Treatment of infections caused by multidrug-resistant Gram-negative bacilli: A practical approach by the Italian (SIMIT) and French (SPILF) Societies of Infectious Diseases

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Highlights

- Treatment of multidrug-resistant Gram negative bacteria is increasingly complex
- ESCMID and IDSA guidelines defined optimal strategies when robust data were available
- However, they could not address more complex infections due to scarcity of literature
- This practical approach paper aimed at providing guidance for these unmet needs

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ABSTRACT

Introduction: The emergence of multidrug-resistant Gram-negative bacilli, and the development of new antibiotics have complexified selection of optimal regimens. International guidelines are valuable tools, though limited by scarcity of high-quality randomized trials in many situations.

Methods: A panel of experts from the French and Italian Societies of Infectious Diseases aimed to address unresolved issues in clinical practice based on their experience, updated literature review, and open discussions.

Results: The panel reached a consensus for the following 'first-choices': i) cefepime for ventilator-acquired pneumonia due to AmpC β-lactamase-producing *Enterobacterales*; ii) The β-lactam/β-lactamase inhibitors combination most active *in vitro*, or cefiderocol combined with fosfomycin, and aerosolized colistin or aminoglycosides, for severe pneumonia due to *Pseudomonas aeruginosa* resistant to ceftolozane-tazobactam; iii) high-dose piperacillin-tazobactam (including loading dose and continuous infusion), for complicated urinary tract infections (cUTIs) caused by ESBL-producing *Enterobacterales* with piperacillin-tazobactam MIC ≤8 mg/L; iv) high-dose cefepime for cUTIs due to AmpC β-lactamase-producing *Enterobacterales* other than *Enterobacter* species if cefepime MIC ≤2 mg/L; v) ceftolozane-tazobactam or ceftazidime-avibactam plus metronidazole for intra-abdominal infections (IAIs) due to 3rd generation cephalosporin-resistant *Enterobacterales*; vi) ceftazidime-avibactam plus aztreonam plus metronidazole for IAIs due to metallo β-lactamase-producing *Enterobacterales;* vii) ampicillin-sulbactam plus colistin for bloodstream infections (BSIs) caused by carbapenem-resistant *Acinetobacter baumannii* (CRAB); viii) meropenem-vaborbactam for BSI caused by KPC-producing *Enterobacterales*; ix) ceftazidime-avibactam plus fosfomycin for neurological infections caused by carbapenem-resistant *P. aeruginosa.*

Conclusions: These expert choices were based on the necessary balance between antimicrobial stewardship principles, and the need to provide optimal treatment for individual patients in each situation.

Keywords. Carbapenemase; carbapenemase-producing *Enterobacterales;* Extended-spectrum β-lactamase*; Pseudomonas aeruginosa; Acinetobacter baumannii;* β-lactam/β-lactamase inhibitors; cefiderocol; cefepime; antimicrobial stewardship

1. Introduction

The emergence of multidrug-resistant Gram-negative bacilli (MDR-GNB) is a major threat worldwide, especially in countries who failed to implement antimicrobial stewardship (AMS) and infection control programs. In parallel, our armentarium against MDR-GNB has improved over the last decade, with a gradual switch from the exclusive use of last-resort, potentially toxic old drugs such as polymyxins, to the advent of new antibiotics with extended spectrum on MDR-GNB, including β-lactam/β-lactamase inhibitors combinations (BLBLI), cefiderocol, and plazomicin. Unfortunately, application for marketing authorization of plazomicin in the USA was withdrawn by the company for commercial reasons, as the cost required for approval and post-approval would not be viable given the limited indications to be expected. Recent guidelines on treatment of MDR-GNB have been elaborated by the European Society of Clinical Microbiology and Infectious Diseases (ESCMID) (1), and the Infectious Diseases Society of America (2), based on rigorous evaluation of the quality of data available in the literature, according to the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system, and following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA). These methods lead to prioritize randomized controlled trials (RCT), the highest level of evidence, so that recommendations mostly address situations corresponding to inclusion criteria for these RCTs.

The experts in charge of these guidelines have to be commended for the tremendous amount of work, and the robustness of their choices, of great help for clinicians facing treatment challenges with MDR-GNB. However, many situations cannot be resolved with these guidelines, as they were excluded from RCTs, because of patients age, comorbidities, the rarity or severity of their clinical presentation, the presence of foreign devices, etc. We

aimed to address some of these unresolved issues through an international panel of infectious diseases specialists.

2. Methods

On June 2022, the French Society of Infectious Diseases (SPILF) and the Italian Society of Infectious and Tropical Diseases (SIMIT) agreed on a collaboration to produce a consensus document that would propose a 'practical approach' for the main situations not covered by the ESCMID & IDSA guidelines, as an additional tool to select optimal antibiotics for difficult-to-treat MDR-GNB. Each society selected two juniors and two seniors, with the following criteria: i) expertise in the field; ii) regular prescriber of antibacterial treatment for MDR-GNB; iii) willingness to participate. Gender and country balance was taken into account during the selection process.

