

# Real-World Evidence and Multidrug Resistant Infections: How Can We Leverage RWE to Improve Patient Outcome with the Novel Beta-Lactam and Beta-Lactam/Beta-Lactamase Inhibitor Combinations

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**Abstract:** Translating findings emerged from pivotal trials of novel beta-lactams into real-world clinical practice represents a major concern. Real-world evidence assessing the efficacy of novel beta-lactams in different clinical scenarios may provide some benefits in selecting proper place in therapy. This review aims to perform a critical reappraisal of the issues emerged from pivotal trials of novel beta-lactams and leveraging real-world evidence supporting proper place in therapy in the treatment of multidrug-resistant Gram-negative infections. A comprehensive literature search was performed on PubMed-MEDLINE from January 2015 to September 2025 for identifying pivotal trials and real-world evidence concerning the use of cefiderocol and of novel beta-lactam/beta-lactamase inhibitor combination (BL/BLIc) including those of tomorrow (ie, ceftolozane-tazobactam, ceftazidime-avibactam, meropenem-vaborbactam, imipenem-relebactam, cefepime-enmetazobactam, cefepime-taniborbactam, cefepime-zidebactam, sulbactam-durlobactam, aztreonam-avibactam). Critical issues emerged from pivotal trials in terms of potential appropriate place in therapy of each included agent were summarized. Four different therapeutic algorithms were proposed according to the pattern of antibiotic susceptibility of the pathogens, the genotype of resistance, and pharmacokinetic/pharmacodynamic (PK/PD) features of selected agents: a) extended-spectrum beta-lactamase (ESBL)-producing *Enterobacterales*; b) carbapenem-producing *Enterobacterales* (CPE); c) metallo-beta-lactamase (MBL)-producing *Pseudomonas aeruginosa*; d) carbapenem-resistant *Acinetobacter baumannii* (CRAB). Real-world evidence suggested that cefepime-enmetazobactam may represent an effective carbapenem-sparing strategy in the management of infections caused by ESBL-producing *Enterobacterales* and a potential alternative to ceftazidime-avibactam for treating OXA-48-producing infections. Cefepime-taniborbactam, cefepime-zidebactam, and aztreonam-avibactam could finally represent a definitive answer in the challenging scenario of infections caused by MBL-producing *Enterobacterales* and *Pseudomonas aeruginosa*. Lastly, the valuable role of sulbactam-durlobactam in CRAB infections was already recognized by international guidelines. Real-world evidence concerning both well-designed observational studies and PK/PD models may represent a mandatory tool for overcoming issues associated with pivotal trials evaluating novel BL/BLIc. The implementation of dedicated well-designed real-world studies would be warranted for ensuring a constant update of proposed therapeutic algorithms.

**Keywords:** novel beta-lactam/beta-lactamase inhibitor combinations, real-world evidence, multidrug-resistant gram-negative infections, PK/PD optimization, place in therapy, therapeutic algorithms

## Introduction

The worldwide diffusion of multidrug-resistant (MDR) Gram-negative pathogens and the ever-growing resistance spread against the currently available beta-lactams (BL) and/or beta-lactam/beta-lactamase inhibitor combinations (BL/BLIc)

represent a major health concern nowadays.<sup>1–5</sup> Some novel BL/BLIc are currently under way (ie, cefepime-enmetazobactam, cefepime-taniborbactam, cefepime-zidebactam, sulbactam-durlobactam, aztreonam-avibactam) and could represent a valuable enrichment of the therapeutic armamentarium. They could concur either in counteracting the ever-growing spread of resistance against the currently licensed BL/BLIc or in offering a solution to some unmet clinical needs in covering peculiar pathogen-specific mechanisms of resistance (namely metallo-beta-lactamase [MBL]-producing *Enterobacterales/Pseudomonas aeruginosa* or carbapenem-resistant *Acinetobacter baumannii* [CRAB]).<sup>6–10</sup>

Figure 1A and B summarize the activity that novel BL and BL/BLIc recently licensed and under clinical development, respectively, exhibit against different types of MDR Gram-negatives.

Unfortunately, only a minority of the pivotal trials concerning the currently licensed novel BL and/or BL/BLIc were designed as pathogen-driven study.<sup>11–14</sup> This makes often difficult translating the emerged findings into something adding value for properly placing them in daily clinical practice. The case of ceftazidime-avibactam may be mentioned as a paradigmatic example. In the four pivotal trials of this agent, no case of infection due to carbapenem-producing *Enterobacterales* was included.<sup>15–18</sup> Nevertheless, this agent has become first-line therapy for managing KPC- and OXA-48-producing *Enterobacterales* based on real-world evidence (RWE), as issued by both the Infectious Disease Society of America (IDSA) guidance and the European Society of Clinical Microbiology and Infectious Disease (ESCMID) guidelines.<sup>19,20</sup> To be honest, it should be recognized that the way for implementing specific pathogen-driven randomized controlled trials (RCTs) may be burdened by a major issue. In fact, the epidemiological prevalence of some types of MDR Gram-negatives may be quite low (ie, MBL-producing *Enterobacterales* and/or *Pseudomonas aeruginosa*), so that the duration of RCTs for enrolling an high enough representative number of patients could be unacceptably too long, and the study may be stopped prematurely, as recently occurred for that of aztreonam-avibactam.<sup>21</sup>

A valuable complementary way for attributing a proper place in therapy to the incoming BL/BLIc of tomorrow could be that of planning prospective real-world specific well-design pathogen-driven observational studies.<sup>14</sup> This approach coupled with population pharmacokinetic/pharmacodynamic (PK/PD) studies focused on selecting the most appropriate

| A | Novel licensed BL/BLIc  | ESBL-producing Enterobacterales | KPC-producing Enterobacterales | OXA-48-producing Enterobacterales | MBL-producing Enterobacterales | MBL-producing PA | CRAB  |
|---|-------------------------|---------------------------------|--------------------------------|-----------------------------------|--------------------------------|------------------|-------|
|   | Ceftolozane-tazobactam  | Yellow                          | Red                            | Red                               | Red                            | Red              | Red   |
|   | Ceftazidime-avibactam   | Green                           | Green                          | Green                             | Red                            | Red              | Red   |
|   | Meropenem-vaborbactam   | Green                           | Green                          | Red                               | Red                            | Red              | Red   |
|   | Imipenem-relebactam     | Green                           | Green                          | Red                               | Red                            | Red              | Red   |
|   | Cefiderocol             | Green                           | Green                          | Green                             | Yellow                         | Green            | Green |
| B | Novel incoming BL/BLIc  | ESBL-producing Enterobacterales | KPC-producing Enterobacterales | OXA-48-producing Enterobacterales | MBL-producing Enterobacterales | MBL-producing PA | CRAB  |
|   | Cefepime-enmetazobactam | Green                           | Red                            | Yellow                            | Red                            | Red              | Red   |
|   | Cefepime-zidebactam     | Green                           | Green                          | Green                             | Yellow                         | Green            | Red   |
|   | Cefepime-taniborbactam  | Green                           | Green                          | Green                             | Yellow                         | Yellow           | Red   |
|   | Aztreonam-avibactam     | Green                           | Green                          | Green                             | Green                          | Red              | Red   |
|   | Sulbactam-durlobactam   | Green                           | Green                          | Green                             | Red                            | Red              | Green |

**Figure 1** Spectrum of activity against MDR Gram-negative pathogens of novel BL and BL/BLIc both recently licensed (A) and under clinical development (B). Green box: agent with documented in vitro and/or in vivo activity and recommended in clinical practice; yellow box: agent with documented in vitro activity but some concerns may occur during clinical practice or more in vitro/in vivo data are required for clinical use; red box: lack of in vitro and/or in vivo activity and not recommended in clinical practice.

**Abbreviations:** BL/BLIc, beta-lactam/beta-lactamase inhibitor combinations; CRAB, carbapenem-resistant *Acinetobacter baumannii*; ESBL, extended-spectrum beta-lactamase; MBL, metallo-beta-lactamase; PA, *Pseudomonas aeruginosa*.

dosing regimens in each clinical scenario could represent a helpful way for overcoming this issue, as recently proposed by the IDSA guidance.<sup>19</sup>

The aim of this review was to perform a critical reappraisal of the issues emerged from pivotal trials of novel beta-lactams and leveraging RWE supporting an appropriate place in for treating MDR Gram-negative infections.

## Materials and Methods

A literature search was performed on PubMed-MEDLINE (from January 2015 until October 2025) for retrieving both RCTs and available real-world observational studies concerning novel BL and BL/BLIc, namely ceftazidime-avibactam, ceftolozane-tazobactam, meropenem-vaborbactam, imipenem-relebactam, cefiderocol, cefepime-enmetazobactam, sulbactam-durlobactam, cefepime-taniborbactam, cefepime-zidebactam, and aztreonam-avibactam. The rationale for selecting these agents was based on the in vitro activity against one or more difficult-to-treat resistant (DTR) Gram-negative pathogens, namely extended-spectrum beta-lactamase (ESBL)-producing *Enterobacterales*, carbapenemase-producing *Enterobacterales* (CPE) [including KPC, OXA-48 and MBL], MBL-producing *Pseudomonas aeruginosa* or CRAB. Regarding *Pseudomonas aeruginosa*, the susceptibility profile to be reviewed concerned only MBL-producing and not DTR-producing genotype as the former has much more limited treatment options than the latter.<sup>22,23</sup>

Overall, clinical trials and RWE of these agents coming from observational clinical studies and/or case report/series together with studies concerning in vitro susceptibility, PK/PD target attainment, and dosing optimization strategies against specific MDR Gram-negatives were retrieved. Specifically, regarding the novel BL/BLIc just recently licensed, given their availability in the therapeutic armamentarium for some years, the retrieved data concerned, over that RCTs, RWE based on large real-world observational studies, systematic reviews, and real-world PK/PD studies.<sup>19,24–26</sup> Considering that two reviews on this topic were published in 2021,<sup>24,26</sup> these were searched, and only data published since then were updated. For previous RWE on this topic, the readers are referred to those reviews.<sup>24,26</sup> Conversely, regarding the BL/BLIc incoming tomorrow, due to the recent or under way approval by the regulatory agencies (cefepime-enmetazobactam and aztreonam-avibactam were recently approved by both the Food and Drug Administration [FDA] and the European Medicine Agency [EMA], only sulbactam-durlobactam was recently approved by the FDA only, and cefepime-taniborbactam, cefepime-zidebactam are currently under development), strong RWE is currently lacking, so that it was retrieved, other than RCTs, only RWE based on case series/reports and/or supported by in vitro studies suggesting theoretical benefits in different DTR scenarios. The following terms, alone and/or in combination, were searched: “ceftazidime-avibactam, ceftolozane-tazobactam, meropenem-vaborbactam, imipenem-relebactam, cefiderocol, cefepime-enmetazobactam, sulbactam-durlobactam, cefepime-taniborbactam, cefepime-zidebactam, aztreonam-avibactam, PK/PD target, dosing optimization, MIC, ESBL-producing *Enterobacterales*, CPE, DTR *Pseudomonas aeruginosa*, CRAB”. Only articles in English published in the last ten years were included.

