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Guidelines

European Society of Clinical Microbiology and Infectious Diseases (ESCMID) guidelines for the treatment of infections caused by multidrug-resistant Gram-negative bacilli (endorsed by European society of intensive care medicine)

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ABSTRACT

Scope: These ESCMID guidelines address the targeted antibiotic treatment of third-generation cephalosporin-resistant *Enterobacterales* (3GCephRE) and carbapenem-resistant Gram-negative bacteria, focusing on the effectiveness of individual antibiotics and on combination versus monotherapy.
Methods: An expert panel was convened by ESCMID. A systematic review was performed including randomized controlled trials and observational studies, examining different antibiotic treatment regimens for the targeted treatment of infections caused by the 3GCephRE, carbapenem-resistant Enterobacterales, carbapenem-resistant *Pseudomonas aeruginosa* and carbapenem-resistant *Acinetobacter baumannii*. Treatments were classified as head-to-head comparisons between individual antibiotics and between monotherapy and combination therapy regimens, including defined monotherapy and combination regimens only. The primary outcome was all-cause mortality, preferably at 30 days and secondary outcomes included clinical failure, microbiological failure, development of resistance, relapse/recurrence, adverse events and length of hospital stay. The last search of all databases was conducted in December 2019, followed by a focused search for relevant studies up until ECCMID 2021. Data were summarized narratively. The certainty of the evidence for each comparison between antibiotics and between monotherapy and combination therapy regimens was classified by the GRADE recommendations. The strength of the recommendations for or against treatments was classified as strong or conditional (weak).
Recommendations: The guideline panel reviewed the evidence per pathogen, preferably per site of infection, critically appraising the existing studies. Many of the comparisons were addressed in small observational studies at high risk of bias only. Notably, there was very little evidence on the effects of the new, recently approved, β-lactam/β-lactamase inhibitors on infections caused by carbapenem-resistant Gram-negative bacteria. Most recommendations are based on very-low- and low-certainty evidence. A high value was placed on antibiotic stewardship considerations in all recommendations, searching for carbapenem-sparing options for 3GCephRE and limiting the recommendations of the new antibiotics for severe infections, as defined by the sepsis-3 criteria. Research needs are addressed. **Mical Paul, Clin Microbiol Infect 2022;28:521**

Scope and context

According to estimates from the European Center of Disease and Control (ECDC), antibiotic-resistant bacteria caused 600 000 infections and 27 000 attributable deaths in 2015 in Europe [2]. Almost 70% of this disease burden, in terms of both number of cases and attributable deaths, is caused by multi-drug-resistant Gram-negative bacteria (MDR-GNB). Ratios of attributable deaths compared with the non-infected population or with a population infected with susceptible isolates of the same bacteria are positive, with a factor-increase ranging from 1.5 for MDR *Pseudomonas aeruginosa* to 6.2 for carbapenem-resistant (CR) *Klebsiella pneumoniae* from 2007 to 2015 [2]. The substantial burden of disease, together with the paucity of available treatments and slowly progressing antibiotic pipeline have led the World Health Organization to prioritize four MDR-GNB phenotypes as of critical priority for future research and development investments: CR-*Acinetobacter baumannii*, CR-*P. aeruginosa* and CR- and third-generation cephalosporin-resistant Enterobacterales [3]. Since the issuing of the priority list in 2017, five new antibiotics with activity against MDR-GNB were approved by the European Medicines Agency (EMA) and and the US Food and Drug Administration (FDA), none of which has a new mode of action and all followed a fast-track development pathway that is granted to drugs potentially addressing unmet medical needs [4].

In parallel with huge efforts by pharmaceutical companies, and profit and non-profit organizations to promote research and development of new antibiotics, the scientific community and public health agencies are strongly calling for an increasingly parsimonious use of available antibiotics in order to prevent further development of resistance. In this paradoxical scenario prescribing antibiotics for MDR-GNB infections has become a significant challenge for clinicians worldwide, stretched between the well-known limitations of the old drugs, fear of promoting resistance by using the new antibiotics, the paucity of data on the effects of newly developed antibiotics against MDR-GNB and the costs of the new antibiotics [5]. The objective of these evidence-based guidelines is to provide recommendations for treatment of infections caused by MDR-GNB in hospitalized patients.

Questions addressed by the guideline

Target MDR-GNB and the questions addressed were selected by consensus in the first panel meeting. The guidelines address the targeted treatment of infections caused by third-generation cephalosporin-resistant Enterobacterales (3GCephRE), CR Enterobacterales (CRE), CR *P. aeruginosa* (CRPA) and CR *A. baumannii* (CRAB). The following questions were addressed. (a) What is the antibiotic of choice for patients infected with the target MDR-GNB? (b) Should combination antibiotic therapy be used for patients infected with the target CR-GNB?

The recommendations are summarized in Table 1. The potential *in vitro* activity of antibiotics reviewed against the target MDR-GNB is provided in Table 2. *In vitro* data point to specific antibiotic combinations that are synergistic against specific CR-GNB or prevent resistance emergence. Yet for patient management, evidence from clinical studies is necessary to select the optimal treatment, including both single and combination therapies [6,7] Therefore, the guidelines are based on a systematic review of clinical evidence. Expected users of these guidelines include both policy-makers and in-hospital antibiotic prescribers, especially infectious disease, clinical microbiology and intensive care specialists.