The panel first selected the main situations to be covered by the 'practical approach' document, based on their frequency, and the absence of definite answer from the ESCMID and IDSA guidelines. Each situation was assigned to a pair of junior/senior taking into account their expertise and wishes with the following tasks: i) literature review of paper published since the reviews performed for the ESCMID and IDSA guidelines; ii) elaborate a draft of first-line antibacterial treatment choices, and their rationale. These documents were presented to the whole panel through on-line meetings, and discussed until a consensus was reached. The kick-off meeting was conducted on September 2022. All sections were completed by May 2023, and the first draft of the full paper circulated on July 2023..

3. Results

3.1 Respiratory tract infections

3.1.1 Ventilator-acquired pneumonia (VAP) due to AmpC β-lactamase-producing Enterobacterales

In the ESCMID guidelines, cefepime is not recommended for the treatment of 3rd generation cephalosporin-resistant *Enterobacterales* (3GCephRE) due to low level of evidence for its efficacy in this indication (1). However, cefepime retains *in vitro* activity on most AmpC β-lactamase-producing *Enterobacterales* (3). In the IDSA guidelines, cefepime is recommended for AmpC *Enterobacterales* with MIC ≤2 mg/L or less (2), with large experience in this indication, including in intensive care unit (ICU). For pneumonia, cefepime achieved pharmacokinetic/pharmacodynamic (PK/PD) target in most critically ill patients with high levels in epithelium lining fluid (4). VAP is associated with high morbidity, but much lower mortality than septic shock, which leaves more space for AMS considerations, as a carbapenem-sparing alternative.

For these reasons, we would recommend high-dose cefepime (ie, 2 g every 8 h) as first-line treatment of VAP due to AmpC β-lactamase-producing *Enterobacterales*.

3.1.2 Severe pneumonia due to Pseudomonas aeruginosa resistant to ceftolozane-tazobactam

Because ceftolozane-tazobactam has demonstrated excellent efficacy in the treatment of *P. aeruginosa* infections, this combination is recommended as first-line treatment for severe infections due to difficult-to-treat resistant *P. aeruginosa* (DTR-PA), including hospital-acquired pneumonia (HAP), and VAP (1). Unfortunately, resistance to ceftolozane-tazobactam in *P. aeruginosa* has emerged, driven by various mechanisms, mainly *Pseudomonas*-derived cephalosporinase variants or metallo-*β*-lactamases (MBL), but also chromosomally-encoded resistance such as up-regulated efflux transports systems, porin defects or extended-spectrum *β*-lactamase (ESBL) (5). Because of these multiple intrinsic and/or acquired resistances, reliable susceptibility testing is a key issue.

In case of severe ceftolozane-tazobactam resistant DTR-PA pneumonia, imipenem-relebactam or ceftazidime-avibactam might be an option, depending on susceptibility testing, while meropenem-vaborbactam should not be used. *P. aeruginosa* isolates resistant to ceftolozane-tazobactam are more likely to be susceptible to imipenem-relebactam than ceftazidime-avibactam (52% and 39%, respectively) (6). For example, mutations within the Omega loop of AmpC confer cross-resistance to ceftolozane-tazobactam and ceftazidime-avibactam while isolates remain susceptible to imipenem-relebactam. Moreover, imipenem-relebactam may retain activity when carbapenem resistance is related to the association of impermeability (OprD porin loss) and AmpC overproduction, as relebactam inhibits AmpC. Although ceftazidime-avibactam combined with aztreonam would be active on MBL-producing *Enterobacterales* (7), this is seldom true for *P. aeruginosa*. Cefiderocol could also be an option, preferably in combination with an active partner (eg, fosfomycin), given the high burden of failures with cefiderocol monotherapy in DTR-PA infections (8). Colistin remains frequently active on DTR-PA, but is often used as a last-resort, due to poor tolerability.

Aerosolized antibiotics, such as colistin, tobramycin or amikacin, may be considered in DTR-PA pneumonia. Adjunctive aerosolized therapy for VAP was associated with improved rates of clinical cure and microbiological eradication, with better tolerability than systemic use of aminoglycosides or colistin, and favorable PK/PD profile (9).

For these reasons, we would recommend a combination therapy for the treatment of ceftolozane-tazobactam resistant DTR-PA pneumonia, including the BLBLI most active *in vitro* or cefiderocol, in combination with fosfomycin for MBL-producing *P. aeruginosa*, and aerosolized colistin or aminoglycosides.

3.2 Urinary tract infections (UTI)

3.2.1 Severe complicated UTI (cUTI) due to ESBL-producing Enterobacterales

Carbapenems became the first-line regimen for severe infections due to ESBL-producing *Enterobacterales*, as a consequence of the MERINO trial. IDSA and ESCMID guidelines also prioritize carbapenem over piperacillin-tazobactam for pyelonephritis or cUTIs due to ESBL-producing *Enterobacterales*. However, the emergence of carbapenem-resistant organisms is a major challenge (10), which advocates for carbapenem-sparing strategies.