Four different clinical scenarios of MDR-related infections were investigated namely, ESBL-producing *Enterobacterales*, CPE, MBL-producing *Pseudomonas aeruginosa* and CRAB.<sup>24–26</sup> Overall, data were organized in two different sections, namely the first one analyzing the potential critical issues emerged from the pivotal trials and the second one analyzing RWE supporting potential algorithms for proper place in therapy of novel BL/BLIc.

## Critical Issues Emerged from the Pivotal Trials of the Licensed and the Incoming Novel BL and BL/BLIc

Table 1 summarizes the Phase III pivotal trials of cefiderocol and of the novel BL/BLIc, either recently licensed or still under way.<sup>15–18,21,27–39</sup> Among the 17 identified RCTs, selecting a “weak” comparator and lacking inclusion of patients affected by infections caused by DTR Gram-negative pathogens were the most frequent critical issues emerging for most of them. Consequently, the added value of these RCTs for properly placing these new agents in therapy was very limited, if any.

A well-established pathogen-driven design addressing, specifically, one or more DTR Gram-negative pathogens was adopted in only 5 of these 17 RCTs.<sup>21,30,33,34,37</sup> However, also in these trials the emerging findings were affected by some issues that limited their generalizability.

**Table 1** Summary of Clinical Characteristics and Critical Issues of Available Pivotal Trials for Novel BL/BLlc

| Novel BL/BLlc                                                 | No. of Included Patients | Comparator in RCT                                                                                                                                 | Setting                          | Proportion of MDR Isolates                                                                                                                                                       | Comment                                                                                                                                                                                                                   |
|---------------------------------------------------------------|--------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Ceftazidime-Avibactam (RECAPTURE) <sup>18</sup>               | 393 vs 417               | Doripenem                                                                                                                                         | cUTI                             | 73/393 (18.6%) ESBL-producing <i>Enterobacterales</i><br>0.0% CPE-producing isolates                                                                                             | No CPE included;<br>Selected comparator inadequate for assessing comparatively the efficacy of ceftazidime-avibactam against KPC- and OXA-producing <i>Enterobacterales</i>                                               |
| Ceftazidime-Avibactam (RECLAIM-I and RECLAIM-2) <sup>17</sup> | 529 vs 529               | Meropenem                                                                                                                                         | cIAI                             | 111/823 (13.5%) ceftazidime-resistant Gram-negative pathogens (80.0% ESBL-producing)                                                                                             | No CPE included;<br>Selected comparator inadequate for assessing comparatively the efficacy of ceftazidime-avibactam against KPC- and OXA-producing <i>Enterobacterales</i>                                               |
| Ceftazidime-Avibactam (REPRISE) <sup>15</sup>                 | 165 vs 168               | BAT<br>(97% carbapenem)                                                                                                                           | cUTI and cIAI                    | 100% ceftazidime-resistant <i>Enterobacterales</i> and <i>Pseudomonas aeruginosa</i>                                                                                             | No CPE included;<br>Selected comparator inadequate for assessing comparatively the efficacy of ceftazidime-avibactam against KPC- and OXA-producing <i>Enterobacterales</i>                                               |
| Ceftazidime-Avibactam (REPROVE) <sup>16</sup>                 | 356 vs 370               | Meropenem                                                                                                                                         | HAP/VAP                          | 28% ceftazidime-resistant <i>Enterobacterales</i> and <i>Pseudomonas aeruginosa</i>                                                                                              | No CPE included;<br>Selected comparator inadequate for assessing comparatively the efficacy of ceftazidime-avibactam against KPC- and OXA-producing <i>Enterobacterales</i>                                               |
| Ceftolozane-Tazobactam (ASPECT-cUTI) <sup>28</sup>            | 398 vs 402               | Levofloxacin                                                                                                                                      | cUTI and AP                      | 61/398 (15.3%) ESBL-producing <i>Enterobacterales</i>                                                                                                                            | Limited number of cases with ESBL-producing <i>Enterobacterales</i> ;<br>Selected comparator inadequate for assessing comparatively the efficacy of ceftolozane-tazobactam against ESBL-producing <i>Enterobacterales</i> |
| Ceftolozane-Tazobactam (ASPECT-NP) <sup>29</sup>              | 362 vs 364               | Meropenem                                                                                                                                         | HAP/VAP                          | 84/259 (32.4%) ESBL-producing <i>Enterobacterales</i><br>34/259 (13.1%) MDR/XDR <i>Pseudomonas aeruginosa</i>                                                                    | Limited number of cases with ESBL-producing <i>Enterobacterales</i> and MDR/XDR <i>Pseudomonas aeruginosa</i> strains                                                                                                     |
| Ceftolozane-Tazobactam (ASPECT-cIAI) <sup>27</sup>            | 389 vs 417               | Meropenem                                                                                                                                         | cIAI                             | 58/806 (7.2%) ESBL-producing <i>Enterobacterales</i>                                                                                                                             | Limited number of cases with ESBL-producing <i>Enterobacterales</i>                                                                                                                                                       |
| Cefiderocol (APEKS-NP) <sup>31</sup>                          | 148 vs 152               | Meropenem<br>(high-dose administered by EI)                                                                                                       | HAP/VAP                          | Carbapenemase-producers in cefiderocol group:<br>9/69 (13%) <i>Enterobacterales</i> ;<br>2/24 (8%) <i>Pseudomonas aeruginosa</i> ;<br>16/23 (70%) <i>Acinetobacter baumannii</i> | Limited number of cases with carbapenem-resistant isolates                                                                                                                                                                |
| Cefiderocol (CREDIBLE-CR) <sup>30</sup>                       | 101 vs 51                | BAT                                                                                                                                               | HAP/VAP, BSI, and cUTI           | 100% carbapenem-resistant pathogens                                                                                                                                              | Pathogen-driven study                                                                                                                                                                                                     |
| Meropenem-Vaborbactam (TANGO I) <sup>32</sup>                 | 272 vs 273               | Piperacillin-tazobactam                                                                                                                           | cUTI                             | 0.0% CPE strains                                                                                                                                                                 | No case with CPE<br>Selected comparator inadequate for assessing comparatively the efficacy of meropenem-vaborbactam against KPC-producing <i>Enterobacterales</i>                                                        |
| Meropenem-Vaborbactam (TANGO II) <sup>33</sup>                | 32 vs 15                 | BAT<br>(ceftazidime-avibactam monotherapy, or monotherapy/combination therapy including carbapenems, aminoglycosides, polymyxin, and tigecycline) | BSI, HAP/VAP, cIAI, cUTI, and AP | 100.0% CPE isolates (all KPC-producing <i>Enterobacterales</i> except for 4 NDM or OXA-48-producing <i>Klebsiella pneumoniae</i> )                                               | Pathogen-driven study                                                                                                                                                                                                     |

|                                                   |            |                                                                                                  |                          |                                                                                     |                                                                                                                                                                                                                                                                                                          |
|---------------------------------------------------|------------|--------------------------------------------------------------------------------------------------|--------------------------|-------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Imipenem-Relebactam (RESTORE-IMI 1) <sup>34</sup> | 21 vs 10   | Imipenem + Colistin                                                                              | HAP/VAP, cIAI, and cUTI  | 100% imipenem non-susceptible isolates                                              | Pathogen-driven study                                                                                                                                                                                                                                                                                    |
| Imipenem-Relebactam (RESTORE-IMI 2) <sup>35</sup> | 264 vs 267 | Piperacillin-tazobactam                                                                          | HAP/VAP                  | Not provided                                                                        | No CPE or DTR <i>Pseudomonas aeruginosa</i> included<br>Selected comparator inadequate for assessing comparatively the efficacy of imipenem-relebactam against KPC-producing <i>Enterobacterales</i>                                                                                                     |
| Cefepime-Enmetazobactam (ALLIUM) <sup>36</sup>    | 345 vs 333 | Piperacillin-tazobactam                                                                          | cUTI or AP               | 90/678 (13.3%) ESBL-producing strains                                               | Limited number of cases with ESBL-producing <i>Enterobacterales</i><br>Selected comparator inadequate for assessing comparatively the efficacy of cefepime-enmetazobactam against ESBL-producing <i>Enterobacterales</i>                                                                                 |
| Sulbactam-Durlobactam (ATTACK) <sup>37</sup>      | 63 vs 62   | Imipenem-cilastatin + Colistin (Imipenem-cilastatin + Sulbactam-Durlobactam in intervention arm) | HAP, VAP, and/or BSI     | 100% CRAB                                                                           | Pathogen-driven study                                                                                                                                                                                                                                                                                    |
| Cefepime-Taniborbactam (CERTAIN-I) <sup>38</sup>  | 293 vs 143 | Meropenem                                                                                        | cUTI                     | 13/437 (3.0%) CPE strains<br>1/23 (4.3%) MBL-producing <i>P. aeruginosa</i> strains | Limited number of cases with CPE and MBL-producing <i>Pseudomonas aeruginosa</i><br>Selected comparator inadequate for assessing comparatively the efficacy of cefepime-taniborbactam against KPC-, OXA-48-, and MBL-producing <i>Enterobacterales</i> , and MBL-producing <i>Pseudomonas aeruginosa</i> |
| Aztreonam-Avibactam (REVISIT) <sup>39</sup>       | 282 vs 140 | Meropenem ± Colistin                                                                             | cIAI or HAP/VAP          | 19/308 (6.2%) carbapenemase-producing pathogens, of which 10 (3.2%) MBL-positive    | Limited number of cases with MBL-producing <i>Enterobacterales</i><br>Selected comparator inadequate for assessing comparatively the efficacy of aztreonam-avibactam against KPC-, OXA-48-, and MBL-producing <i>Enterobacterales</i>                                                                    |
| Aztreonam-Avibactam (ASSEMBLE) <sup>21</sup>      | 12 vs 5    | BAT                                                                                              | cIAI, cUTI, BSI, HAP/VAP | 100% MBL-producing <i>Enterobacterales</i>                                          | Pathogen-driven study                                                                                                                                                                                                                                                                                    |
| Cefepime-Zidebactam (ENHANCE I)                   | 530        | Meropenem                                                                                        | cUTI or AP               | Not available                                                                       | No results available yet<br>Selected comparator inadequate for assessing comparatively the efficacy of cefepime-zidebactam against KPC-, OXA-48-, and MBL-producing <i>Enterobacterales</i> , and MBL-producing <i>Pseudomonas aeruginosa</i>                                                            |

**Abbreviations:** AP, acute pyelonephritis; BL/BLIC, beta-lactam/beta-lactamase inhibitor combination; BAT, best available therapy; BSI, bloodstream infection; cIAI, complicated intrabdominal infection; CPE, carbapenemase-producing *Enterobacterales*; CRAB, carbapenem-resistant *Acinetobacter baumannii*; cUTI, complicated urinary tract infection; DTR, difficult-to-treat resistant; EI, extended infusion; ESBL, extended-spectrum beta-lactamase; HAP, hospital-acquired pneumonia; MBL, metallo-beta-lactamase; MDR, multidrug-resistant; RCT, randomized controlled trial; VAP, ventilator-associated pneumonia; XDR, extensively drug-resistant.