Table 1
Summary of recommendations

Recommendation	Strength of recommendation	Level of evidence
Third-generation cephalosporin-resistant Enterobacterales (3GCephRE)		
Recommendations on the choice of antibiotic treatment for 3GCephRE		
For patients with BSI and severe infection due to 3GCephRE, we recommend a carbapenem (imipenem or meropenem) as targeted therapy	Strong	Moderate
For patients with BSI due to 3GCephRE without septic shock, ertapenem instead of imipenem or meropenem may be used.	Conditional	Moderate
For patients with low-risk, non-severe infections due to 3GCephRE, under the consideration of antibiotic stewardship, we suggest piperacillin-tazobactam, amoxicillin/clavulanic acid or quinolones. It may be good practice to consider cotrimoxazole for non-severe cUTI.	Conditional/good practice statement	Moderate/expert opinion
For cUTI in patients without septic shock, we conditionally recommend aminoglycosides when active *in vitro* for short durations of therapy, or IV fosfomycin.	Conditional/strong	Moderate/high
Among all patients with 3GCephRE infections, stepdown targeted therapy following carbapenems once patients are stabilized, using old BLBLI, quinolones, cotrimoxazole or other antibiotics based on the susceptibility pattern of the isolate, is good clinical practice.	Good practice statement	Expert opinion
We do not recommend tigecycline for infections caused by 3GCephRE.	Strong	Very low
Among all patients with 3GCephRE infections the new BLBLI are reserved antibiotics for extensively resistant bacteria and therefore, we consider it good clinical practice to avoid their use for infections caused by 3GCephRE, due to antibiotic stewardship considerations.	Good practice statement	Expert opinion
We suggest that cephamycins (e.g. cefoxitin, cefmetazole, flomoxef) and cefepime not be used for 3GCephRE infections.	Conditional	Very low
For cefoperazone-sulbactam, ampicillin-sulbactam, ticarcillin-clavulanic acid, temocillin and mecillinam there is insufficient evidence for the management of patients with 3GCephRE infections at the time of writing and therefore no recommendation can be issued.	No recommendation	
Carbapenem-resistant Enterobacterales (CRE)		
Recommendations on the choice of antibiotic treatment for CRE		
For patients with severe infections due to CRE, we suggest meropenem-vaborbactam or ceftazidime-avibactam if active *in vitro*.	Conditional	Moderate/low
For patients with severe infections due to CRE carrying metallo-β-lactamases and/or resistant to all other antibiotics, including ceftazidime-avibactam and meropenem-vaborbactam, we conditionally recommend treatment with cefiderocol.	Conditional	Low
For patients with non-severe infections due to CRE, under the consideration of antibiotic stewardship, we consider the use of an old antibiotic, chosen from among the *in vitro* active on an individual basis and according to the source of infection, as good clinical practice. For patients with cUTI, we suggest aminoglycosides, including plazomicin, over tigecycline.	Good practice statement/conditional	Expert opinion/low
We suggest that tigecycline not be used for BSI and HAP/VAP; if necessary, in patients with pneumonia, clinicians may use high-dose tigecycline.	Conditional	Low
There is no evidence to recommend for or against the use of imipenem-relebactam and fosfomycin monotherapies for CRE at the time of writing.	No recommendation	
Recommendations on combination therapy for CRE		
For patients with CRE infections susceptible to and treated with ceftazidime-avibactam, meropenem-vaborbactam or cefiderocol, we do not recommend combination therapy.	Strong	Low
For patients with severe infections caused by CRE carrying metallo-β-lactamases and/or resistant to new antibiotic monotherapies, we suggest aztreonam and ceftazidime-avibactam combination therapy.	Conditional	Moderate
For patients with severe infections caused by CRE susceptible *in vitro* only to polymyxins, aminoglycosides, tigecycline or fosfomycin, or in the case of non-availability of new BLBLI, we suggest treatment with more than one drug active *in vitro*. No recommendation for or against specific combinations can be provided.	Conditional	Moderate
We suggest that clinicians avoid carbapenem-based combination therapy for CRE infections, unless the meropenem MIC is $\leq$ 8 mg/L, where high-dose extended-infusion meropenem may be used as part of combination therapy if the new BLBLI are not used.	Conditional	Low
In patients with non-severe infections or among patients with low-risk infections, under the consideration of antibiotic stewardship, we consider the use of monotherapy chosen from among the *in vitro* active old drugs, on an individual basis and according to the source of infection as good clinical practice	Good practice statement	Expert opinion
Carbapenem-resistant *Pseudomonas aeruginosa* (CRPA)		
Recommendations on the choice of antibiotic treatment for CRPA		
In patients with severe infections due to difficult to treat CRPA, we suggest therapy with ceftolozane-tazobactam if active *in vitro*. Insufficient evidence is available for imipenem-relebactam, cefiderocol and ceftazidime-avibactam at this time.	Conditional	Very low
In patients with non-severe or low-risk CRPA infections, under the consideration of antibiotic stewardship, we consider it good clinical practice to use the old antibiotics, chosen from among the *in vitro* active antibiotics on an individual basis and according to the source of infection.	Good practice statement	Expert opinion
Recommendations on combination therapy for CRPA		
Lacking evidence, we cannot recommend for or against the use of combination therapy with the new BLBLI (ceftazidime-avibactam and ceftolozane-tazobactam) or cefiderocol for CRPA infections.	No recommendation	
When treating severe infections caused by CRPA with polymyxins, aminoglycosides, or fosfomycin, we suggest treatment with two *in vitro* active drugs. No recommendation for or against specific combinations can be provided.	Conditional	Very low
In patients with non-severe or low-risk CRPA infections, under the consideration of antibiotic stewardship, we consider it good clinical practice to use monotherapy chosen from among the drugs active *in vitro*, on an individual basis and according to the source of infection.	Good practice statement	Expert opinion

(*continued on next page*)

Table 1 (*continued*)

Recommendation	Strength of recommendation	Level of evidence
Carbapenem-resistant *Acinetobacter baumannii* (CRAB)		
Recommendations on the choice of antibiotic treatment for CRAB		
For patients with CRAB susceptible to sulbactam and HAP/VAP, we suggest ampicillin-sulbactam.	Conditional	Low
For patients with CRAB resistant to sulbactam, a polymyxin or high-dose tigecycline can be used if active *in vitro*. Lacking evidence, we cannot recommend on the preferred antibiotic.	No recommendation	
We conditionally recommend against cefiderocol for the treatment of infections caused by CRAB.	Conditional	Low
Recommendations on combination therapy for CRAB		
For all patients with CRAB infections, we do not recommend polymyxin-meropenem combination therapy or polymyxin-rifampin combination therapy.	Strong	High/moderate
For patients with severe and high-risk CRAB infections, we suggest combination therapy including two *in vitro* active antibiotics among the available antibiotics (polymyxin, aminoglycoside, tigecycline, sulbactam combinations).	Conditional	Very low
For patients with CRAB infections with a meropenem MIC $\leq$8 mg/L, we consider carbapenem combination therapy, using high-dose extended-infusion carbapenem dosing, as good clinical practice.	Good practice statement	Expert opinion
All carbapenem-resistant Gram-negative bacteria		
For pan-resistant CR-GNB (resistant also to polymyxins), treatment with the least resistant antibiotic/s based on MICs relative to the breakpoints is considered as good clinical practice.	Good practice statement	Expert opinion

Abbreviations: BLBLI, β-lactamase/β-lactamase inhibitors; BSI, bloodstream infections; cUTI, complicated urinary tract infections; HAP, hospital-acquired pneumonia; IV, intravenous; VAP, ventilator-associated pneumonia.