Several observational studies found that piperacillin-tazobactam was non-inferior to carbapenems for UTIs due to ESBL-producing *Enterobacterales*, including in patients with bacteremia, and immunocompromised (11,12). A recent meta-analysis and a post-hoc analysis from the MERINO trial showed non-inferiority of piperacillin-tazobactam for ESBL-producing *Enterobacterales* with piperacillin-tazobactam MICs ≤8 mg/L. For these isolates, PK/PD analyses suggest that continuous infusion of piperacillin-tazobactam (4.5 g every 6 to 8 h) following a loading dose (9 g over 30 minutes) would achieve an efficacy comparable to carbapenems in infections with low inoculum and high diffusion of antibiotics, such as UTIs (13).

For these reasons, pending the results of larger RCTs (14), we would recommend high-dose continuous infusion piperacillin-tazobactam, with loading dose, for complicated and severe UTIs caused by ESBL-producing *Enterobacterales* with piperacillin-tazobactam MIC ≤8 mg/L. For ESBL-*Enterobacterales* with piperacillin-tazobactam MIC >8 mg/L, aminoglycosides or intravenous fosfomycin are seducing alternatives with *in vitro* efficacy for >90% of current ESBL-producing *Enterobacterales* strains and high urinary concentrations. However, aminoglycosides monotherapy failed to reach non-inferiority for bloodstream infections (BSI) of urinary source due to ESBL-*Enterobacterales* other than *E. coli* (15). Intravenous fosfomycin monotherapy may be an option, based on the results of 2 RCTs

(ZEUS and FOREST), but the prevalence of ESBL-producing *Enterobacterales* was low in these studies, piperacillin-tazobactam administration was not optimized, and exclusion criteria were particularly large, so that we would not recommend intravenous fosfomycin monotherapy for cUTIs due to ESBL-producing *Enterobacterales* at this stage. Cefoxitin may be an alternative for ESBL-producing *E. coli* BSI, especially secondary to urinary tract infection. Meropenem and ceftolozane-tazobactam remain options, as well as cefoxitin for ESBL-producing *E. coli*, or temocillin, based on drug-susceptibility testing studies.

3.2.2 Severe cUTI due to AmpC β-lactamase-producing Enterobacterales

The management of AmpC-producing *Enterobacterales* infections represents an emerging challenge, poorly explored in recent guidelines for several reasons. First, the detection methods for AmpC expression are expensive, labor-intensive, range-limited, and phenotypic screening may require molecular confirmation (16). Second, resistance mechanisms may differ between species: i) inducible resistance via chromosomally-encoded AmpC genes (eg, *Enterobacter cloacae, Serratia marcescens, Citrobacter freundii*); ii) non-inducible chromosomal resistance due to promoter mutations (eg, *E. coli*); iii) plasmid-mediated resistance (eg, *K. pneumoniae, E. coli*). Among bacteria with chromosomal-inducible AmpC, cefepime MIC is often increased by AmpC derepression, but the risk of resistance depends on the species (17), higher for *E. cloacae complex, C. freundii and Hafnia alvei*. High-doses cefepime remains an option for other species, and for non-severe, low-inoculum infections such as UTIs. For non-inducible AmpC resistance, the REDUCE-UTI study supports the use of cefepime for UTIs due to 3rd generation-resistant *E. coli and K. pneumoniae*: 78% of patients (n=133) received cefepime as a definitive treatment, and 90% of isolates were susceptible to cefepime with low MICs (18).

For these reasons, we would recommend high-dose cefepime (loading dose of 2 g followed by 2 g every 8 hours, with extended infusion) for the treatment of cUTIs due to AmpC β-lactamase-producing *Enterobacterales* if cefepime MIC is ≤2 mg/L, when adequate source control is achieved. For severe cUTIs with cefepime MIC >2 mg/L, meropenem or new BLBLIs are alternative options.

3.3 Intra-abdominal infections (IAI)

3.3.1 IAIs caused by 3rd generation cephalosporin-resistant Enterobacterales

In patients with infections due to 3GCephRE, ESCMID guidelines recommend different strategies according to severity, with carbapenems as first-line for severe infections, sparing BLBLIs for AMS purposes (1). This choice raises comments. First, the preference for carbapenems as first-line treatment for severe infections due to 3GCephRE mainly stems from studies comparing old BLBLIs to carbapenems in patients with BSI, with limited representation of IAIs (<20% in the MERINO trial). The MERINO-III RCT aiming to compare ceftolozane-tazobactam and meropenem in BSI due to ESBL-producing *Enterobacterales* was withdrawn due to supply issues with ceftolozane-tazobactam during the COVID-19 pandemic. Studies conducted in the setting of IAIs showed non-inferiority of new BLBLIs compared to carbapenems but were underpowered in the subgroup of IAIs due to 3GCephRE (19,20). The ASPECT-cIAI trial demonstrating the non-inferiority of ceftolozane-tazobactam plus metronidazole *versus* meropenem included 50 cases of 3GCephRE IAIs (20). The REPRISE trial showing the non-inferiority of ceftazidime-avibactam compared to meropenem included 19 cases of 3GCephRE IAIs (19). Finally, the RECLAIM-1 and 2 trials (ceftazidime-avibactam plus metronidazole *versus* meropenem) included 106 IAIs due to 3GCephRE. Hence, new BLBLIs may be valuable options for severe IAIs due to 3GCephRE.