Specifically, the Phase 3 RCT CREDIBLE-CR assessed the efficacy and safety of cefiderocol vs best available therapy (BAT) in 150 patients affected by life-threatening carbapenem-resistant Gram-negative related infections.<sup>30</sup> No significant difference in terms of clinical cure and microbiological eradication was documented between the two arms.<sup>30</sup> Unfortunately, the imbalance in terms of clinical severity among patients affected by CRAB infections resulted in an overall excess of mortality in the cefiderocol arm.<sup>30</sup> Consequently, the guidelines issued by the ESCMID recommended against the use of cefiderocol for the management of CRAB infections.<sup>20</sup>

The RCT TANGO II assessed the efficacy and safety of meropenem-vaborbactam vs best available therapy (BAT) (including monotherapy/combination therapy with carbapenems, aminoglycosides, polymyxin, and tigecycline) in 47 patients affected by severe CPE-related infections.<sup>33</sup> In the meropenem-vaborbactam arm, the clinical cure rate was higher both at the end of treatment (65.6% vs 33.3%;  $p=0.03$ ) and at the test of cure (59.4% vs 26.7%;  $p=0.02$ ), and the risk of nephrotoxicity was lower compared to BAT (4.0% vs 24.0%;  $p<0.001$ ).<sup>33</sup> Unfortunately, the limited number of included patients and the lack of a strong comparator (ie, ceftazidime-avibactam) could have limited the generalizability of the findings to real-world clinical scenarios.

The RCT RESTORE-IMI 1 assessed the efficacy and safety of imipenem-relebactam vs combination therapy of imipenem plus colistin in 31 patients affected by imipenem non-susceptible Gram-negative isolates (mainly DTR *Pseudomonas aeruginosa*).<sup>34</sup> No significant difference between the two arms was shown in terms of clinical cure (71.4% vs 70.0%) and of 28-day mortality rate (9.5% vs 30.0%), even if treatment-emergent nephrotoxicity in the imipenem-relebactam arm was lower than in the imipenem plus colistin arm (10.3% vs 56.3%;  $p=0.002$ ).<sup>34</sup> Unfortunately, likewise the aforementioned TANGO II trial, also in this RCT the limited number of included patients, the heterogeneity of clinical isolates other than DTR *Pseudomonas aeruginosa*, and the lack of a strong comparator could have limited the generalizability of the findings to real-world scenarios.

The ATTACK trial evaluated the efficacy and safety of sulbactam-durlobactam (plus imipenem-cilastatin compared to colistin (plus imipenem-cilastatin) in 125 patients affected by CRAB infections.<sup>37</sup> In the sulbactam-durlobactam arm, both the 28-day mortality rate (19% vs 32%; difference  $-13.2\%$  [95% confidence interval (CI)  $-30.0$ – $3.5\%$ ]) and the nephrotoxicity occurrence (13% vs 38%;  $p<0.001$ ) were lower compared to colistin.<sup>37</sup> Unfortunately, the study findings were biased by the presence of combination therapy with imipenem and by infections being polymicrobial in more than 30% of cases.

The ASSEMBLE trial was designed for assessing the efficacy and safety of aztreonam-avibactam vs BAT in the scenario of severe MBL-producing Gram-negative related infections.<sup>21</sup> Unfortunately, the study was closed prematurely because of difficulty in recruiting patients (namely only 15). Besides, the findings at interim analysis showed that aztreonam-avibactam had a higher clinical cure rate (41.7% vs 0.0%), a favorable microbiological response (60.0% vs 0.0%), and lower 28-day mortality rate (8% vs 33%).<sup>21</sup>

The other 12 RCTs involving novel BL/BLIC did not have a pathogen-driven design and were flawed by a very limited number, if any, of enrolled cases due to those types of resistant pathogens representing the main target of each BL/BLIC in daily clinical practice.<sup>15–18,27–29,31,32,35,36,38,39</sup>

Specifically, none of the 4 phase III RCTs of ceftazidime-avibactam included patients affected by KPC- and/or OXA-48-producing *Enterobacterales*-related infections.<sup>15–18</sup> Likewise, pivotal trials evaluating ceftolozane-tazobactam in different types of infections included only a limited number of patients affected by ESBL-producing *Enterobacterales* (ranging from 7.2% to 32.4%) or DTR *Pseudomonas aeruginosa* (less than 15%).<sup>27–29</sup> In the ALLIUM trial evaluating the efficacy and safety of cefepime-enmetazobactam in the setting of complicated urinary tract infection (cUTI) or acute pyelonephritis (AP), the proportion of patients having infections caused by ESBL-producing *Enterobacterales* was very limited (13.3%). Additionally, selecting as comparator for testing efficacy an agent with limited activity against ESBL, namely piperacillin-tazobactam instead of one fully active, namely meropenem, could be arguable.<sup>36</sup> In the CERTAIN-1 trial assessing the efficacy and safety of cefepime-taniborbactam in the setting of cUTI, the proportion of patients affected by infections caused by CPE or MBL-producing *Pseudomonas aeruginosa* was very limited (3.0% and 4.3%, respectively). Again, selecting as comparator for testing efficacy a drug inactive in vitro against these pathogens, namely meropenem, instead of active one may be arguable.<sup>38</sup>

Overall, summarizing, it could be concluded that, likewise to what occurred for the most of the recently licensed novel BL and BL/BLIc, even for the incoming ones the RCTs did not add significant knowledge for supporting properly the benefit that they could have in specific scenarios of MDR-related infections.

Fortunately, RWE has just played a major role in finding a proper place of the former in the treatment of MDR Gram-negative infections caused by some types of pathogens producing specific mechanisms of resistance.<sup>24–26</sup>

Conversely, the RWE concerning the incoming novel BL/BLIc is still limited to case series/reports, so that currently the potential theoretical benefits that these agents may offer in these scenarios could only be presumed and supported by some interesting in vitro studies. In the next two sections, we provide an update for both novel licensed and incoming BL/BLIc.

## Recent RWE Concerning the Role of the Licensed Novel BL/BLIc Against Some Specific Targeted Types of MDR Gram-Negatives

### ESBL-Producing *Enterobacterales*

Previous expert opinion articles suggested ceftolozane-tazobactam and ceftazidime-avibactam as carbapenem-sparing agents in the management of ESBL-producing *Enterobacterales*.<sup>25,26</sup> A large multicenter retrospective study, including 153 patients affected by documented infections caused by ESBL-producing *Enterobacterales* (mainly pneumonia [30.0%] and complicated urinary tract infection [22.2%]) found an overall clinical success rate of 83.7% with ceftolozane-tazobactam.<sup>40</sup> A monocentric retrospective observational study comparing the effectiveness of ceftolozane-tazobactam vs meropenem in 115 patients affected by bloodstream infections (BSIs) due to ESBL-producing *Enterobacterales* found no significant difference at the inverse probability of treatment weighting analysis in terms of clinical cure (odds ratio [OR] 0.43; 95% CI 0.12–1.53;  $p=0.19$ ), hospital mortality (OR 1.72; 95% CI 0.54–5.51;  $p=0.36$ ) and 30-day mortality (OR 1.72; 95% CI 0.54–5.48;  $p=0.35$ ) between the two agents.<sup>41</sup> A meta-analysis including five RCTs comparing ceftazidime-avibactam vs carbapenems reported no significant difference in terms of clinical response at test of cure between the two arms (risk ratio [RR] 1.02; 95% CI 0.97–1.08;  $p=0.45$ ).<sup>42</sup>

Indeed, it should be mentioned that some recent findings have raised some concerns about the use of these two agents against ESBL-producers. First, ceftolozane-tazobactam is highly active against ESBL-producing *Escherichia coli*, but not against ESBL-producing *Klebsiella pneumoniae*, whose strains may be resistant in 35% of cases.<sup>43</sup> Second, a recent population PK study found that the current dosing regimens of ceftolozane-tazobactam, even if delivered by CI, failed to attain an aggressive joint PK/PD target in the majority of cases against ESBL-producing *Enterobacterales*, with the cumulative fraction of response ranging between 29% and 54%.<sup>44</sup> Third, an interesting in vitro study showed that 96% and 34.5% of ESBL-producing *Escherichia coli* and *Klebsiella pneumoniae* isolates may exhibit an inoculum effect against ceftolozane-tazobactam and ceftazidime-avibactam, respectively, with a 4- to 64-fold minimum inhibitory concentration (MIC) increase in the presence of high bacterial loads ( $10^7$  colony forming-unit [CFU]/mL) compared to low bacterial loads ( $10^5$  CFU/mL)<sup>45</sup> thus possibly affecting the role of these agents in severe deep-seated infections with high ESBL-producing bacterial burden such as pneumonia. Besides, it should not be overlooked that these agents should be preferentially reserved for treating CPE or DTR *Pseudomonas aeruginosa*, as recommended by both the IDSA guidance and the ESCMID guideline.<sup>19,20</sup>

### CPE

#### KPC-Producing *Enterobacterales*

Both the IDSA guidance and the ESCMID guideline recommended ceftazidime-avibactam and meropenem-vaborbactam as first-line treatment KPC-producing *Enterobacterales* related infections.<sup>19,20</sup> Unfortunately, the prevalence of KPC-producing isolates resistant to ceftazidime-avibactam has recently challenged the therapeutic approach of this scenario.<sup>46,47</sup>