Table 2
Potential *in vitro* activity of antibiotics against target carbapenem-resistant Gram-negative bacteria and approved indications

	CRAB	ESBLs	CRPA non-MBL	CRE non-CP	CRE-KPC	CRE-OXA-48	CRE-MBL	Current clinical indications/approval
New antibiotics								
Ceftolozane-tazobactam	No	Yes	Yes	No	No	No	No	FDA and EMA approved for cUTI, cIAI, HAP and VAP
Ceftazidime-avibactam	No	Yes	Yes	+/−	Yes	Yes	No	FDA and EMA approved for cIAI and cUTI, HAP and VAP, and (in EMA only) for the treatment Gram-negative infections in patients with limited treatment options
Meropenem-vaborbactam	No	Yes	No	+/−	Yes	No	No	FDA approved for cUTI, EMA approved for cUTI, HAP and VAP, and for the treatment Gram-negative infections in patients with limited treatment options
Imipenem-cilastatin/ relebactam	No	Yes	Yes	+/−	Yes	No	No	FDA approved for cUTI and cIAI; EMA approved for HAP and VAP and for BSI with a suspected respiratory source, and for the treatment Gram-negative infections in patients with limited treatment options
Plazomicin	No	Yes	+/−	Yes	Yes	Yes	+/−	FDA approval cUTI, EMA application withdrawn
Eravacycline	Yes	Yes	No	Yes	Yes	Yes	Yes	FDA and EMA approved for cIAI
Cefiderocol	Yes	Yes	Yes	Yes	Yes	Yes	Yes	FDA cUTI, HAP and VAP; EMA for the treatment of infections due to aerobic Gram-negative organisms in adults with limited treatment options
Old antibiotics								
Polymyxins	Yes	Yes	Yes	Yes	Yes	Yes	Yes	FDA: serious infections caused by susceptible strains, when less potentially toxic drugs are ineffective or contraindicated. EMA: treatment of serious infections due to aerobic Gram-negative pathogens in patients with limited treatment options
Aminoglycosides	+/−	+/−	+/−	+/−	+/−	+/−	+/−	EMA and FDA: for the treatment of a variety of bacterial infections
Fosfomycin iv	No	Yes	+/−	+/−	+/−	+/−	+/−	EMA: to treat serious infections when other antibiotic treatments are not suitable. FDA: under review
Aztreonam	No	No	+/−	No	No	No	+/−	EMA and FDA: for the treatment of infections caused by susceptible Gram-negative microorganisms
Tigecycline	Yes	Yes	No	Yes	Yes	Yes	Yes	EMA and FDA: complicated SSTI and IAI (FDA also CAP)
Temocillin	No	Yes	No	No	+/−	No	No	EMA and FDA: orphan drug status for the treatment of infections caused by *Burkholderia cepacia* in patients with cystic fibrosis

The table presents the spectrum of potential *in vitro* activity of the listed antibiotics; resistance can develop and treatment should be directed by susceptibility testing.
Abbreviations: BSI, bloodstream infection; CAP, community-acquired pneumonia; cIAI, complicated intra-abdominal infections; CRAB, carbapenem-resistant *Acinetobacter baumannii*; CRE non-CP, non-carbapenemase-producing carbapenem-resistant Enterobacterales; CRPA non-MBL, carbapenem-resistant *Pseudomonas aeruginosa* non-metallo-β-lactamase-producing; cUTI, complicated urinary tract infections; EMA, European Medicines Agency; ESBLs, extended-spectrum β-lactmases; FDA, US Food and Drug Administration; HAP, hospital-acquired pneumonia; MBL, metallo-β-lactamase; SSTI, skin and soft-tissue infections; VAP, ventilator-associated pneumonia.

Methods

First, a systematic review was performed to support the recommendations. The certainty of the evidence was classified using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system. Second, an expert panel translated the evidence to recommendations and the strength of recommendations was adjudicated. Finally, the recommendations were discussed and revised until consensus was achieved and the final list of recommendations was formally approved by the whole panel. The review protocol followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [8] and foresaw the inclusion of all studies evaluating the efficacy of any antibiotic regimen on clinical outcomes in hospitalized patients with infections caused by MDR-GNB.

Description of the developing group

A guideline panel was convened by the ESCMID Executive Committee in 2018. Experts on the management of MDR-GNB infections, bacteriology and mechanisms of resistance were selected from the fields of infectious diseases, clinical microbiology, intensive care and pharmacokinetics-pharmacodynamics, targeting multinational representation. Conflict of interest statements were collected from all panel members before starting and after completion of the guideline development. The guideline development process is further detailed in the Supplementary material (Appendix S1).

Literature search

Relevant clinical studies were identified through computerized literature searches using PubMed, the Cochrane Database of Systematic Reviews, the Cochrane Central Register of Controlled Trials, ClinicalTrials.gov, FDA drug approval documents and the panel experts' own studies. Three separate search strategies for each target organism (*Acinetobacter*, Enterobacterales and *P. aeruginosa*) were developed through the combination of Medical Subject Headings and equivalent terms and adapted for the different databases (Appendix 1). The last systematic search was conducted in December 2019. After the final search date, studies (including randomized controlled trials from international conferences) having a significant impact on the recommendations were identified by the authors and added, until 12 July (ECCMID) 2021.

Inclusion criteria

We included comparative randomized controlled trials (RCT) or observational studies (both retrospective or prospective), examining different antibiotic treatment regimens for infections caused by the designated MDR-GNB. Only studies reporting on the defined clinical and/or microbiological outcomes were included. We did not include conference proceedings and excluded case reports, small case series with fewer than ten patients, *in vitro* and animal studies and studies on prophylaxis or decolonization.