Second, antibiotics recommended for non-severe IAIs (amoxicillin-clavulanate and quinolones) may not be active against 3GCephRE. The Study for Monitoring Antimicrobial Resistance Trends (SMART) found that ESBL-producing *E. coli* isolates from IAIs in Europe were highly resistant to most antibiotics, except carbapenems (21). Ampicillin-sulbactam resistance rate was 71.1%, while ciprofloxacin and levofloxacin resistance rates were 73.9% and 69.9%, respectively.

Third, ESCMID guidelines suggest to avoid BLBLIs due to AMS considerations. However, the achievement of optimal PK/PD in the site of infection may play a crucial role in difficult-to-treat infections. Mean peritoneal fluid-to-plasma concentrations ratio was 0.74 and 1.15 for ceftolozane, after one and two doses, respectively, and 0.49 for piperacillin. In addition, optimal source control will reduce the bacterial inoculum, allow short duration of antibiotic and reduce the risk of resistance.

For these reasons, we would recommend a non-carbapenem BLBLI (ceftolozane-tazobactam or ceftazidime-avibactam) plus metronidazole for IAIs due to 3GCephRE. This may not apply to septic shock, rarely enrolled in RCTs. Empirical treatment with carbapenems followed by early de-escalation to ceftolozane-tazobactam plus metronidazole as soon as patient achieves clinical stability may be reasonable.

3.3.2 Severe IAIs caused by carbapenem-resistant Enterobacterales (CRE)

In patients with IAIs, even more than in other situations, the knowledge of rectal colonization by carbapenemase-producing organisms may guide the choice of empirical therapy (22). The knowledge of underlying molecular mechanisms may also guide the choice of targeted treatment due to different activity of antibiotics against KPC and MBL. Thus, a molecular-based approach may be particularly useful for IAIs due to CRE.

Ceftazidime-avibactam and meropenem-vaborbactam were categorized as first-line options while no recommendation was made for imipenem-relebactam, despite comparable *in*

vitro activity against KPC, because of limited data by the time ESCMID guidelines were elaborated. The only observational study comparing ceftazidime-avibactam and meropenem-vaborbactam for CRE infections (20% IAIs) showed no differences in clinical success rates, despite ceftazidime-avibactam being used more often as a combination therapy (23). Data about imipenem-relebactam in patients with IAIs are scarce. A multicenter non-comparative study reported clinical response in 85.7% of patients with complicated IAI treated with imipenem-relebactam. The following considerations may be useful to select one of the 3 available BLBLIs in patients with IAIs due to KPC-producing CRE: i) ceftazidime-avibactam, unlike meropenem-vaborbactam and imipenem-relebactam, has no activity against anaerobes and should be associated with metronidazole in patients with IAIs; ii) imipenem-relebactam retains high *in vitro* activity against most isolates of *P. aeruginosa*, including DTR-PA; iii) meropenem-vaborbactam and imipenem-relebactam display activity against KPC-3 isolates resistant to ceftazidime-avibactam (24); iv) imipenem-relebactam is the only antibiotic among the 3 new BLBLIs with activity against enterococci. For these reasons, we would suggest imipenem-relebactam as first-line treatment, for severe IAIs due to KPC-producing CRE.

Ceftazidime-avibactam plus aztreonam was associated with better outcome than comparators in an observational study of BSI due to MBL-producing CRE, but IAIs represented only 8.8% of cases (7). Colistin has a complex PK and its concentration in peritoneal fluid is unknown. Rapid emergence of resistant mutants and reduced *in vitro* activity of colistin in the presence of a high bacterial inoculum has been demonstrated in a peritonitis model. Cefiderocol monotherapy is not the first option for IAIs due to MBL-producing CRE due to poor performance in clinical studies. Concerns about the emergence of cefiderocol resistance in MBL-producing CRE implies that *in vitro* activity of cefiderocol must be robustly documented before its use in difficult-to-treat infections such as IAIs.

For these reasons, we would recommend ceftazidime-avibactam plus aztreonam plus metronidazole as the preferred treatment for IAIs due to MBL-producing CRE.

3.4 Primary bloodstream infections

3.4.1 BSI caused by carbapenem-resistant Acinetobacter baumannii (CRAB)

A. baumannii, a glucose-non-fermentative aerobic GNB, is one of the most resistant bacteria encountered in common practice, and can be responsible for dreadful epidemics, particularly in ICU. It is considered as a 'critical priority' pathogen in the antibiotic-resistant bacteria list developed by the WHO (25). The most common resistance mechanism is the production of OXA-23, OXA-24 and OXA-58 clusters (2). The majority of *A. baumannii* in ICU are carbapenem-resistant. When this opportunistic pathogen causes clinical infection, mortality rates may be as high as 60% (26).

Data to guide antibiotic management are scarce for *A. baumannii*. The combination of at least two antibiotics active *in vitro* has been associated with better 14-day survival rate in a recent observational study of CRAB BSI (25). The combination of carbapenem and colistin was the most common option in recent years. However, a small RCT comparing ampicillin-sulbactam to colistin, both associated with levofloxacin, found better survival in patients treated with ampicillin-sulbactam. A meta-analysis including 1835 patients showed that ampicillin-sulbactam combined with another agent was the regimen with the highest ranking in clinical cure (27).