Real-world observational studies comparing the clinical efficacy of these two BL/BLIc against KPC-producing *Enterobacterales*<sup>48–50</sup> and PK/PD studies highlighting some potential issues associated with the use of standard-dosing regimens of ceftazidime-avibactam<sup>51–53</sup> provided helpful evidence to clinicians for selecting the most appropriate agent in specific situations. Specifically, a retrospective study that included 131 patients affected by CPE infections found no

difference in clinical success between patients treated with ceftazidime-avibactam (n=105) or with meropenem-vaborbactam (n=26) (62% vs 69%; p=0.49).<sup>48</sup> Likewise, a multicenter retrospective study comparing 131 patients receiving ceftazidime-avibactam with 37 receiving meropenem-vaborbactam found no significant difference in the management of CPE infections between the two agents in terms of clinical success (67.9% vs 64.9%; p=NS), in-hospital mortality (20.6% vs 29.7%; p=NS), and relapse rate (11.5% vs 5.4%; p=0.34).<sup>49</sup> Conversely, a retrospective multicenter study comparing 52 patients receiving ceftazidime-avibactam with 36 receiving meropenem-vaborbactam showed in the propensity score analysis that meropenem-vaborbactam granted better clinical improvement at 72 hours (OR 2.19; 95% CI 1.35–3.55), whereas 30-day mortality rate did not differ (OR 0.65; 95% CI 0.55–1.68).<sup>50</sup> A recent population PK study conducted among 112 critically ill patients reported that the ceftazidime-to-avibactam ratio was not fixed at 4:1, but it was subjected to wide fluctuations according to renal function.<sup>51</sup> Furthermore, the tested permissible ceftazidime-avibactam dosing regimens administered by continuous infusion (CI) did not allow to achieve an optimal probability of target attainment (defined as an aggressive joint PK/PD target) in case of augmented renal clearance or of KPC-producing strains having an MIC equal to the clinical breakpoint of 8 mg/L.<sup>51</sup> According to these novel real-world findings, it could be suggested that meropenem-vaborbactam should be preferred over ceftazidime-avibactam in case of KPC-producing isolates having borderline susceptibility to ceftazidime-avibactam, or in patients exhibiting augmented renal clearance or affected by hospital-acquired pneumonia (HAP) and/or ventilator-associated pneumonia (VAP) according to the lower penetration rate of ceftazidime-avibactam in the epithelial lining fluid and its unfavorable BL:BLI ratio.<sup>53,54</sup>

Overall, the current prevalence of KPC-producing isolates resistant to ceftazidime-avibactam may be around 20% in some centers. These findings suggest that in these centers it may be prudent avoiding empirical treatment with ceftazidime-avibactam for suspected KPC-related infections and reserving it preferably for the targeted therapy of documented infections caused by strains showing phenotypic susceptibility to ceftazidime-avibactam. Interestingly, an innovative population PK/PD study predicted that by administering the licensed dosages of ceftazidime-avibactam by CI rather than by 2-h infusion, it may be possible to attain a cumulative fraction of response against KPC-*K. pneumoniae* related infections occurring in critically ill patients in as much as 70–90% of cases, OXA-48-*K. pneumoniae* and OXA-48-*Enterobacterales*.<sup>51</sup>

### OXA-48-Producing *Enterobacterales*

Both the IDSA guidance<sup>19</sup> and the ESCMID guidelines<sup>20</sup> recommend ceftazidime-avibactam as first-line therapy for treating OXA-48-producing *Enterobacterales* related infections on the basis of RWE.<sup>55–58</sup> A recent multicenter retrospective matched cohort study including 180 patients affected by OXA-48-producing *Enterobacterales* infections found in multivariable logistic regression analyses that ceftazidime-avibactam treatment was protective against mortality (adjusted odds ratio [aOR]=0.37; 95% CI 0.19–0.71; p=0.003) and had better 21-day clinical response (aOR=3.32; 95% CI 1.68–6.53; p<0.001) compared to other best available therapies.<sup>58</sup> Likewise, a retrospective monocentric study conducted among 76 patients with OXA-48-producing *Klebsiella pneumoniae* BSI reported that ceftazidime-avibactam compared to BAT granted better clinical success (OR 6.69; 95% CI 1.68–26.60; p=0.007) and lower 14-day mortality rate (p=0.013).<sup>57</sup>

Overall, these recent findings may support the use of ceftazidime-avibactam in the management of OXA-48-producing related infections. Interestingly, the aforementioned population PK/PD study predicted that even against OXA-48-*K. pneumoniae* and OXA-48-*Enterobacterales* related infections occurring in critically ill patients the cumulative fraction of response may be as high as 70–90% of cases when administering the licensed dosages of ceftazidime-avibactam by CI rather than by 2-h infusion.<sup>51</sup>

### MBL-Producing *Enterobacterales*

Both the IDSA guidance<sup>19</sup> and the ESCMID guidelines<sup>20</sup> recommend combining aztreonam with ceftazidime-avibactam or ceftiderocol for treating MBL-producing *Enterobacterales* based on RWE.<sup>59,60</sup> A recent meta-analysis, including four observational studies assessing the efficacy of aztreonam combined with ceftazidime-avibactam compared to polymyxin-based regimens, reported a significant lower 30-mortality rate with the former in treating MBL-producing

*Enterobacterales* infections (OR 0.51; 95% CI 0.34–0.76;  $p < 0.001$ ).<sup>59</sup> Cefiderocol should be reserved as second-line in this setting, considering the non-negligible resistance rate observed among NDM-producing strains.<sup>61</sup> Interestingly, a prospective observational study assessed the efficacy of different therapeutic regimens among 343 patients with documented infections caused by MBL-producing *Enterobacterales* (328 NDM-producing and 15 VIM-producing, respectively).<sup>62</sup> By considering colistin containing regimens as the reference, combination treatment of ceftazidime-avibactam plus aztreonam was independently associated at the sensitivity propensity score analysis with a reduced 30-day mortality rate (adjusted hazard ratio [aHR] 0.39; 95% CI 0.18–0.86;  $p = 0.02$ ), differently from what observed with cefiderocol-containing regimens (aHR 0.83; 95% CI 0.31–2.24;  $p = 0.72$ ).<sup>62</sup>

Overall, the findings may support the use of ceftazidime-avibactam plus aztreonam as best therapeutic regimen in the challenging scenario of infections caused by MBL-producing *Enterobacterales*.

### MBL-Producing *P. Aeruginosa*

IDSA guidance<sup>19</sup> recommended the use of cefiderocol as first-line therapy for the management of severe infections caused by MBL-producing *Pseudomonas aeruginosa*, despite the very low number of patients having such an isolate in pivotal trials.<sup>63</sup> The real-world multicenter retrospective observational PERSEUS study included 261 patients being treated with cefiderocol because of severe Gram-negative infections other than CRAB.<sup>64</sup> In the subgroup analysis of the 174 patients affected by DTR *Pseudomonas aeruginosa* (42% MBL-producers), clinical cure and 28-day mortality rate were 84.5% and 17.2%, respectively.<sup>64</sup> Specifically, in infections caused by *Pseudomonas aeruginosa* showing resistance to both ceftolozane-tazobactam and ceftazidime-avibactam, clinical cure rate and 28-day mortality rate were 82.8% and 17.2%, respectively.<sup>64</sup> Consequently, these promising findings emerged from RWE may support the use of cefiderocol in this challenging scenario.

### CRAB

The ESCMID guidelines<sup>20</sup> recommended against the use of cefiderocol for treating CRAB infections based on the findings emerged from the CREDIBLE-CR trial.<sup>30</sup> Conversely, the IDSA guidance<sup>19</sup> recommended the use of cefiderocol provided that in combination with high-dose ampicillin-sulbactam based on different RWE.<sup>65–67</sup> Specifically, a meta-analysis including one RCT and seven observational studies providing adjustment for confounders showed that the use of cefiderocol-containing regimens in treating CRAB infections was associated with significantly lower mortality rate compared with other regimens (mainly colistin-based) (OR 0.53; 95% CI 0.41–0.68;  $p < 0.001$ ).<sup>65,67</sup> Indeed, caution should be warranted in defining the proper place of cefiderocol in this setting since most of RWE came from retrospective studies using cefiderocol in combination therapy and includes a limited number of patients.<sup>68</sup>

## RWE Supporting the Use of Novel Incoming BL/BLIC in Some Types of MDR Gram-Negative Related Infections

RWE for supporting the use of novel BL/BLIC in specific settings of MDR-Gram negative related infections is summarized in Table 2. Available RWE concerned only cefepime-zidebactam vs MBL-producing *P. aeruginosa* and sulbactam-durlobactam vs CRAB, namely the only two recently included in the therapeutic armamentarium.

### MBL-Producing *P. Aeruginosa*

One case series<sup>69</sup> and five case reports<sup>70–74</sup> including a total of 10 patients assessed the efficacy of cefepime-zidebactam in the management of MBL-producing *Pseudomonas aeruginosa* infections, 80% of which caused by NDM-producing strains. Specifically, bone and joint infections (50.0%) and pneumonia (30.0%) were the most frequent ones. Cefepime-zidebactam was used in monotherapy in all but one case in which combination with eravacycline was implemented.<sup>71</sup> Favorable clinical outcome was reported in all of the included cases without any emergence of resistance development.

### CRAB

Two case series<sup>75,76</sup> and six case report<sup>77–82</sup> including a total of 18 patients assessed the efficacy of sulbactam-durlobactam in the management of different types of CRAB infections, with HAP/VAP (72.2%) and meningoventriculitis

**Table 2** Real-World Evidence Supporting the Use of Novel Incoming BL/BLic in Some Types of MDR Gram-Negative Related Infections