The guidelines address two main questions on selection of the optimal monotherapy and on monotherapy versus combination therapy for the different MDR-GNB. The questions were posed in the PICO framework (Population/participant, Intervention, Comparator/control, Outcome). The full PICO questions are detailed in the Supplementary material (Appendix S1). In brief, the research questions were formulated as follow:

Population: Hospitalized patients with infections requiring systemic treatment due to the selected microorganisms (3GCephRE, CRE, CRPA and CRAB). We excluded studies assessing patients with uncomplicated urinary tract infections (UTI) and tracheobronchitis.

Intervention: Targeted treatment (following pathogen and susceptibility identification) with systemic antibiotics, preferably defined in terms of dosage and duration. We included EMA- or FDA-approved antibiotics, approved for any indication.

Comparator: Patients receiving another antibiotic/antibiotic scheme. The two comparisons assessed any antibiotic versus different antibiotic/s and monotherapy versus combination therapy.

Outcomes: The primary outcome considered for all analyses was all-cause mortality, preferably at 30 days. If 30-day data were unavailable, we used the closest defined time-point and if unavailable in-hospital all-cause mortality. Secondary outcomes included clinical failure (or cure), microbiological failure, development of resistance, relapse/recurrence, adverse events and length of hospital stay. All outcomes reported in the studies, of the defined outcomes, were extracted.

Definitions

Sepsis: We adopted the sepsis-3 definition for sepsis, as severe presentation of infection with life-threatening organ dysfunction caused by a dysregulated host response to infection [9].

Septic shock: We similarly accept the sepsis-3 definitions for septic shock when the underlying circulatory and cellular/metabolic abnormalities are profound enough to substantially increase mortality [9].

Severe infections: sepsis or septic shock.

Low and high-risk infections: Based on the INCREMENT score, we defined infections (including bloodstream infections (BSI)) originating from a urinary tract source of infection or biliary infections after source control as infections at low risk for mortality and other infections as high-risk infections [10,11].

New antibiotics: Antibiotics approved after 2010.

Uncomplicated UTI: Infection causing local bladder signs and symptoms, without fever, other signs of systemic infection, or findings suggestive of kidney involvement.

Difficult to treat resistance (DTR): Resistance to all β-lactams, including carbapenems, β-lactamase inhibitor combinations and fluoroquinolones [12].

Risk of bias assessment

Risk of bias assessment was performed for each study by two reviewers independently using adapted versions of the Effective Practice and Organization of Care guidelines for RCT and the Newcastle–Ottawa Scale for non-randomized studies [13,14] Individual studies were classified overall as providing low, moderate or high risk of bias evidence.

Review procedures and data extraction

All articles identified by the search were screened on the basis of the abstract against eligibility criteria and non-relevant documents or duplicates were excluded. Full texts of potentially eligible articles were then assessed by two reviewers independently who applied eligibility criteria. Relevant data were extracted into a pre-defined database. Data extraction and risk of bias assessment were performed independently by two reviewers among the guideline expert panel and discrepancies were resolved through discussion between the two reviewers and, if necessary, with the guideline expert panel. All and only panel members participated in the eligibility assessment and data extraction.

Data synthesis and development of recommendations

Because of the large, expected heterogeneity of study designs, treatment schemes, patient populations and resistance definitions the expert panel agreed not to perform quantitative synthesis of the data using meta-analysis and results were summarized qualitatively. When possible, recommendations tried to address severe infections versus others, at-risk infection sources versus others and different mechanisms of resistance. Available evidence for each treatment comparison was classified by the panel following the GRADE system [15]. Certainty of the evidence was classified as high, moderate, low or very low. Recommendations were classified as strong or conditional (weak). When no evidence was available, good practice statements were designated based on expert opinion. All recommendations are conditional on the *in vitro* activity of the recommended antibiotics.

1. Third-generation cephalosporin-resistant Enterobacterales

Question 1.1: What is the antibiotic of choice for 3GCephRE

Recommendations

- For patients with BSI and severe infection due to 3GCephRE, we recommend a carbapenem (imipenem or meropenem) as targeted therapy (**strong recommendation for use, moderate certainty of evidence**).
- For patients with BSI due to 3GCephRE without septic shock, ertapenem instead of imipenem or meropenem may be used (**conditional recommendation for use, moderate certainty of evidence**).
- For patients with low-risk, non-severe infections due to 3GCephRE, under the consideration of antibiotic stewardship, we suggest piperacillin-tazobactam, amoxicillin/clavulanic acid or quinolones (**conditional recommendation for use, moderate certainty of evidence/good practice statement**). It may be good practice to consider cotrimoxazole for non-severe complicated UTI (cUTI) (**good practice statement**).
- For cUTI in patients without septic shock, we conditionally recommend aminoglycosides when active *in vitro*, for short durations of therapy (**conditional recommendation for use, moderate certainty of evidence**), or intravenous fosfomycin (**strong recommendation for use, high certainty of evidence**)
- Among all patients with 3GCephRE infections, stepdown targeted therapy following carbapenems once patients are stabilized, using old β-lactam/β-lactamase inhibitors (BLBLI), quinolones, cotrimoxazole or other antibiotics based on the susceptibility pattern of the isolate, is good clinical practice (**good practice statement**).
- We do not recommend tigecycline for infections caused by 3GCephRE (**strong recommendation against use, very low certainty of evidence**).
- Among all patients with 3GCephRE infections, the new BLBLI are reserve antibiotics for extensively resistant bacteria and therefore, we consider it good clinical practice to avoid their use for infections caused by 3GCephRE, due to antibiotic stewardship considerations (**good practice statement**).
- We suggest that cephamycins (e.g. cefoxitin, cefmetazole, flomoxef) and cefepime not be used for 3GCephRE infections (**conditional recommendation against use, very low certainty of evidence**).
- For cefoperazone-sulbactam, ampicillin-sulbactam, ticarcillin-clavulanic acid, temocillin and mecillinam there is insufficient evidence for the management of patients with 3GCephRE infections at the time of writing and therefore no recommendation can be issued.

Review of the evidence

The data available on 3GCephRE are derived mainly from observational studies in the hospital setting including patients with BSI and urinary source of infection. In many studies there was a lack of information on the bacterial species and mechanisms of resistance. Extended-spectrum β-lactamase (ESBL) production was the most commonly reported resistance mechanism, mostly without specifying the type of β-lactamases conferring the ESBL phenotype. The main comparison is between the older BLBLI (amoxicillin-clavulanate and piperacillin-tazobactam) and carbapenems and discusses the conflict between the MERINO RCT [16] and the observational data [17,18]. An underlying stewardship consideration for this comparison was the association between carbapenem use and CRE [19]. Data on new antibiotics are sparse because most new antibiotic approval RCT were syndrome-based and the subgroups of patients with 3GCephRE infections were small. For 3GcephRE, only PICO 1 on the choice of antibiotic treatment was addressed.

