipenem substantially restores the activity of imipenem against the majority of imipenem nonsusceptible *P. aeruginosa* and KPC-producing Enterobacterales, but not against *A. baumannii* or *Stenotrophomonas maltophilia* (figure 1) [78, 79].

In the SMART 2017 surveillance programme, a worldwide collection of clinical isolates, imipenem-relebactam susceptibility was >90% against most Enterobacterales species [80]. In detail, the susceptibility rates were 99.6% for *E. coli*, 93.0% for *K. pneumoniae* and 97.8% for *Enterobacter cloacae*. As for *P. aeruginosa*, high susceptibility rates were also observed, with up to 90% of the strains being sensitive to imipenem-relebactam [81]. Of importance, the combination was also active against the majority of imipenem-resistant *P. aeruginosa* isolates, especially when imipenem resistance was mediated by AmpC overproduction or OprD porin loss [82, 83]. Regarding tissue distribution, both drugs showed, in different studies, their capacity of reaching good levels both in plasma and ELF. These results prove that imipenem-relebactam can be used to treat nosocomial infections [84, 85].

The safety and efficacy of imipenem-relabactam for the treatment of HAP/VAP have been investigated in two phase 3 noninferiority trials. RESTORE-IMI 1 was a prospective study performed to investigate the efficacy of the proposed imipenem-relebactam dosage in a population of patients with different complicated infections (table 3). This multicentre, randomised, double-blind, noninferiority study compared imipenem-relebactam as a single agent with the combination of colistin plus imipenem in 47 patients with imipenem-nonsusceptible pathogens, including HAP/VAP (35.5%), complicated urinary tract infections (25.8%), acute pyelonephritis (25.8%) or complicated intra-abdominal infections (12.9%). The most

common pathogen in the mMITT population was *P. aeruginosa* (77.4%), followed by *K. pneumoniae* (12.9%) [86]. An overall favourable response was observed in 71% imipenem-relebactam and 70% colistin plus imipenem patients (90% CI −27.5–21.4%), day 28 favourable 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. Among patients with HAP/VAP, clinical response was observed in seven out of eight patients in the imipenem-relebactam group (87.5%) *versus* two out of three in the colistin plus imipenem group (66.7%, 95% CI 50.8–99.9%). In addition, 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%) [86].

RESTORE IMI-2 was a phase 3 randomised double-blind noninferiority trial comparing imipenem-relebactam with piperacillin-tazobactam in 537 patients with HAP/VAP, with Enterobacterales as the most common causative pathogen (table 3) [87]. Patients in both groups were treated with intravenous agents for 7–14 days. The primary end-point was all-cause day 28 mortality in the mITT population. The noninferiority of imipenem-relebactam was demonstrated for the primary end-point (adjusted treatment difference −5.3%, 95% CI −11.9–1.2%) [87]. Additionally, in the subgroup of ventilated patients, as well as in the subgroup of patients with an APACHE II score >15, the day 28 mortality rate was lower with imipenem-relebactam in comparison to piperacillin/tazobactam [87].

In our opinion, imipenem-relebactam should be always considered for the treatment of suspected or confirmed HAP/VAP caused by KPC-producing Enterobacterales or by CR *P. aeruginosa* (nonmetallo-carbapenemases) (table 2).

Aztreonam-avibactam

Aztreonam is a β-lactam which has activity against MBL. However, aztreonam alone has no activity against most ESBL and AmpC producers. These enzymes are frequently produced by Gram-negative bacteria resistant to carbapenems [88]. Accordingly, avibactam confers aztreonam stability against most MDR Gram-negative bacteria, including those coharbouring class A, C and D β-lactamases [89, 90].

Drug efficacy and safety are currently being evaluated in an ongoing pivotal trial for the treatment of serious Gram-negative infections [91]. However, while waiting for more robust data, the clinical efficacy of ceftazidime-avibactam plus aztreaonam in comparison to the BAT was evaluated in a retrospective study including 102 patients with New Delhi MBL-producing Enterobacterales bloodstream infection. This combination was associated with lower 30-day mortality rate, lower clinical failure at 14 days and shorter hospitalisation when compared to other active *in vitro* regimens. At present, thanks to these data, aztreonam plus ceftazidime-avibactam is used as a combination therapy in those infections caused by MBL-producing strains [92].

Plazomicin

Plazomicin is a parenteral aminoglycoside recently approved by the FDA for the treatment of complicated urinary tract infections, including pyelonephritis. In comparison to other aminoglycosides, plazomicin remains stable against the inactivation by aminoglycoside-modifying enzymes, but it is not active against the less common 16s ribosomal ribonucleic acid methyltransferase [93].