| Author, Year and Reference                                                   | Study Design | No. of Patients/ Isolates | Dosing Regimen                                                                                      | Mono-/Combo-Therapy              | Infection Site                          | Isolated Pathogens                                                | Clinical Outcome / Resistance Rate to Specific Targeted MDR Pathogens                  |
|------------------------------------------------------------------------------|--------------|---------------------------|-----------------------------------------------------------------------------------------------------|----------------------------------|-----------------------------------------|-------------------------------------------------------------------|----------------------------------------------------------------------------------------|
| <i>MBL-producing Pseudomonas aeruginosa infections – Cefepime-zidebactam</i> |              |                           |                                                                                                     |                                  |                                         |                                                                   |                                                                                        |
| Shah 2025 <sup>69</sup>                                                      | Case series  | 5                         | 2g/1g q8h II 1h                                                                                     | Monotherapy                      | 4 BJI<br>I endovascular graft infection | DTR-PA<br>(3 NDM-producing strains)                               | Clinical cure 100%                                                                     |
| Polati 2025 <sup>70</sup>                                                    | Case report  | I                         | 2g/1g q8h II 1h                                                                                     | Monotherapy                      | HAP                                     | NDM-producing-PA                                                  | Microbiological eradication and clinical cure                                          |
| Tsai 2025 <sup>71</sup>                                                      | Case report  | I                         | 2g/1g q8h II 1h                                                                                     | Eravacycline                     | IAI                                     | IMP/NDM-producing-PA + NDM-producing <i>Klebsiella pneumoniae</i> | Clinical cure                                                                          |
| Soman 2024 <sup>72</sup>                                                     | Case report  | I                         | 2g/1g q12 II 1.5h<br>IHD<br>1g/0.5g q48h                                                            | Monotherapy                      | HAP + BJI                               | NDM-producing-PA                                                  | Microbiological eradication and clinical cure                                          |
| Tirlangi 2023 <sup>73</sup>                                                  | Case report  | I                         | 2g/1g q8h II 1h                                                                                     | Monotherapy                      | SSTI + HAP + BSI                        | NDM-producing-PA                                                  | Microbiological eradication and clinical cure                                          |
| Dubey 2023 <sup>74</sup>                                                     | Case report  | I                         | 2g/1g q8h II 1h                                                                                     | Monotherapy                      | IAI                                     | NDM-producing-PA                                                  | Clinical cure                                                                          |
| <i>CRAB infection – Sulbactam-Durlobactam</i>                                |              |                           |                                                                                                     |                                  |                                         |                                                                   |                                                                                        |
| Zhang 2025 <sup>75</sup>                                                     | Case series  | 10                        | 1g/1g q6h EI 3h<br>Renal adjustment in case of renal failure                                        | Meropenem 90%<br>Polymyxin B 10% | HAP/VAP                                 | CRAB                                                              | Microbiological eradication 60%<br>Clinical cure 90%                                   |
| Pouya 2025 <sup>76</sup>                                                     | Case series  | 2                         | 1g/1g q6h EI 3h                                                                                     | Meropenem 50%<br>Cefiderocol 50% | Ventriculitis                           | CRAB                                                              | Microbiological eradication 100%<br>Clinical cure 50%                                  |
| Fu 2025 <sup>77</sup>                                                        | Case report  | I                         | 50 mg/kg / 50 mg/kg q6h EI 3h                                                                       | Meropenem                        | BSI                                     | CRAB                                                              | Microbiological eradication and clinical cure                                          |
| Kufel 2025 <sup>78</sup>                                                     | Case report  | I                         | 1g/1g q4h EI 3h<br>CVVH Q <sub>ef</sub><br>6 L/h<br>Attainment of aggressive joint PK/<br>PD target | Monotherapy                      | VAP + BSI                               | CRAB                                                              | Microbiological and clinical failure (CRAB BSI breakthrough)<br>Resistance development |
| Tamma 2024 <sup>79</sup>                                                     | Case report  | I                         | 1g/1g q6h EI 3h<br>ARC occurrence<br>CSF penetration: sulbactam 37.1%<br>durlobactam 25.5%          | Meropenem                        | Meningoventriculitis                    | CRAB                                                              | Microbiological eradication and clinical cure                                          |
| Snowdin 2024 <sup>80</sup>                                                   | Case report  | I                         | 1g/1g q6h EI 3h                                                                                     | Cefiderocol +<br>minocycline     | Meningoventriculitis                    | CRAB                                                              | Clinical cure                                                                          |
| VanNatta 2023 <sup>81</sup>                                                  | Case report  | I                         | 1.5g/1.5g q6h<br>CRRT                                                                               | Meropenem +<br>Tigecycline       | VAP                                     | CRAB                                                              | Microbiological eradication and clinical cure                                          |
| Tiseo 2023 <sup>82</sup>                                                     | Case report  | I                         | 1.5g/1.5g q6h<br>CRRT                                                                               | Colistin                         | VAP                                     | CRAB                                                              | Microbiological eradication and clinical cure                                          |

**Abbreviations:** ARC, augmented renal clearance; BL/BLic, beta-lactam/beta-lactamase inhibitor combination; BAT, best available therapy; BJI, bone and joint infection; BSI, bloodstream infection; CPE, carbapenemase-producing *Enterobacteriales*; CRAB, carbapenem-resistant *Acinetobacter baumannii*; CRE, carbapenem-resistant *Enterobacteriales*; CRRT, continuous renal replacement therapy; CSF, cerebrospinal fluid; CVVH, continuous venovenous hemofiltration; DTR, difficult-to-treat resistant; EI, extended infusion; ESBL, extended-spectrum beta-lactamase; HAP, hospital-acquired pneumonia; II, intermittent infusion; MBL, metallo-beta-lactamase; MDR, multidrug-resistant; PA, *Pseudomonas aeruginosa*; PK/PD, pharmacokinetic/pharmacodynamic; Q<sub>ef</sub>, effluent flow rate; SSTI, skin and soft tissue infection; VAP, ventilator-associated pneumonia; XDR, extensively drug-resistant.

(22.2%) being the two most represented. Sulbactam-durlobactam was used in all but one case in combination therapy (mainly with meropenem).<sup>78</sup> Favorable clinical outcome was reported in 83.3% of the included patients, and in one case (5.6%) resistance development to sulbactam-durlobactam was reported. Interestingly, Tamma et al evaluated the penetration rate of sulbactam-durlobactam in cerebrospinal fluid in one patient affected by CRAB meningoventriculitis, reporting a penetration rate of 37.1% and 25.5% for sulbactam and durlobactam, respectively.<sup>79</sup>

## In vitro, Preclinical Studies, and Potential Place in Therapy of Novel Incoming BL/BLIc Against Some Specific Targeted Types of MDR Gram-Negatives Related Infections

In vitro and preclinical studies supporting the potential role of novel incoming BL/BLIc against some specific targeted types of MDR Gram-negatives related infections are summarized in Tables 3 and 4. Figure 2 shows the four different potential positioning algorithms for targeted therapy of infections caused by ESBL-producing *Enterobacterales* (panel A), CPE (panel B), MBL-producing *Pseudomonas aeruginosa* (panel C), and CRAB (panel D) according to potential place in therapy of novel incoming BL/BLIc.

**Table 3** In Vitro Studies Supporting the Potential Role of the Incoming Novel BL/BLIc in Treating Some Specific Targeted Types of MDR Gram-Negative Related Infections

| Author, Year and Reference                                                    | Study Design                          | No Isolates | Number of Clinical Isolates                                                                                                                      | Resistance Rate to Specific Targeted MDR Pathogens                                                                                                                                                                                               |
|-------------------------------------------------------------------------------|---------------------------------------|-------------|--------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <i>ESBL-producing Enterobacterales infections – Cefepime-enmetazobactam</i>   |                                       |             |                                                                                                                                                  |                                                                                                                                                                                                                                                  |
| Falagas 2025 <sup>83</sup>                                                    | Systematic review of in vitro studies | 15,408      | 2,094 ESBL<br>3,375 CRE                                                                                                                          | 0.0–2.8% ESBL-E<br>1.2–13.2% OXA-48<br>36.7–57.8% KPC                                                                                                                                                                                            |
| <i>KPC-producing Enterobacterales infections – Cefepime-taniborbactam</i>     |                                       |             |                                                                                                                                                  |                                                                                                                                                                                                                                                  |
| Karlowsky 2023 <sup>84</sup>                                                  | In vitro study                        | 18,350      | 13,731 <i>Enterobacterales</i><br>4,619 <i>Pseudomonas aeruginosa</i>                                                                            | 5.5% meropenem-resistant <i>Enterobacterales</i><br>KPC 0.0%<br>OXA-48 1.2%<br>MBL 13.6%<br>NDM 15.4%<br>VIM 0.0%<br>11.0% meropenem-resistant PA<br>21.9% ceftolozane-tazobactam-resistant PA<br>GES 2.0%<br>MBL 33.5%<br>VIM 12.6%<br>VEB 0.0% |
| Jacobs 2024 <sup>85</sup>                                                     | In vitro study                        | 397         | 200 <i>Klebsiella pneumoniae</i> (192 KPC; 7 OXA-48)<br>197 <i>Pseudomonas aeruginosa</i> (73 carbapenem-intermediate/resistant; 20 KPC; 15 VIM) | 0.0–0.5% (KPC/OXA-48-producing <i>K. pneumoniae</i> )<br>4.1–16.4% (PA carbapenem-intermediate/resistant)<br>26.7–53.3% (VIM-producing PA)<br>40.0–65.0% (KPC-producing PA)                                                                      |
| <i>KPC-producing Enterobacterales infections – Aztreonam-avibactam</i>        |                                       |             |                                                                                                                                                  |                                                                                                                                                                                                                                                  |
| Sader 2023 <sup>86</sup>                                                      | In vitro study                        | 1,098       | 473 KPC<br>347 MBL<br>205 OXA-48                                                                                                                 | 0.2% KPC<br>0.0% MBL<br>0.0% OXA-48                                                                                                                                                                                                              |
| <i>OXA-48-producing Enterobacterales infections – Cefepime-enmetazobactam</i> |                                       |             |                                                                                                                                                  |                                                                                                                                                                                                                                                  |
| Falagas 2025 <sup>83</sup>                                                    | Systematic review of in vitro studies | 15,408      | 2,094 ESBL<br>3,375 CRE                                                                                                                          | 0.0–2.8% ESBL-E<br>1.2–13.2% OXA-48<br>36.7–57.8% KPC                                                                                                                                                                                            |

(Continued)