The evidence on treatment of infections caused by 3GCephRE is provided by clinical syndrome: BSI, UTI, pneumonia and intra-abdominal infection (IAI). All studies referred to in the text are described in Table 3.

Bloodstream infections

BLBLI versus carbapenems. The MERINO trial compared piperacillin-tazobactam with meropenem among patients with BSI caused by third-generation cephalosporin-resistant *Escherichia coli* and *K. pneumoniae* [16]. The primary outcome was 30-day mortality and the study did not prove the non-inferiority of piperacillin-tazobactam, with 30-day mortality rates of 23/187 (12.3%) with piperacillin-tazobactam versus 7/191 (3.7%) with meropenem (risk difference (RD) 8.6%, one-sided 97.5% CI $-\infty$ to 14.5%). The risk difference was lower in the subgroup of patients with UTI (RD 3.7%, $-\infty$ to 10.7%) than among patients with other sources of BSI (RD 14.1%, $-\infty$ to 24.5%). Following the trial, the authors found a high rate of false susceptibility to piperacillin-tazobactam among OXA-1 producers with automatic methods or strip-gradient tests performed in the trial sites. A further analysis of the trial excluded patients with BSI caused by non-susceptible strains (piperacillin-tazobactam MIC >16 mg/L; meropenem MIC >1 mg/L CLSI, or MIC >2 mg/L EUCAST), as assessed by broth microdilution in a reference laboratory [20] The difference between groups decreased and was non-significant with a smaller sample size, mortality 13/134 (9.7%) with piperacillin-tazobactam versus 6/149 (4%) with meropenem, risk difference 5.7% (95% CI −1% to 11%). The certainty from this trial showing advantage of meropenem compared with piperacillin-tazobactam was classified as moderate, due to indirectness related to the high rate of OXA-1-producers with high MICs to piperacillin-tazobactam and to the small sample size of the further subgroup analyses. The MERINO-2 was a pilot RCT comparing piperacillin-tazobactam and meropenem among patients with BSI caused by presumed Amp-C β-lactamase-producing but third-generation cephalosporin-susceptible *Enterobacter* spp., *Citrobacter freundii*, *Morganella morganii*, *Providencia* spp., *Klebsiella aerogenes* or *Serratia marcescens* [21]. Among 70 included patients, mortality was very low (two patients in the meropenem arm) and there was no significant difference in clinical failure (8/38, 21% with piperacillin-tazobactam versus 4/34, 12% with meropenem).

A large number of observational studies compared carbapenem therapy with old BLBLI for the therapy of 3GCephRE BSI (20 studies, Table 3) [22–41]. Empirical and targeted therapies were assessed in about half of the studies each, and all reported on mortality,

Table 3
Studies evaluating the treatment of third-generation cephalosporin-resistant Enterobacterales infections