ESCMID guidelines recommend ampicillin-sulbactam monotherapy for patients with non-severe CRAB infections (1), while IDSA recommends ampicillin-sulbactam as part of a combination for severe infections (2). The choice of the second agent is at the discretion of the prescriber. One of the few RCTs available showed better efficacy of ampicillin-sulbactam and colistin combination compared with colistin monotherapy (28). In addition, polymyxins

have the highest *in vitro* activity against *A. baumannii*, colistin being the most widely used. Cefiderocol is active against CRAB *in vitro* and in observational studies (29). However the CREDIBLE-CR RCT has limited its use (30), with higher mortality in patients treated with cefiderocol as compared to best available therapy, particularly with *A. baumannii* infections. ESCMID guidelines recommend against the use of cefiderocol for CRAB, whereas IDSA restricts its use to CRAB resistant to all other antibiotics. However, in a recent observational study on VAP-associated BSI caused by CRAB in COVID-19 patients, cefiderocol combination regimens, especially with fosfomycin, were associated with better 30-day survival.

For these reasons, we would recommend a combination of high-dose ampicillin-sulbactam (24/12 g daily), and colistin (9 M IU daily after a loading dose of 4.5 M IU) for the treatment of BSI caused by CRAB. Cefiderocol, if active *in vitro*, represents an alternative option for strains resistant to sulbactam or to avoid colistin-related toxicity.

3.4.2 Catheter-related BSI caused by KPC-producing K. pneumoniae

Nosocomial *K. pneumoniae* is the main cause of CRE infections in Europe. According to ECDC, the mean prevalence of carbapenem resistance in *K. pneumoniae* was 7% in Europe in 2019, with striking heterogeneity, from <1% (Northern Europe countries) to >50% (Greece). Among CRE, mortality is higher for carbapenemase-producing *Enterobacterales* (CPE). KPC-producing *Enterobacterales* are mostly reported in Italy and Greece, while OXA-48-producing *Enterobacterales* are more widespread in Belgium, France, or Spain. New BLBLIs are active *in vitro* against most KPC, as is cefiderocol. IDSA and ESCMID guidelines recommend against combination therapy for KPC-producing CRE susceptible to meropenem-vaborbactam, ceftazidime-avibactam, imipenem-relebactam or cefiderocol. Comparative trials to choose between these agents are limited. A retrospective multicentre cohort study, including 73% of KPC-producing CRE, found no difference in terms of mortality between

patients treated with ceftazidime-avibactam or meropenem-vaborbactam (23). However, the Tango 2 unblinded RCT showed a lower mortality in patients treated with meropenem-vaborbactam, as compared with best-available treatment, including ceftazidime-avibactam (31).

Among CPE, meropenem-vaborbactam is only active against KPC, while ceftazidime-avibactam also has potential activity against OXA-48. Cefiderocol may be active on KPC, OXA-48, and MBL. Imipenem-relebactam, ceftazidime-avibactam and cefiderocol may be active against DTR-PA, which is not the case for meropenem-vaborbactam. Hence, meropenem-vaborbactam may be considered as the new BLBLI with the narrowest spectrum on CPE. Likewise, a sparing strategy would consider ceftazidime-avibactam as the last resort BLBLI for OXA-48. Finally, the emergence of resistant KPC-mutants (mainly D179Y variants of KPC-3) during treatment with ceftazidime-avibactam may be of concern, with preliminary data suggesting a decreased risk of on-treatment resistance selection with meropenem-vaborbactam. These concerns should be interpreted with caution, as ceftazidime-avibactam was the first new BLBLI available, and has been the most used worldwide (32,33), which increases the risk to document the emergence of resistance.

For these reasons, we would recommend meropenem-vaborbactam for BSI caused by KPC-producing CRE. Ceftazidime-avibactam and imipenem-relebactam are alternative options.

3.5 Central nervous system (CNS) infections

3.5.1 Ventriculitis and post-neurosurgical meningitis caused by carbapenem-resistant P. aeruginosa (CR-PA)

For patients with severe infections due to CR-PA, ESCMID guidelines prioritize ceftolozane-tazobactam if active *in vitro* (1), while IDSA guidelines included three new

BLBLIs (ceftolozane-tazobactam, ceftazidime-avibactam and imipenem-relebactam) as preferred agents (2). Only two RCTs have been published for treatment of CR-PA, one comparing imipenem-relebactam with the combination of colistin and imipenem: RESTORE-IMI 1 (34), and one comparing imipenem-relebactam with piperacillin-tazobactam in patients with HAP/VAP (RESTORE-IMI-2). Both RCT demonstrated similar efficacy to comparators, but no patients enrolled in the studies had CNS infections. Patients with CNS infections are often excluded from RCT, hence available data for optimal treatment of CR-PA CNS infections come from experimental and observational studies, often non-comparative, with limited sample size. In a rat model, the combination of ceftazidime-avibactam plus fosfomycin had greater efficacy than each drug alone: fosfomycin downregulates the expression of penicillin-binding protein 3 (PBP-3), which induces the expression of *Pseudomonas*-derived cephalosporinase while avibactam hinders the hydrolysis induced by several pseudomonal β-lactamases.