**Table 3** (Continued).

| Author, Year and Reference                                                   | Study Design   | No Isolates | Number of Clinical Isolates                                                                                                                                                                                                                  | Resistance Rate to Specific Targeted MDR Pathogens                                                                                                                                                                                               |
|------------------------------------------------------------------------------|----------------|-------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Bonnin 2025 <sup>87</sup>                                                    | In vitro study | 2,212       | 2,089 CPE (1,000 OXA-48; 49 KPC; 697 NDM; 180 VIM, 1 IMP, 9 IMI, and 158 multiple carbapenemases) + 123 CRE not producing carbapenemase                                                                                                      | 3.3% OXA-48<br>33.1% CRE not-CPE<br>36.7% KPC                                                                                                                                                                                                    |
| <i>OXA-48-producing Enterobacterales infections – Cefepime-taniborbactam</i> |                |             |                                                                                                                                                                                                                                              |                                                                                                                                                                                                                                                  |
| Karlowsky 2023 <sup>84</sup>                                                 | In vitro study | 18,350      | 13,731 <i>Enterobacterales</i><br>4,619 <i>Pseudomonas aeruginosa</i>                                                                                                                                                                        | 5.5% meropenem-resistant <i>Enterobacterales</i><br>KPC 0.0%<br>OXA-48 1.2%<br>MBL 13.6%<br>NDM 15.4%<br>VIM 0.0%<br>11.0% meropenem-resistant PA<br>21.9% ceftolozane-tazobactam-resistant PA<br>GES 2.0%<br>MBL 33.5%<br>VIM 12.6%<br>VEB 0.0% |
| Jacobs 2024 <sup>85</sup>                                                    | In vitro study | 397         | 200 <i>Klebsiella pneumoniae</i> (192 KPC; 7 OXA-48)<br>197 <i>Pseudomonas aeruginosa</i> (73 carbapenem-intermediate/resistant; 20 KPC; 15 VIM)                                                                                             | 0.0–0.5% (KPC/OXA-48-producing <i>K. pneumoniae</i> )<br>4.1–16.4% (PA carbapenem-intermediate/resistant)<br>26.7–53.3% (VIM-producing PA)<br>40.0–65.0% (KPC-producing PA)                                                                      |
| <i>OXA-48-producing Enterobacterales infections – Aztreonam-avibactam</i>    |                |             |                                                                                                                                                                                                                                              |                                                                                                                                                                                                                                                  |
| Sader 2023 <sup>86</sup>                                                     | In vitro study | 1,098       | 473 KPC<br>347 MBL<br>205 OXA-48                                                                                                                                                                                                             | 0.2% KPC<br>0.0% MBL<br>0.0% OXA-48                                                                                                                                                                                                              |
| <i>MBL-producing Enterobacterales infections – Aztreonam-avibactam</i>       |                |             |                                                                                                                                                                                                                                              |                                                                                                                                                                                                                                                  |
| Sader 2023 <sup>86</sup>                                                     | In vitro study | 1,098       | 473 KPC<br>347 MBL<br>205 OXA-48                                                                                                                                                                                                             | 0.2% KPC<br>0.0% MBL<br>0.0% OXA-48                                                                                                                                                                                                              |
| <i>MBL-producing Enterobacterales infections – Cefepime-Taniborbactam</i>    |                |             |                                                                                                                                                                                                                                              |                                                                                                                                                                                                                                                  |
| Karlowsky 2023 <sup>84</sup>                                                 | In vitro study | 18,350      | 13,731 <i>Enterobacterales</i><br>4,619 <i>Pseudomonas aeruginosa</i>                                                                                                                                                                        | 5.5% meropenem-resistant <i>Enterobacterales</i><br>KPC 0.0%<br>OXA-48 1.2%<br>MBL 13.6%<br>NDM 15.4%<br>VIM 0.0%<br>11.0% meropenem-resistant PA<br>21.9% ceftolozane-tazobactam-resistant PA<br>GES 2.0%<br>MBL 33.5%<br>VIM 12.6%<br>VEB 0.0% |
| <i>MBL-producing Pseudomonas aeruginosa infections – Cefepime-zidebactam</i> |                |             |                                                                                                                                                                                                                                              |                                                                                                                                                                                                                                                  |
| Sader 2022 <sup>88</sup>                                                     | In vitro study | 24,220      | 17,524 <i>Enterobacterales</i> (681 CRE)<br>4,808 <i>Pseudomonas aeruginosa</i> (286 ceftolozane-tazobactam-resistant)<br>1,139 <i>Acinetobacter baumannii</i><br>636 <i>Stenotrophomonas maltophilia</i><br>113 <i>Burkholderia cepacia</i> | 2.2% CRE<br>9.1% ceftolozane-tazobactam-resistant PA                                                                                                                                                                                             |

(Continued)

**Table 3** (Continued).

| Author, Year and Reference                                                      | Study Design   | No Isolates | Number of Clinical Isolates                                                                                                                      | Resistance Rate to Specific Targeted MDR Pathogens                                                                                                                                                                                               |
|---------------------------------------------------------------------------------|----------------|-------------|--------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <i>MBL-producing Pseudomonas aeruginosa</i> infections – Cefepime-Taniborbactam |                |             |                                                                                                                                                  |                                                                                                                                                                                                                                                  |
| Karlowisky 2023 <sup>84</sup>                                                   | In vitro study | 18,350      | 13,731 <i>Enterobacterales</i><br>4,619 <i>Pseudomonas aeruginosa</i>                                                                            | 5.5% meropenem-resistant <i>Enterobacterales</i><br>KPC 0.0%<br>OXA-48 1.2%<br>MBL 13.6%<br>NDM 15.4%<br>VIM 0.0%<br>11.0% meropenem-resistant PA<br>21.9% ceftolozane-tazobactam-resistant PA<br>GES 2.0%<br>MBL 33.5%<br>VIM 12.6%<br>VEB 0.0% |
| Jacobs 2024 <sup>85</sup>                                                       | In vitro study | 397         | 200 <i>Klebsiella pneumoniae</i> (192 KPC; 7 OXA-48)<br>197 <i>Pseudomonas aeruginosa</i> (73 carbapenem-intermediate/resistant; 20 KPC; 15 VIM) | 0.0–0.5% (KPC/OXA-48-producing <i>K. pneumoniae</i> )<br>4.1–16.4% (PA carbapenem-intermediate/resistant)<br>26.7–53.3% (VIM-producing PA)<br>40.0–65.0% (KPC-producing PA)                                                                      |
| <i>CRAB – Sulbactam-Durlobactam</i>                                             |                |             |                                                                                                                                                  |                                                                                                                                                                                                                                                  |
| Karlowisky 2022 <sup>89</sup>                                                   | In vitro study | 5,032       | 4,038 <i>Acinetobacter baumannii</i> (62.3% CRAB)                                                                                                | 1.7% overall resistant rate against <i>Acinetobacter spp</i><br>2.0% <i>Acinetobacter baumannii</i>                                                                                                                                              |

**Abbreviations:** CPE, carbapenemase-producing *Enterobacterales*; CRAB, carbapenem-resistant *Acinetobacter baumannii*; CRE, carbapenem-resistant *Enterobacterales*; DTR, difficult-to-treat resistant; ESBL, extended-spectrum beta-lactamase; MBL, metallo-beta-lactamase; MDR, multidrug-resistant; PA, *Pseudomonas aeruginosa*; XDR, extensively drug-resistant.

**Table 4** Preclinical Studies Supporting the Potential Role of the Incoming Novel BL/BLlc in Treating Some Specific Targeted Types of MDR Gram-Negative Related Infections

| Author, Year and Reference                                                    | Study Design                       | Isolates                                                                                                                     | Bacterial Killing                                                                                                                                                                                                                                                                                             |
|-------------------------------------------------------------------------------|------------------------------------|------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <i>KPC-producing Enterobacterales</i> infections – Cefepime-taniborbactam     |                                    |                                                                                                                              |                                                                                                                                                                                                                                                                                                               |
| Lasko 2022 <sup>90</sup>                                                      | Murine cUTI model                  | Three KPC-producing <i>Klebsiella pneumoniae</i> isolates                                                                    | Cefepime-taniborbactam resulted in a statistically significant bacterial density reduction ( $p < 0.001$ ), ie $> 4 \log_{10}$ cfu/kidney reduction compared with 48 h controls                                                                                                                               |
| <i>OXA-48-producing Enterobacterales</i> infections – Cefepime-enmetazobactam |                                    |                                                                                                                              |                                                                                                                                                                                                                                                                                                               |
| Albac 2024 <sup>91</sup>                                                      | Murine neutropenic pneumonia model | Three strains of OXA-48/CTX-M-I or -CTX-M-15-producing <i>Klebsiella pneumoniae</i>                                          | Significant reduction in bacterial burden in the lungs of treated animal (from $-1.91$ to $-3 \log_{10}$ CFU/g) compared to controls confirmed also at the highest MIC of 8 mg/L                                                                                                                              |
| <i>OXA-48-producing Enterobacterales</i> infections – Cefepime-taniborbactam  |                                    |                                                                                                                              |                                                                                                                                                                                                                                                                                                               |
| Lasko 2022 <sup>90</sup>                                                      | Murine cUTI model                  | Four OXA-48-producing isolates (2 <i>Klebsiella pneumoniae</i> ; 1 <i>Enterobacter cloacae</i> ; 1 <i>Escherichia coli</i> ) | Cefepime-taniborbactam resulted in a statistically significant bacterial density reduction ( $p < 0.001$ ), ie $> 4 \log_{10}$ cfu/kidney reduction compared with 48 h controls, exhibiting profound average $-4.79 \pm 0.94 \log_{10}$ cfu/kidney reduction against OXA-48-producing <i>Escherichia coli</i> |

(Continued)

**Table 4** (Continued).

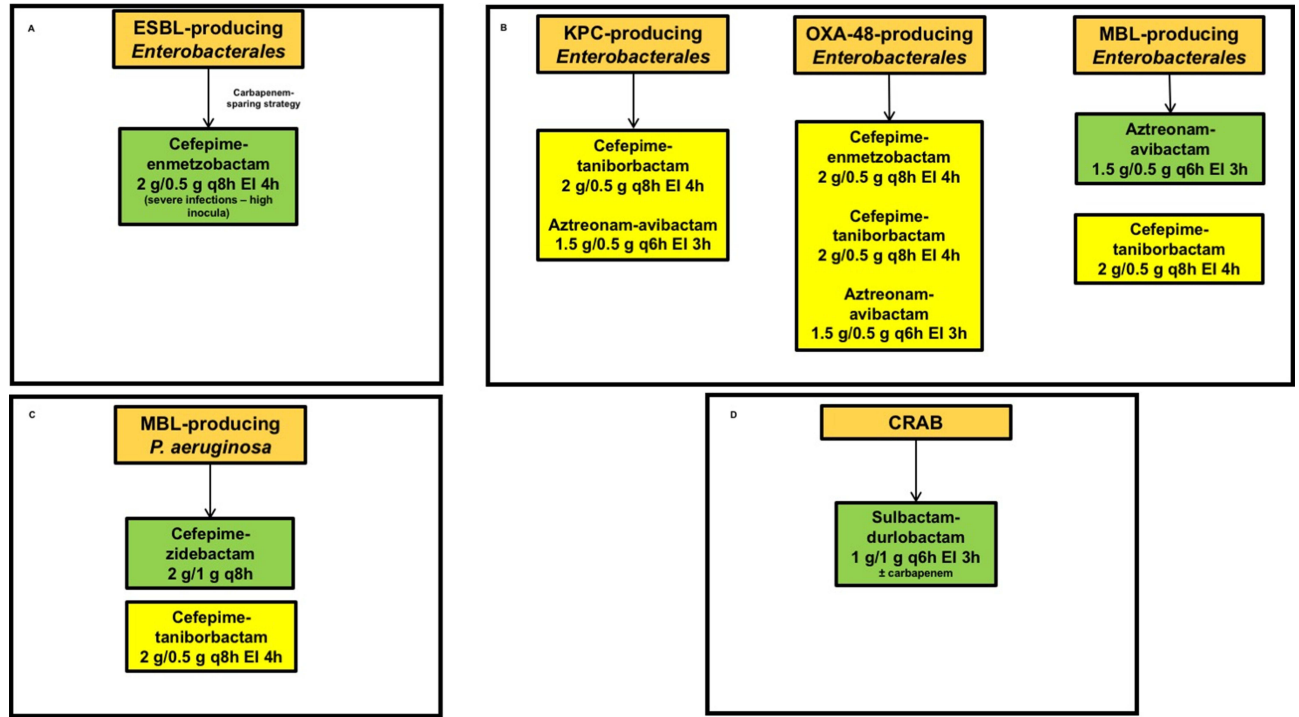
| Author, Year and Reference                                                   | Study Design                       | Isolates                                                                                                                                | Bacterial Killing                                                                                                                                                                                                                                                     |
|------------------------------------------------------------------------------|------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| MBL-producing <i>Enterobacterales</i> infections – Aztreonam-avibactam       |                                    |                                                                                                                                         |                                                                                                                                                                                                                                                                       |
| Amoura 2025 <sup>92</sup>                                                    | Murine model of peritonitis        | NDM-1/CTX-M-15-producing <i>Escherichia coli</i> at standard inoculum ( $10^5$ ) and at high inoculum ( $5 \times 10^7/2 \times 10^8$ ) | At standard inoculum survival was reported for 20/20 animals associated with significant decrease in bacterial counts compared to controls<br>At high inoculum survival was reported for 0/10 animals associated with absence of reduction in spleen bacterial counts |
| MBL-producing <i>Pseudomonas aeruginosa</i> infections – Cefepime-zidebactam |                                    |                                                                                                                                         |                                                                                                                                                                                                                                                                       |
| Kidd 2019 <sup>93</sup>                                                      | Neutropenic murine pneumonia model | 19 MDR <i>Pseudomonas aeruginosa</i> strains (6 VIM-producing and 3 NDM-producing) at high inoculum ( $10^7$ – $10^8$ )                 | Significant reduction in bacterial burdens in 14/19 strains ( $-1.59 \pm 1.27$ cfu/lungs)                                                                                                                                                                             |
| Moya 2020 <sup>94</sup>                                                      | Mouse lung/thigh infection model   | 3 VIM-producing <i>Pseudomonas aeruginosa</i> isolates                                                                                  | Significant bacterial eradication effect in all the three strains (from $-1.70$ to $-2.23$ log <sub>10</sub> CFU reduction)                                                                                                                                           |