Author year	Design	Infection/s included	Pathogen	% ICU	% UTI	% BSI	Treatment phase	Group 1	Group 2	Outcome measured	Statistic used	Effect estimate	CI low	CI high	Risk of bias
Zanetti 2003 [88]	Subgroup analysis of RCT	HAP	Any GNB	100	0		Any	Cefepime, $n = 13$	Imipenem, $n = 10$	Clinical cure	Crude	9/13 vs. 10/10			H
Endimiani 2004 [66]	Cohort retrospective	BSI	*Klebsiella*	62		100	Targeted	FQ, $n = 7$	Carbapenem, $n = 10$	Clinical cure	Crude unadjusted	2/7 vs. 8/10, p 0.03			H
Paterson 2004 [254]	Cohort prospective	BSI	*Klebsiella*	39.4	14.1	100	Targeted	Carbapenem, $n = 42$	Other than carbapenem, $n = 29$	Mortality	OR adjusted	0.28	0.08	1	H
Goethaert 2006 [91]	Cohort retrospective	Any, mainly pneumonia	Enterobacter	100	5	15.9	Targeted	Cefepime, $n = 21$	Imipenem or meropenem, $n = 23$	Mortality	Crude unadjusted	11/21 vs. 8/23, NS			H
Goethaert 2006 [91]	Cohort retrospective	Any, mainly pneumonia	Enterobacter	100	5	15.9	Targeted	Cefepime, $n = 21$	Imipenem or meropenem, $n = 23$	Clinical improvement	Crude unadjusted	13/21 vs. 16/23, p 0.59			H
Goethaert 2006 [91]	Cohort retrospective	Any, mainly pneumonia	Enterobacter	100	5	15.9	Targeted	Cefepime, $n = 21$	Imipenem or meropenem, $n = 23$	Microbiological cure	Crude unadjusted	5/21 vs. 2/23, p 0.76			H
Huang 2006 [45]	Cohort retrospective	BSI	Enterobacterales	33.3	20.4	100	Targeted	Non-carbapenems, $n = 32$	Imipenem or meropenem, $n = 22$	Mortality	Crude unadjusted	9/32 vs. 2/22, p 0.09			H
Lee 2006 [55]	Cohort retrospective	BSI	*Klebsiella*	48.1	11.1	100	Targeted	Flomoxef, $n = 7$	Imipenem or meropenem, $n = 20$	Mortality	Crude unadjusted	2/7 vs. 5/20, p 0.86			H
Chaubey 2010 [42]	Cohort retrospective	BSI	*E. coli* and *Klebsiella*		48	100	Any	BLBLI, $n = 28$	Other than BLBLI, $n = 51$	Mortality	RR unadjusted	1.09	0.44	2.69	H
Chaubey 2010 [42]	Cohort retrospective	BSI	*E. coli* and *Klebsiella*		48	100	Any	Carbapenem, $n = 30$	Other than carbapenem, $n = 49$	Mortality	RR unadjusted	0.54	0.19	1.53	H
Chaubey 2010 [42]	Cohort retrospective	BSI	*E. coli* and *Klebsiella*		48	100	Any	FQ, $n = 4$	Other than FQ, $n = 75$	Mortality	RR unadjusted	1.25	0.22	7.24	H
Chaubey 2010 [42]	Cohort retrospective	BSI	*E. coli* and *Klebsiella*		48	100	Any	Aminoglycosides, $n = 10$	Other than aminoglycosides, $n = 69$	Mortality	RR unadjusted	0.46	0.07	3.11	H
Chaubey 2010 [42]	Cohort retrospective	BSI	*E. coli* and *Klebsiella*		48	100	Any	Sulfamethoxazole, $n = 3$	Other than sulfametoxazole, $n = 76$	Mortality	RR unadjusted	1.69	0.32	8.91	H
Freire 2010 [87]	Subgroup analysis of RCT	HAP/VAP	*E. coli* and *Klebsiella*		0	15.4	Any	Tigecycline, $n = 21$	Imipenem, $n = 20$	Clinical cure	Crude	14/21 vs. 19/20, NS			M
Lee 2010 [30]	Cohort retrospective	BSI	*Enterobacter*	64.4	7.4	100	Targeted	Non carbapenems, $n = 61$	Carbapenem, $n = 53$	Infection-related mortality	Adjusted	Reported as NS, p 0.15			H
Lee 2011 [53]	Cohort retrospective	BSI	*E. coli* and *Klebsiella*			100	Any	Ertapenem, $n = 73$	Imipenem-meropenem, $n = 171$	Mortality	Crude unadjusted	12/73 vs. 30/171, p 1.0			H
Chopra 2012 [43]	Cohort retrospective	BSI	Enterobacterales	25.5		100	Targeted	Cefepime, $n = 31$	Other than cefepime, $n = 79$	Mortality	OR adjusted	0.8	0.34	2.29	M
Chopra 2012 [43]	Cohort retrospective	BSI	Enterobacterales	25.5		100	Targeted	Carbapenem, $n = 78$	Other than carbapenem, $n = 32$	Mortality	OR adjusted	0.5	0.25	1.21	M
Collins 2012 [50]	Cohort retrospective	BSI	Enterobacterales		41.4	100	Empirical	Ertapenem, $n = 24$	Imipenem or meropenem, $n = 103$	Mortality	OR adjusted	0.82	0.17	3.81	M
Collins 2012 [50]	Cohort retrospective	BSI	Enterobacterales		41.4	100	Targeted	Ertapenem, $n = 72$	Imipenem OR meropenem, $n = 132$	Mortality	OR adjusted	0.5	0.12	2.1	M
Rodríguez-Baño 2012 [31]	Cohort prospective	BSI	*E. coli*	12.6	41.9	100	Empirical	BLBLI, $n = 72$	Carbapenem, $n = 31$	Mortality	HR adjusted	0.93	0.25	3.51	M
Rodríguez-Baño 2012 [31]	Cohort prospective	BSI	*E. coli*	8.7	41.9	100	Targeted	BLBLI, $n = 54$	Carbapenem, $n = 120$	Mortality	HR adjusted	0.76	0.28	2.07	M
Vazquez 2012 [83]	Subgroup analysis of RCT	UTI	Enterobacterales		100	7.3	Targeted	Ceftazidime-avibactam, $n = 7$	Imipenem, $n = 11$	Microbiological cure	Crude	6/7 vs. 9/11, NS			L
Wu 2012 [51]	Cohort prospective	BSI	*E. coli*	16.3	38.8	100	Targeted	Ertapenem, $n = 27$	Imipenem-meropenem, $n = 22$	Mortality	HR adjusted	0.02	0.001	1.1	H
Yang 2012 [56]	Cohort retrospective	BSI	*Klebsiella*	50.9	0	100	Targeted	Flomoxef, $n = 19$	Carbapenem, $n = 23$	Mortality	OR adjusted	3.52	1.19	58.17	H

(*continued on next page*)

Table 3 (*continued*)