CNS infections have peculiar aspects and deserve specific recommendations. First, the ability to penetrate brain tissue and achieve PK/PD targets is of utmost importance. The exposure time to free (non-protein bound) drug concentrations above the MIC (fT>MIC) is the main parameter for the activity of β-lactams. Ceftolozane, ceftazidime, avibactam, tazobactam, and aztreonam have good CSF/serum concentrations ratio (35). Few observations reported favorable outcomes with ceftazidime-avibactam or ceftolozane-tazobactam, while in one small series, CSF penetration of ceftolozane-tazobactam was inadequate (36). High CSF penetration of fosfomycin (45–50%) has also been reported but, unfortunately, a breakpoint for fosfomycin against CR-PA is not available. The combination of high-dose cefiderocol plus fosfomycin may be an option (8). Therapeutic drug monitoring, when available, seems particularly important for optimal treatment of CR-PA CNS infections (37). Severe adverse events may restrict our armamentarium for CNS infections: in particular, the risk of seizures

associated with high-doses imipenem is a major limitation for the use of imipenem-relebactam in CNS infections.

To achieve maximum drug efficacy in CNS infections due to CR-PA, extended or continuous infusions are strongly recommended. Currently, insufficient data are available on the benefits and limitations of intrathecal administration for antibiotics, particularly the most recent. Evidence is also scarce regarding the optimal duration of treatment: IDSA guidelines recommend a treatment of 10-14 days for CNS infections due to GNB, tailored according to clinical response (38).

For these reasons, we would recommend ceftazidime-avibactam in combination with fosfomycin as the preferred treatment for CNS infections due to CR-PA. Second choice could be either ceftolozane-tazobactam or cefiderocol in combination with fosfomycin. The combination of aztreonam and avibactam may also be appealing, but additional data are requested.

4. Discussion

The panel reached a consensus for the following 'first-choices': i) cefepime for VAP due to AmpC β-lactamase-producing *Enterobacterales*; ii) The BLBLI combination most active *in vitro*, or cefiderocol combined with fosfomycin, and aerosolized colistin or aminoglycosides, for severe pneumonia due to *P. aeruginosa* resistant to ceftolozane-tazobactam; iii) high-dose piperacillin-tazobactam for cUTIs caused by ESBL-producing *Enterobacterales* with piperacillin-tazobactam MIC $\leq$8 mg/L; iv) high-dose cefepime for cUTIs due to AmpC β-lactamase-producing *Enterobacterales* other than *Enterobacter* species if cefepime MIC $\leq$2 mg/L; v) ceftolozane-tazobactam or ceftazidime-avibactam plus metronidazole for IAIs due to 3GCephRE; vi) imipenem/relebactam for IAIs due to KPC-producing *Enterobacterales;* vii) ceftazidime-avibactam plus aztreonam plus metronidazole for IAIs due to metallo β-

lactamase-producing *Enterobacterales;* viii) ampicillin-sulbactam plus colistin for CRAB BSIs; ix) meropenem-vaborbactam for BSI caused by KPC-producing *Enterobacterales*; x) ceftazidime-avibactam plus fosfomycin for CNS infections caused by carbapenem-resistant *P. aeruginosa.*

Our panel did not aim at revising IDSA and ESCMID guidelines, as they both were products of high-quality and comprehensive literature reviews, followed by rigorous analysis of data available by top experts, to provide optimal choices for major difficult-to-treat MDR GNB infections. Our aim was to contribute to better informed clinical decisions for topics unresolved by these guidelines. Our approach was based on merging clinical experience, open panel discussions, and literature review of papers not included in previous guidelines, either because they did not fulfill their rigorous selection criteria, or they were published after guidelines were finalized.

One of our major challenges was to reach an agreement on optimal choices for situations were both new non-carbapenems BLBLIs, and carbapenems could be used. When different treatment options are associated with similar chances of therapeutic success, AMS considerations become a major parameter to select first-line treatment. However, AMS could either prioritize carbapenems as drugs with narrower spectrum, or non-carbapenem BLBLIs due to their lower impact on microbiota (39). As we were unable to resolve this dilemma, neither with literature data nor expert opinions, our first-line choices were often based on other parameters, including i) PK/PD data, with a special focus on optimal administration (mostly continuous infusion with loading dose, prioritizing high doses for all difficult-to-treat MDR GNB infections), taking into account diffusion at infected site(s); ii) local data on antimicrobial resistance and antibiotic consumption, when available; iii) the risk of on-treatment resistance emergence with specific bacteria/antibiotic couples.

In conclusion, despite these limitations, our 'practical approach' paper aims to be synergistic to previous guidelines, filling some of their gaps, using a synergistic approach, mostly based on clinical experience.