**Abbreviations:** CFU, colony formant unit; cUTI, complicated urinary tract infection; MDR, multidrug-resistant.

Regarding the novel BL/BLIc just recently licensed, we recall here the algorithms of potential place in therapy just previously published in the aforementioned reviews (Table 5).<sup>24,26</sup> Most of the recent updating RWE may further support these algorithms.

**ESBL-Producing *Enterobacterales***

Some in vitro studies assessed the susceptibility of cefepime-enmetazobactam against ESBL-producing *Enterobacterales*.<sup>83,87</sup> Specifically, a recent systematic review including ten in vitro studies assessing the susceptibility of 15,408 Gram-negative isolates to cefepime-enmetazobactam reported a resistance rate ranging from 0.0% to 2.8% among 2,094 ESBL-producing *Enterobacterales*.<sup>83</sup> An in vitro study showed that the proportion of ESBL-producing



**Figure 2** Algorithms for targeted treatment of infections caused by Gram-negative pathogens showing different pattern of susceptibility. (A) ESBL-producing *Enterobacterales*; (B) CPE; (C) MBL-producing *Pseudomonas aeruginosa*; (D) CRAB.

**Abbreviations:** CRAB, carbapenem-resistant *Acinetobacter baumannii*; EI, extended infusion; ESBL, extended-spectrum beta-lactamase; MBL, metallo-beta-lactamase.

**Table 5** Proposed Algorithms for the Management of Infections Caused by *Enterobacterales*, *Pseudomonas Aeruginosa*, and *Acinetobacter Baumannii* with Different Pattern of Antibiotic Susceptibility (Adapted with Permission From)<sup>24,26</sup>

| Selected Agents     | <i>Enterobacterales</i>                     |                                                                                                       |                                                           |                                                                                                          |                                                  |                                                                                     | <i>Pseudomonas Aeruginosa</i>                                         |                                               |                                                                                                                             |                                                                                                      | <i>Acinetobacter Baumannii</i>                  |                                                                                                                 |
|---------------------|---------------------------------------------|-------------------------------------------------------------------------------------------------------|-----------------------------------------------------------|----------------------------------------------------------------------------------------------------------|--------------------------------------------------|-------------------------------------------------------------------------------------|-----------------------------------------------------------------------|-----------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------|-------------------------------------------------|-----------------------------------------------------------------------------------------------------------------|
|                     | Multi-Susceptible                           | ESBL                                                                                                  | AmpC                                                      | KPC                                                                                                      | OXA-48                                           | MBL                                                                                 | Multi-Susceptible                                                     | MDR MBL and GES Negative                      | MDR MBL Negative GES Positive                                                                                               | MBL                                                                                                  | Carbapenem-Susceptible                          | Carbapenem-Resistant                                                                                            |
| First-line therapy  | Ampicillin/sulbactam LD 3 g – MD 3 g q8h CI | Meropenem LD 2 g – MD 0.5–1 g q6h CI                                                                  | Meropenem LD 2 g – MD 0.5–1 g q6h CI                      | Ceftazidime/avibactam LD 2.5 g – MD 2.5 g q8h CI or Meropenem/vaborbactam LD 2 g/2 g – MD 2 g/2 g q8h CI | Ceftazidime/avibactam LD 2.5 g – MD 2.5 g q8h CI | Ceftazidime/avibactam LD 2.5 g – MD 2.5 g q8h CI + Aztreonam LD 2 g – MD 2 g q8h CI | Piperacillin/tazobactam LD 6.75 g – MD 18 g/day CI                    | Ceftolozane/tazobactam LD 3 g – MD 9 g/day CI | Ceftazidime/avibactam LD 2.5 g – MD 2.5 g q8h CI or Cefiderocol LD 2 g – MD 2 g q8h CI ± Fosfomycin LD 6 g – MD 16 g/day CI | Cefiderocol LD 2 g – MD 2 g q8h CI ± Inhaled colistin 2 g q8h                                        | Meropenem LD 2 g – MD 1–1.5 g q6h CI            | Cefiderocol LD 2 g – MD 2 g q8h CI                                                                              |
| Second-line therapy | Ceftriaxone 2 g/day                         | Ceftolozane/tazobactam LD 1.5 g – MD 4.5 g/day CI or Ceftazidime/avibactam LD 2.5 g – MD 2.5 g q8h CI | Cefepime LD 2 g – MD 2 g q8h CI (if in vitro susceptible) | Imipenem/relebactam 0.5 g/0.25 g q6h EI 3h                                                               | Cefiderocol LD 2 g – MD 2 g q8h CI               | Cefiderocol LD 2 g – MD 2 g q8h CI                                                  | Ceftazidime LD 2 g – MD 2 g q8h CI or Cefepime LD 2 g – MD 2 g q8h CI | Cefiderocol LD 2 g – MD 2 g q8h CI            |                                                                                                                             | Meropenem LD 2 g – MD 1–1.5 g q6h CI + Fosfomycin LD 6 g – MD 16 g/day CI ± Inhaled colistin 2 g q8h | Imipenem/cilastatin LD 1 g – MD 0.5 g q6h EI 3h | Fosfomycin LD 6 g – MD 16 g/day CI + Ampicillin/sulbactam LD 6/3 g – MD 6/3 g q8h CI + Inhaled colistin 2 g q8h |
| Third-line therapy  |                                             | Piperacillin/tazobactam LD 6.75 g – MD 18 g/day CI (if MIC ≤ 8 mg/L and no deep-seated infection)     |                                                           | Cefiderocol LD 2 g – MD 2 g q8h CI                                                                       |                                                  | Meropenem LD 2 g – MD 1–1.5 g q6h CI + Fosfomycin LD 6 g – MD 16 g/day CI           |                                                                       |                                               |                                                                                                                             |                                                                                                      |                                                 |                                                                                                                 |

**Abbreviations:** CI, continuous infusion; EI, extended infusion; ESBL, extended-spectrum beta-lactamase; LD, loading dose; MBL, metallo-beta-lactamase; MD, maintenance dose; MDR, multidrug-resistant.

*Escherichia coli* and *Klebsiella pneumoniae* clinical isolates exhibiting an inoculum effect, namely a 4- to 64-fold MIC increase in the presence of high bacterial loads ( $10^7$  CFU/mL) compared to low bacterial loads ( $10^5$  CFU/mL), may greatly vary among the different BL/BLIC. Interestingly, it was as low as 10.3% against cefepime-enmetazobactam compared to 34.5% and 96% against ceftazidime-avibactam and ceftolozane-tazobactam, respectively.<sup>45</sup>

Based on available data,<sup>45,83</sup> it may be speculated that cefepime-enmetazobactam could represent a promising and valuable carbapenem-sparing agent in the treatment ESBL-producing *Enterobacterales* (Figure 2A). Interestingly, the low propensity to the inoculum effect could favor its role in severe infections with high bacterial burden, namely HAP or VAP. However, clinical RWE would be warranted for confirming this hypothesis.

## CPE

### KPC-Producing Enterobacterales

Both cefepime-taniborbactam and aztreonam-avibactam exhibit excellent in vitro activity against KPC-producing *Enterobacterales*.<sup>84–86</sup> Regarding cefepime-taniborbactam, an in vitro study collecting 13,731 *Enterobacterales* isolates found that all of the 5.5% KPC producing strains were susceptible to cefepime-taniborbactam.<sup>84</sup> Likewise, another in vitro study collecting 192 KPC-producing *Klebsiella pneumoniae* strains reported that the resistance rate to cefepime-taniborbactam was very low, if any (0.0–0.5%).<sup>85</sup> Interestingly, a murine model of complicated urinary tract infection caused by KPC-producing *Klebsiella pneumoniae* showed that cefepime-taniborbactam resulted in a statistically significant reduction of bacterial density  $>4 \log_{10}$  CFU/kidney at 48 hours compared to controls.<sup>90</sup>

Regarding aztreonam-avibactam, an in vitro study collecting 473 KPC-producing *Enterobacterales* found that the resistance rate was of 0.2%.<sup>86</sup> These data may provide a good basis for considering these two agents as potentially active against KPC-producing *Enterobacterales* related infections, but obviously clinical RWE should be collected before any definitive conclusion on this.

Based on the available data,<sup>84–86</sup> both cefepime-taniborbactam and aztreonam-avibactam could represent valuable alternatives in treating infections caused by KPC-producing *Enterobacterales* (Figure 2B), especially in settings burdened by high resistance rates to both ceftazidime-avibactam and meropenem-vaborbactam.<sup>95</sup> Unfortunately, no clinical RWE is currently available for these novel incoming BL/BLIC, and further studies would be warranted for confirming their place in therapy in this scenario.