Author year	Design	Infection/s included	Pathogen	% ICU	% UTI	% BSI	Treatment phase	Group 1	Group 2	Outcome measured	Statistic used	Effect estimate	CI low	CI high	Risk of bias
Doi 2013 [76]	Cohort retrospective	UTI	Enterobacterales		100	36.3	Targeted	Cefmetazole, $n = 10$	Carbapenem, $n = 12$	Clinical cure	Crude unadjusted	9/10 vs. 12/12, p 0.46			H
Kang 2013 [70]	Cohort retrospective	BSI	*E. coli*		39.1	100	Targeted	Aminoglycoside, $n = 5$	Carbapenem, $n = 61$	Mortality	Crude unadjusted	0/5 vs. 6/61			H
Lee 2013 [81]	Cohort retrospective	BSI	Enterobacterales		78	100	Targeted	Cefepime, $n = 17$	Carbapenem, $n = 161$	Mortality	OR adjusted	9.93	2.77	31.91	M
Lee 2013 [81]	Cohort retrospective	UTI	Enterobacterales		100	4	Any	Non-carbapenems, $n = 23$	Carbapenem, $n = 4$	Clinical cure	Crude unadjusted	23/23 vs. 4/4			H
Lee 2013 [81]	Cohort retrospective	UTI	Enterobacterales		100	4	Any	Non-carbapenems, $n = 23$	Carbapenem, $n = 4$	Relapse	Crude unadjusted	1/23 vs. 0/4			H
Tamma 2013 [61]	Cohort retrospective	Any	Enterobacterales	57.8		48.7	Targeted	Cefepime, $n = 46$	Meropenem, $n = 32$	Mortality	OR adjusted	0.63	0.23	2.11	H
To 2013 [46]	Cohort retrospective	BSI	*E. coli*	3.9	43.6	100	Targeted	Non-carbapenem, $n = 52$	Carbapenem, $n = 91$	Mortality	Crude unadjusted	6/52 vs. 10/91, p 1.0			H
To 2013 [46]	Cohort retrospective	BSI	*E. coli*	3.9	43.6	100	Targeted	Non-BLBLI, $n = 122$	BLBLI, $n = 21$		Crude unadjusted	13/122 vs. 3/21, p 0.626			H
Blanchette 2014 [62]	Case-control, matched	Any	Enterobacterales	18.7	31.2	20.8	Targeted	Cefepime, $n = 32$	Ertapenem, $n = 16$	Clinical cure	Matched	88% vs. 69%, p 0.138			H
Falcone 2014 [44]	Cohort retrospective	BSI	Enterobacterales	37.2	12.8	100	Targeted	Non-carbapenem	Carbapenem	Mortality	Crude unadjusted	54.3% vs. 28.5%, p 0.02			H
Falcone 2014 [44]	Cohort retrospective	BSI	Enterobacterales	37.2	12.8	100	Empirical	Non-carbapenem, $n = 52$	Carbapenem, $n = 42$	Mortality	Crude unadjusted	15/52 vs. 20/42, p 0.08			H
Park 2014 [82]	Cohort retrospective	UTI	*E. coli*	13.8	100	34.2	Targeted	Non-carbapenem containing regimen, $n = 67$	Carbapenems, $n = 85$	Microbiological failure	HR adjusted	0.99	0.31	3.19	M
Park 2014 [82]	Cohort retrospective	UTI	*E. coli*	13.8	100	34.2	Targeted	Non-carbapenem containing regimen, $n = 67$	Carbapenems, $n = 85$	Clinical failure	HR adjusted	1.05	0.24	4.62	M
Pilmis 2014 [77]	Cohort retrospective	Any	Enterobacterales		75.5	24.5	Targeted	Non-carbapenem, $n = 22$	Carbapenem, $n = 31$	Clinical cure	Crude unadjusted	22/22 vs. 30/31, NS			H
Pilmis 2014 [77]	Cohort retrospective	Any	Enterobacterales		75.5	24.5	Targeted	Non-carbapenem, $n = 22$	Carbapenem, $n = 31$	Relapse	Crude unadjusted	3/22 vs. 7/31, NS			H
Siedner 2014 [64]	Cohort retrospective	BSI	*Enterobacter*	24	7	100	Empirical	Cefepime, $n = 28$	Carbapenem, $n = 32$	Microbiological cure	Crude unadjusted	5/28 vs. 6/32			H
Tsai 2014 [26]	Cohort retrospective	BSI	*Proteus*		51.1	100	Not specified	Piperacillin-tazobactam, $n = 13$	Carbapenem, $n = 21$	Mortality	OR adjusted	4.38	0.35	54.9	H
Harris 2015 [23]	Cohort retrospective	BSI	*E. coli* and *Klebsiella*	14.9	46.8	100	Targeted	BLBLI, $n = 24$	Carbapenem, $n = 23$	Mortality	HR adjusted	0.91	0.13	6.28	H
Lee 2015 [63]	Cohort retrospective	BSI	*Enterobacter*		21.9	100	Targeted	Cefepime, $n = 72$	Carbapenem, $n = 72$	Mortality	Crude unadjusted	19/72 vs. 16/72, p 0.7			H
Lee 2015 [57]	Cohort retrospective	BSI	*E. coli* and *Klebsiella*		22.6	100	Targeted	Flomoxef, $n = 132$	Carbapenem, $n = 257$	Mortality	OR adjusted	1.4	0.5	4.2	M
Matsumura 2015 [58]	Cohort retrospective	BSI	*E. coli*		52.8	100	Empirical	Cefmetazole or flomoxef, $n = 26$	Carbapenem, $n = 45$	Mortality	HR adjusted	0.87	0.11	6.52	H
Matsumura 2015 [58]	Cohort retrospective	BSI	*E. coli*		52.8	100	Targeted	Cefmetazole or flomoxef, $n = 59$	Carbapenem, $n = 54$	Mortality	HR adjusted	1.04	0.24	4.49	H
Ofer-Friedman 2015 [41]	Cohort retrospective	BSI	Enterobacterales		0	100	Targeted	Piperacillin-tazobactam, $n = 10$	Carbapenem, $n = 69$	Mortality	OR adjusted	7.9	1.2	53	H
Solomkin 2015 [255]	Subgroup analysis of RCT	IAI	Enterobacterales		0	2.5	Targeted	Ceftolozane-tazobactam + metronidazole, $n = 24$	Meropenem, $n = 26$	Clinical cure	Crude	23/24 (95.8%) vs. 23/26 (88.5%), NS			L
Tamma 2015 [25]	Cohort retrospective	BSI	Enterobacterales	13.8	20.6	100	Empirical	Piperacillin-tazobactam, $n = 103$	Carbapenem, $n = 110$	Mortality	OR adjusted	1.92	1.07	3.45	M
Wagenlehner 2015 [86]	Subgroup analysis of RCT	UTI	Enterobacterales		100	7.7	Any	Ceftolozane-tazobactam, $n = 61$	Levofloxacin, $n = 57$	Clinical cure	Crude absolute difference	55/61 (90.2%) vs. 42/57 (73.7%), difference 16.5% (95% CI 2.6–30.2)			H
Carmeli 2016 [84]	Subgroup analysis of RCT	UTI	Enterobacterales		100	3.5	Targeted	Ceftazidime-avibactam, $n = 130$	Best available treatment, $n = 132$	Microbiological cure	Crude	107/130 (82.3%) vs. 85/132 (64.4%), p 0.002			L
Carmeli 2016 [84]	Subgroup analysis of RCT	UTI	Enterobacterales		100	3.5	Targeted	Ceftazidime-avibactam, $n = 130$	Best available treatment, $n = 132$	Clinical cure	Crude	120/130 (92.3%) vs. 124/132 (93.9%), NS			L
Carmeli 2016 [84]	Subgroup analysis of RCT	IAI	Enterobacterales		0	0	Targeted	Ceftazidime-avibactam (+metronidazole), $n = 9$	Best available treatment, $n = 10$	Microbiological cure	Crude	7/9 vs. 5/10, NS			M
Dizbay 2016 [28]	Cohort retrospective	UTI	*E. coli* and *Klebsiella*		100		Targeted	Piperacillin-tazobactam, $n = 60$	Ertapenem, $n = 170$	Microbiological cure	Crude unadjusted	60/60 vs. 170/170, NS			H
Fukuchi 2016 [59]	Cohort retrospective	BSI	Enterobacterales	31.8	50.7	100	Targeted	Cefmetazole, $n = 26$	Carbapenem, $n = 43$	Mortality	Crude unadjusted	1/26 vs. 5/43			H