Declarations

Funding. None

Competing Interests. PT contributed to scientific committees for MSD, Shionogi, Advanz Pharma, and Pfizer. M. F. received unconditional grants from MSD and Gilead (paid to the University of Pisa) and speaker honoraria from Shionogi, Pfizer, Menarini, MSD, Gilead, GSK, MundiPharma, and Thermo Fisher. G. T. received speaker honoraria for educational meetings from Shionogi and honoraria for participation on a scientific board from MSD. All the reported conflicts of interest are outside this study. All other authors report no potential conflicts.

Ethical Approval: Not required

Sequence Information: Not applicable

Tables

Table 1. Pneumonia

Pathogens	**ESCMID Recommendations**	**Comments and practical approach**
Ventilator-associated pneumonia (VAP) caused by AmpC-producing *Enterobacterales*	No specific recommendations for AmpC-producing *Enterobacterales* pneumonia For 3GCephRE infections: Piperacillin-tazobactam or quinolones for non-severe infections; carbapenems for severe infections	**Cefepime as first-line treatment** - Cefepime as monotherapy when MIC is ≤2 mg/L - Higher mortality was only found in ESBL-producing *Enterobacterales* infections with high cefepime MIC - For AmpC-producing *Enterobacterales* infections, cefepime performed at least as well as comparators in observational studies, including in ICU
Severe pneumonia caused by difficult-to-treat resistant (DTR) *Pseudomonas aeruginosa* with resistance to ceftolozane-tazobactam	No recommendation in case of ceftolozane-tazobactam resistance Lack of evidence for imipenem-relebactam, cefiderocol and ceftazidime-avibactam use No clear recommendation for combination therapy	**Combination therapy: at least one *in vitro* active agent + aerosolized antibiotics** If susceptible: imipenem-relebactam or ceftazidime-avibactam For MBL: Cefiderocol in combination regimen with *in vitro* active partner, such as fosfomycin Systematic use of aerosolized colistin or tobramycin therapy: favorable PK/PD profile, improved microbiological outcomes, good tolerability

3GCephRE, 3rd generation cephalosporin-resistant *Enterobacterales*; BLBLI, β-lactam/β-lactamase inhibitors combinations; MBL, metallo-β-lactamases; ESBL, expanded-spectrum beta-lactamases; ICU, intensive care unit; PK/PD, pharmacokinetic/pharmacodynamic

Table 2. Severe complicated urinary tract infections (cUTI)

Pathogens	ESCMID Recommendations	Comments and practical approach
ESBL-producing *Enterobacterales*	- Carbapenems (mero- or imipenem; ertapenem if no septic shock) - Under AMS consideration, Piperacillin-tazobactam can be used as first-line therapy in low-inoculum, non-severe 3GCephRE infections, and as a step-down therapy for severe infections - Conditional recommendation/ good practice statement against the use of new BLBLI for 3GCephRE	**For AMS purpose, consider carbapenems-sparing strategies:** - cUTIs due to ESBL-producing *Enterobacterales* with piperacillin tazobactam MIC <8 mg/L: high-dose piperacillin tazobactam, with loading dose and continuous infusion - cUTIs due to ESBL-*Enterobacterales* with piperacillin tazobactam MIC >8 mg/L, aminoglycosides or intravenous fosfomycin are seducing alternatives alone or in combination strategies, due to high urinary concentrations and low prevalence of resistance - cefoxitin may be an option for ESBL-producing *E. coli*, as well as temocillin, based on drug-susceptibility testing studies. - new BLBLIs should be reserved for settings with concomitant high rates of resistance to piperacillin tazobactam and carbapenems
AmpC-producing *Enterobacterales*	- Carbapenems (mero- or imipenem; ertapenem if no septic shock) - No recommendations for organisms with moderate to high likelihood of AmpC production due to inducible AmpC gene (e.g. *Enterobacter cloacae*, *Citrobacter freundii)* - Conditional recommendation against the use of cefepime for 3GCephRE	**For AMS purposes, consider carbapenems-sparing strategies:** - cUTIs due to AmpC-producing *Enterobacterales* with cefepime MIC ≤2 mg/L: high-dose-cefepime (2 g t.i.d.) - cUTIs due to AmpC-producing *Enterobacterales* with cefepime MIC > 2 mg/L: new BLBLIs may be considered, instead of carbapenems, based on local resistance rates

cUTIs, complicated urinary tract infections; AMS, antimicrobial stewardship; BLBLI, β-lactam/β-lactamase inhibitors combinations; ESBL, expanded-spectrum beta-lactamases; 3GCephRE, 3rd generation cephalosporin resistant *Enterobacterales*

Table 3. Intra-abdominal infections (IAI)