### OXA-48-Producing Enterobacterales

Cefepime-enmetazobactam, cefepime-taniborbactam, and aztreonam-avibactam could be promising alternatives in the management of OXA-48-producing *Enterobacterales* related infections.<sup>83–87</sup> Specifically, in regard to cefepime-enmetazobactam a systematic review of ten in vitro studies including an overall 3,375 CRE reported a resistance rate among 1,423 strains carrying OXA-48-carbapenemase ranging from 1.2% to 13.2%.<sup>83</sup> Likewise, a large in vitro study collecting 2,089 CPE reported a resistance rate to cefepime-enmetazobactam of 3.3% among 1,000 OXA-48-producing strains.<sup>87</sup> Interestingly, a murine neutropenic pneumonia model induced by OXA-48-producing *Klebsiella pneumoniae* showed that cefepime-enmetazobactam significantly reduced the lung bacterial burden of  $-1.91$  to  $-3 \log_{10}$  CFU/g compared to controls.<sup>91</sup> This effect was also confirmed at the highest MIC of 8 mg/L.<sup>91</sup>

A large in vitro study including 13,731 *Enterobacterales* showed that the resistance rate to cefepime-taniborbactam among 168 strains producing OXA-48-carbapenemase was of 1.2%.<sup>84</sup> A murine complicated urinary tract infection model induced by OXA-48-producing *Enterobacterales* showed that cefepime-taniborbactam reduced significantly the bacterial density by  $>4 \log_{10}$  CFU/kidney at 48 hours compared to controls, especially against OXA-48-producing *Escherichia coli* strains (average  $-4.79 \pm 0.94 \log_{10}$  cfu/kidney).<sup>90</sup>

An in vitro study collecting 205 OXA-48-producing *Enterobacterales* reported a resistance rate of 0.0% to aztreonam-avibactam.<sup>86</sup> Larger clinical RWE would be warranted for assessing the role of novel BL/BLIC of tomorrow in the management of infections caused by OXA-48-producing *Enterobacterales*.

Based on available data,<sup>83–87</sup> cefepime-enmetazobactam, cefepime-taniborbactam, and aztreonam-avibactam could represent valuable alternatives to ceftazidime-avibactam in treating infections caused by OXA-48-producing

*Enterobacterales* (Figure 2B). Unfortunately, no clinical RWE is currently available for these novel incoming BL/BLIc, and further studies would be warranted for confirming their place in therapy in this scenario.

### MBL-Producing *Enterobacterales*

Aztreonam-avibactam could become the first-line therapy for treating infections caused by MBL-producing *Enterobacterales*.<sup>96</sup> An in vitro study collecting 347 MBL-producing *Enterobacterales* showed that all were susceptible to aztreonam-avibactam.<sup>86</sup> A murine model of assessing the efficacy of aztreonam-avibactam against NDM-1/CTX-M-1 or CTX-M-15-coproducing *Escherichia coli* causing peritonitis at standard ( $10^5$ ) or high inocula ( $10^7$ – $10^8$ ).<sup>92</sup> Treatment was always effective in granting both animal survival and significant decrease in the bacterial burden compared to controls in presence of standard inoculum whereas conversely failed in presence of high inocula.<sup>92</sup>

Cefepime-taniborbactam could represent an alternative in this setting,<sup>97</sup> but it should not be overlooked that the overall resistance rate to this agent reported by in vitro studies among MBL-producing strains was overall of 13.6%, ranging from 0.0% among VIM-producers to 15.4% among NDM-producers.<sup>84</sup> Indeed, different MBL-producing variants showing resistance to cefepime-taniborbactam have been recently characterized, including IMP, VIM-83, NDM-9, and NDM-30.<sup>98–100</sup>

Based on the limited data of the ASSEMBLE trial<sup>21</sup> and on the available in vitro evidence,<sup>84,86</sup> aztreonam-avibactam could become, in the future, the first-line choice for treating infections caused by MBL-producing *Enterobacterales* (Figure 2B). Cefepime-taniborbactam could be a valuable alternative in some cases, taking care of the resistance development to this agent showed by IMP, VIM-83, NDM-9, or NDM-30-producing strains.<sup>98–100</sup>

### MBL-Producing *P. Aeruginosa*

Several in vitro studies assessed the susceptibility of cefepime-zidebactam and cefepime-taniborbactam against MBL-producing *Pseudomonas aeruginosa* strains. Specifically, in an in vitro study testing cefepime-zidebactam activity against 4,808 *Pseudomonas aeruginosa* isolates, 286 of which were ceftolozane-tazobactam-resistant, the susceptibility rate was of 90.9%.<sup>88</sup> Interestingly, a neutropenic murine pneumonia model assessing 19 MDR *Pseudomonas aeruginosa* strains (of which 6 VIM-producing and 3 NDM-producing) at high inoculum reported that cefepime-zidebactam significantly reduced bacterial burdens in 14/19 isolates (mean reduction of  $-1.59 \pm 1.27$  cfu/lungs).<sup>93</sup> Furthermore, a mouse lung/thigh infection model evaluating three VIM-producing *Pseudomonas aeruginosa* strains found that cefepime-zidebactam ensured a significant bacterial eradication against all the three isolates (from  $-1.70$  to  $-2.23$  log<sub>10</sub> CFU reduction).<sup>94</sup>

Two large in vitro studies<sup>84,85</sup> tested the activity of cefepime-taniborbactam against MBL-producing *Pseudomonas aeruginosa*. Indeed, a large in vitro study including 4,619 *Pseudomonas aeruginosa* isolates reported that the resistance rate to cefepime-taniborbactam was 11.0% and 21.9% among meropenem-resistant and ceftolozane-tazobactam-resistant strains, respectively.<sup>84</sup> Moving to genotypic characterization of DTR *Pseudomonas aeruginosa* strains, cefepime-taniborbactam showed a resistance rate of 12.6% and 33.5% against VIM- and MBL-positive strains, respectively.<sup>84</sup> Another in vitro study including 197 *Pseudomonas aeruginosa* isolates, of which 73 showing intermediate susceptibility and/or resistance to carbapenems reported a resistance rate to cefepime-taniborbactam of 4.1–16.4% in this latter group, whereas higher resistance rate was found against VIM- (26.7–53.3%) and KPC-producing strains (40.0–65.0%).<sup>85</sup> Overall, based on these preliminary data, both cefepime-zidebactam and cefepime-taniborbactam could represent promising alternatives for the management of MBL-producing *Pseudomonas aeruginosa*, although clinical RWE would be warranted for supporting this hypothesis.

Based on available evidence,<sup>69–74,84,85,88</sup> cefepime-zidebactam could become, in future, a valuable alternative to cefiderocol in treating infections caused by MBL-producing *Pseudomonas aeruginosa*, whereas cefepime-taniborbactam could be a second-line alternative for targeted therapy, if an in vitro susceptibility of the clinical isolate is confirmed (Figure 2C).

### CRAB

Sulbactam-durlobactam may represent a promising alternative for treating CRAB infections according to in vitro susceptibility studies. Specifically, in a large in vitro study testing sulbactam-durlobactam activity against 4,038 *Acinetobacter baumannii* isolates, 62.3% of which were CRAB, the resistance rate among CRAB strains was of 2.0%.<sup>89</sup>

Based on the findings of the ATTACK trial,<sup>37</sup> and on RWE,<sup>75–82</sup> the IDSA guidance<sup>19</sup> recommended combination of sulbactam-durlobactam with a carbapenem as first-line treatment of infections caused by CRAB. RWE should provide in future enough evidence to define whether this agent can be used as monotherapy in this setting. Meanwhile, available evidence<sup>37,75–82</sup> may support the role of sulbactam-durlobactam especially for treating pneumonia and/or meningoven-triculitis (Figure 2D).

## Expert Opinion

Overall, RWE concerning both well-designed observational studies and PK/PD studies, by overcoming the issues deriving from the RCTs, should represent the cornerstones for supporting the role of the incoming novel BL/BLIc in the management of some specific types of MDR Gram-negative related infections. In this setting, conducting population PK/PD studies in real-world could be helpful in providing clinicians the most appropriate dosing regimens for either maximizing clinical outcome or preventing resistance development. In this every-changing scenario, continuous update coming from newly available RWE will be fundamental.

In the last years, RWE was revealed very helpful in better defining the place of the recently licensed novel BL/BLIc in treating specific types of MDR Gram-negative infections, as issued by the IDSA guidance.<sup>19</sup> In this context, planning PK/PD studies of novel BL/BLIc in real-world could hopefully provide definitive answers on how relevant maximizing the likelihood of aggressive joint PK/PD target attainment may be in both preventing resistance development<sup>54</sup> and enabling personalized treatment of different types of special populations.<sup>51,52,101,102</sup> Waiting for this, a potential place in therapy of the novel incoming BL/BLIc could be based on preliminary evidence. Based on this, it may be speculated that cefepime-enmetazobactam could represent a carbapenem-sparing strategy in treating infections caused by ESBL-producing *Enterobacterales* and a potential alternative to ceftazidime-avibactam in treating OXA-48-producing infections. Cefepime-taniborbactam, cefepime-zidebactam, and aztreonam-avibactam could represent a definitive answer in treating MBL-producing *Enterobacterales* and MBL-producing *Pseudomonas aeruginosa*. Lastly, sulbactam-durlobactam has already been recognized by international guidelines as potentially having a valuable role in treating CRAB infections.<sup>19</sup> Overall, according to preliminary in vitro data and to RWE, the different incoming novel BL/BLIc seems promising for the management of infections caused by MDR Gram-negative pathogens, including those exhibiting the most challenging susceptibility profile (ie, MBL-producing *Enterobacterales* or *Pseudomonas aeruginosa*, CRAB). However, it should not be overlooked that some concerns need to be addressed. Specifically, the limited tissue penetration rate of these agents could potentially result in aggressive PK/PD target non-attainment at the infection site when treating the deep-seated infections (ie, pneumonia) with standard dosing regimens.<sup>14</sup> Furthermore, there is a need to assess the cost-effectiveness of using these agents compared to current first-line options in terms of length of hospital stay and/or resistance development. Finally, it should be recognized that the availability of the novel incoming BL/BLIc could be limited to only some parts of the world, as just previously occurred for the currently licensed novel BL/BLIc. This could cause disparities in managing MDR Gram-negative infections with the potential consequence of having significant differences in terms of clinical outcomes.

In conclusions, in an era characterized by the widespread diffusion of Gram-negative pathogens and the ever-growing resistance rates, RWE should represent an essential tool for properly placing novel BL/BLIc in routine clinical practice. The ever-growing number of RWE would offer the opportunity for continuously updating algorithms positioning novel BL/BLIc in the management of MDR Gram-negative pathogens.

## Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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MG received personal fees from Angelini, and participated in advisory board for Advanz Pharma and Viartis. FP participated in speaker bureau for Advanz Pharma, Angelini, Gilead, InfectoPharm, Menarini, Merck Sharp & Dohme, Pfizer and Shionogi, and on the advisory board for Advanz Pharma, Merck Sharp & Dohme, Pfizer and Viartis, outside the submitted work. The authors report no other conflicts of interest in this work.

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