Plazomicin showed great *in vitro* efficacy against more than 95% of the isolated Enterobacterales strains ($MIC_{50/90}$, 0.5/1.0 $mg \cdot L^{-1}$) with a susceptibility breakpoint lower than 2 $mg \cdot L^{-1}$ [94]. Regarding *P. aeruginosa* and *Acinetobacter* spp., plazomicin exhibited an $MIC_{50/90}$ comparable to the MIC of amikacin [94].

As for its use in patients with pneumonia, the pharmacokinetics of plazomicin are similar to those of other aminoglycosides, which generally show limited lung penetration (13%) [95].

Clinically, plazomicin has been studied in different nosocomial infections caused by CR Enterobacterales, with results similar to those of its comparators. In a randomised double-blind, phase 3 trial, intravenous plazomicin (15 mg per kilogram of body weight once daily) was compared to colistin (5 mg colistin base per kilogram per day), in combination with adjunctive meropenem or tigecycline, for 7–14 days of therapy. Clinical success rates were similar in all populations. Among patients with HAP/VAP, the primary end-point (a composite end-point of death from any cause at 28 days or clinically significant disease-related complications in the mMITT population) 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 −48–82). Additionally, the incidence and severity of adverse events and laboratory abnormalities were significantly

lower in the plazomicin group than in the colistin one (50% plazomicin *versus* 81% colistin) [96]. Despite these results, plazomicin is currently not FDA approved for the treatment of nosocomial pneumonia, mainly due to the small sample size of patients with lower respiratory tract infection included in the trial (five VAP in the colistin arm and three in the plazomicin arm) [97].

Eravacycline

Eravacycline is a new tetracycline derivate that acts on the 30s ribosomal subunit to inhibit bacterial protein synthesis. The molecule has a fluorine atom and a pyrrolidine acetamide group that help overcome tetracycline resistance. It is available in both an intravenous formulation and an oral one. The activity of eravacycline ranges from Gram-positive to Gram-negative bacteria, showing a great spectrum of effectiveness, which includes difficult-to-treat bacteria such as *A. baumannii* isolates resistant to sulbactam. On the other hand, it shows no activity against *P. aeruginosa* [98, 99].

In a phase 1 study, eravacycline pharmacokinetics were evaluated in healthy adults receiving the drug in its intravenous formulation. In these volunteers, the concentrations of eravacycline were found to be six times greater in the ELF compared to plasma and 50 times in the alveolar macrophages [100]. The role of evaracycline in *A. baumannii* pneumonia was recently investigated in a retrospective study comparing eravacycline to the best previously available therapy. In this study, eravacycline was associated with higher 30-day mortality (33% *versus* 15%; p=0.048), lower microbiologic cure (17% *versus* 59%; p=0.004) and longer durations of mechanical ventilation (10.5 *versus* 6.5 days; p=0.016). According to these results, further data are needed before administering eravacycline for the treatment of pneumonia [101].

Conclusions

Because of the increasing challenges posed by the treatment of Gram-negative pneumonia and the limited therapeutic options for patients with MDR strains, the development of these new antibiotics represents an important therapeutic advance. All these new antibiotics show good *in vitro* and *in vivo* activity against these pathogens, with a low risk of developing *in vivo* resistance at the currently recommended dosage. The available data demonstrate their efficacy and safety in patients with MDR infections, with a low potential for toxicity in comparison with old regimens including colistin or aminoglycosides, which have been the standard of care until very few years ago. Moreover, clinical experiences coming from real life have further confirmed their efficacy, even if these studies included very clinically complex patients with different underlying conditions suffering infections due to extensively drug-resistant strains.

To conclude, there are several newly approved agents which look like promising opportunities for the treatment of serious Gram-negative pneumonia. The increasing rate of resistance to the currently drugs is a serious problem and hopefully new agents will enrich our antimicrobial arsenal in the coming years. Targeted pharmacokinetic and clinical studies in real-life scenarios are important to position these new agents in clinical practice, while a good antimicrobial stewardship and a clever usage of these agents will make it possible to keep the resistance levels as low as they are now, thus ensuring their longevity in our armamentarium.

Points for clinical practice

- The choice of the most appropriate antibiotic for the management of nosocomial pneumonia due to Gram-negative pathogens should not be based only on antibiotic susceptibility testing but also on the genotypic resistance mechanism.
- We need further real-life data about how to optimally use these new antibiotics in the treatment of pneumonia due to MDR Gram-negative strains.

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lung diseases. *Eur Respir Rev* 2022; 31: 220093. No. 7: Lamoth F, Calandra T. Pulmonary aspergillosis: diagnosis and treatment. *Eur Respir Rev* 2022; 31: 220114. No. 8: Niederman MS, Torres A. Severe community-acquired pneumonia. *Eur Respir Rev* 2022; 31: 220123.

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