Pathogens	**ESCMID Recommendations**	**Comments and practical approach**
3rd generation cephalosporin-resistant *Enterobacterales* (3GCephRE)	Severe infections: - carbapebems as first choice	**For AMS purposes, consider early de-escalation to ceftolozane-tazobactam (if *in vitro* active) plus metronidazole** as soon as clinical stability is achieved.
	Non-severe infections: - piperacillin-tazobactam *or* - amoxicillin-clavulanate *or* - quinolones	High prevalence of resistance to piperacillin-tazobactam, amoxicillin-clavulanate or quinolones among ESBL-producing *E. coli* isolates from IAIs in Europe.
Carbapenem-resistant *Enterobacterales*	Severe infections - meropenem-vaborbactam *or* ceftazidime-avibactam as first choice - cefiderocol if MBL or resistant to meropenem-vaborbactam or ceftazidime-avibactam (conditional) - no evidence for or against imipenem-relebactam or fosfomycin monotherapy	First-line antibiotic regimens should be based on carbapenemase type, local epidemiology (prevalence of ceftazidime-avibactam resistance) and concomitant isolates: **KPC:** **- imipenem-relebactam** (also active against enterococci) **or meropenem-vaborbactam or ceftazidime-avibactam plus metronidazole** as first choice **MBL:** **- ceftazidime-avibactam plus aztreonam plus metronidazole** as first choice - cefiderocol combination regimens (plus tygecicline *or* plus fosfomycin and metronidazole as alternative regimen) **OXA-48:** **- ceftazidime/avibactam plus metronidazole or cefiderocol-containing regimens** (plus tigecycline *or* plus fosfomycin and metronidazole)

AMS, antimicrobial stewardship; IAI, intra-abdominal infections; ESBL, expanded-spectrum beta-lactamases; MBL, metallo-beta-lactamase; KPC, *Klebsiella pneumoniae* carbapenemase; 3GCephRE, 3rd generation cephalosporin resistant *Enterobacterales*

Table 4. Primary bloodstream infections (BSI)

Pathogens	**ESCMID Recommendations**	**Comments and practical approach**
Carbapenem-resistant *Acinetobacter baumannii* (CRAB)	- Ampicillin-sulbactam for HAP/VAP with CRAB susceptible to sulbactam. - Combination therapy for patients with severe and high-risk CRAB infections, including two *in vitro* active agents (eg, polymyxin, aminoglycoside, tigecycline, sulbactam)	**Ampicillin sulbactam in association with colistin** as first-choice - Combination therapy associated with better survival for CRAB, particularly for primary BSIs (high-risk infections), particularly with sepsis or septic shock. - New data support the use of ampicillin-sulbactam as part of combination therapy. - We recommend a combination with colistin, because of its *in vitro* activity, its widespread use, and its efficacy with ampicillin-sulbactam documented in a randomized study(40) - Results from CREDIBLE-CR study advocate against the use of cefiderocol as a single agent in this situation.
KPC-producing *K. pneumoniae*	- Meropenem-vaborbactam or ceftazidime-avibactam if active *in vitro* for patients with severe infections due to CRE. - Cefiderocol for severe infections due to CRE carrying MBL or resistant to meropenem-vaborbactam or ceftazidime-avibactam - Monotherapy for patients with CRE infections susceptible to ceftazidime-avibactam or meropenem-vaborbactam	**Meropenem-vaborbactam.** For AMS purposes, consider the following. - Among CPE, meropenem-vaborbactam is only active against KPC, while the spectrum is wider for ceftazidime-avibactam (OXA-48, DTR-PA), imipenem-relebactam (DTR-PA) and cefiderocol (OXA-48, MBL and DTR-PA). - Hence, we may prioritize meropenem-vaborbactam as the new BLBLI with the narrowest spectrum. - Ceftazidime-avibactam and imipenem-relebactam as alternative options.

BSI, bloodstream infections; AMS, antimicrobial stewardship; CRAB, carbapenem-resistant *Acinetobacter baumannii*; CRE: carbapenem-resistant *Enterobacterales*; KPC, *Klebsiella pneumoniae* carbapenemase; MBL, metallo-*β*-lactamases; VAP, ventilator-associated pneumonia.

Table 5. Antibiotic doses suggested for treatment of multidrug-resistant Gram-negative bacilli

Antibiotic	**Loading dose**	**Daily dose in patients with normal renal clearance**
Piperacillin-tazobactam	9 g over 30 min	4.5 g every 6-8 h (continuous infusion)
Ampicillin-sulbactam	No	24 g/12 g
Temocillin	2 g over 30 min	2 g every 8 h (continuous infusion)
Cefoxitin	2 g over 30 min	2 g every 8 h (continuous infusion)
Cefepime	2 g over 30 min	2 g every 8 h (continuous infusion)
Ceftazidime-avibactam	2.5 g over 30 min	2.5 g every 8 h (continuous infusion)
Ceftolozane-tazobactam	1 g/0.5 g over 30 min 3 g over 30 min for HAP/VAP	1 g / 0.5 g every 6 h (continuous infusion) 9 g (continuous infusion) for HAP/VAP
Imipenem-relebactam	no	500 mg / 250 mg every 6 h (bolus 30 min, prolonged infusion over 3 h preferred)
Meropenem-vaborbactam	2g/ 2g over 30 min	2 g / 2 g every 8 h (infusion over 3 h)
Cefiderocol	2 g over 30 min	2 g every 6-8 h (infusion over 3 h)
Colistin	4.5 M IU	9 M IU/day (infusion over 30 min, extended infusion over 6 h preferred)
Fosfomycin	4 g	4-8 g every 6-8 h (infusion over 30 min, 16-24 g continuous infusion, preferred)

HAP, hospital-acquired pneumonia; VAP, ventilator-associated pneumonia

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Graphical Abstract