Gutiérrez-Gutiérrez 2016 [22]	Cohort retrospective	BSI	Enterobacterales	10.7	46	100	Empirical	BLBLI, $n = 170$	Carbapenem, $n = 195$	Mortality	OR adjusted	0.55	0.25	1.18	M
Gutiérrez-Gutiérrez 2016 [22]	Cohort retrospective	BSI	Enterobacterales	10.7	46	100	Empirical	BLBLI, $n = 170$	Carbapenem, $n = 195$	Clinical cure	OR adjusted	1.37	0.69	2.76	M
Gutiérrez-Gutiérrez 2016 [22]	Cohort retrospective	BSI	Enterobacterales	11	45	100	Targeted	BLBLI, $n = 92$	Carbapenem, $n = 509$	Mortality	OR adjusted	0.59	0.19	1.71	M
Gutiérrez-Gutiérrez 2016 [22]	Cohort retrospective	BSI	Enterobacterales	11	45	100	Targeted	BLBLI, $n = 92$	Carbapenem, $n = 509$	Clinical cure	OR adjusted	1.61	0.58	4.86	M
Gutiérrez-Gutiérrez 2016b [52]	Cohort retrospective	BSI	Enterobacterales	13.8	47.2	100	Empirical	Ertapenem, $n = 32$	Meropenem-imipenem, $n = 163$	Clinical cure	OR adjusted	1.87	0.24	20.08	M
Gutiérrez-Gutiérrez 2016b [52]	Cohort retrospective	BSI	Enterobacterales	12.6	45.8	100	Targeted	Ertapenem, $n = 205$	Meropenem-imipenem, $n = 304$	Mortality	OR adjusted	0.93	0.43	2.03	M
Gutiérrez-Gutiérrez 2016b [52]	Cohort retrospective	BSI	Enterobacterales	12.6	45.8	100	Targeted	Ertapenem, $n = 205$	Meropenem-imipenem, $n = 304$	Clinical cure	OR adjusted	1.04	0.44	2.5	M
Mazuski 2016 [93]	Subgroup analysis of RCT	IAI	Enterobacterales		0		Targeted	Ceftazidime-avibactam + metronidazole, $n = 44$	Meropenem, $n = 62$	Clinical cure	Crude absolute difference	−3.7	−19.31	10.44	L
Ng 2016 [24]	Cohort retrospective	BSI	*E. coli* and *Klebsiella*	8.6	59	100	Empirical	Piperacillin-tazobactam, $n = 94$	Carbapenem, $n = 57$	Mortality	OR adjusted	0.99	0.45	2.17	M
Veve 2016 [73]	Cohort retrospective	UTI	Enterobacterales	12.9	100	13.5	Targeted	Fosfomycin oral, $n = 89$	Ertapenem, $n = 89$	Failure	OR adjusted	0.59	0.19	1.8	H
Wagenlehner 2016 [85]	Subgroup analysis of RCT	UTI	Enterobacterales		100		Targeted	Ceftazidime-avibactam, $n = 68$	Doripenem, $n = 79$	Microbiological cure	Absolute difference	5	−10.87	20.5	L
Wang 2016 [65]	Retrospective, propensity-matched	BSI	Enterobacterales	29.4	30.8	100	Empirical	Cefepime, $n = 17$	Carbapenem, $n = 51$	Mortality	HR PS-matched and adjusted	2.87	0.88	9.41	M
Cheng 2017 [27]	Cohort retrospective	BSI	Enterobacterales	40	18.8	100	Targeted	Piperacillin-tazobactam, $n = 88$	Meropenem-cefepime, $n = 77$	Mortality	OR adjusted	0.5	0.13	2	H
Cheng 2017 [27]	Cohort retrospective	BSI	Enterobacterales	40	18.8	100	Targeted	Piperacillin-tazobactam, $n = 41$	Meropenem-cefepime, $n = 41$	Microbiological failure	Propensity-matched	8/41 (20%) vs. 4/41 (10%), p 0.26			H
Gudiol 2017 [29]	Retrospective, propensity-matched	BSI	Enterobacterales	18.3	6.9	100	Empirical	BLBLI, $n = 35$	Carbapenem, $n = 35$	Mortality	PS-matched	7/35 vs. 4/35, p 0.99			H
Gudiol 2017 [29]	Retrospective, propensity-matched	BSI	Enterobacterales	18.3	6.9	100	Targeted	BLBLI, $n = 15$	Carbapenem, $n = 15$	Mortality	PS-matched	2/15 vs. 1/15, p 0.32			H
Lo 2017 [67]	Cohort retrospective	BSI	*E. coli* and *K. pneumoniae*		24.7	100	Targeted	Fluoroquinolone, $n = 24$	Carbapenem, $n = 275$	Mortality	OR adjusted	0.18	0.03	0.92	M
Palacios-Baena 2017 [48]	Cohort retrospective	BSI	Enterobacterales	16	40	100	Empirical	Non-carbapenem, mostly aminoglycosides, $n = 86$	Carbapenem, $n = 249$	Mortality	OR adjusted	0.75	0.38	1.48	M
Palacios-Baena 2017 [48]	Cohort retrospective	BSI	Enterobacterales	16	40	100	Empirical	Non-carbapenem, mostly aminoglycosides, $n = 86$	Carbapenem, $n = 249$	Clinical failure	OR adjusted	0.62	0.29	1.36	M
Rattanaumpawan 2017 [54]	RCT	Any	Enterobacterales	4.6	40.9	50	Targeted	Ertapenem, $n = 32$	Group 2 carbapenems, $n = 34$	Mortality	Absolute difference	−20	−39.3	−0.08	M
Rattanaumpawan 2017 [54]	RCT	Any	Enterobacterales	4.6	40.9	50	Targeted	Ertapenem, $n = 32$	Group 2 carbapenems, $n = 34$	Clinical cure	Absolute difference	14	−2.4	31.1	M
Rattanaumpawan 2017 [54]	RCT	Any	Enterobacterales	4.6	40.9	50	Targeted	Ertapenem, $n = 32$	Group 2 carbapenems, $n = 34$	Microbiological cure	Absolute difference	4.1	−5	13.4	M
Seo 2017 [32]	RCT	UTI	*E. coli*		100	22.2	Targeted	Piperacillin-tazobactam, $n = 33$	Ertapenem, $n = 33$	Mortality	Crude	2/33 vs. 2/33			H
Seo 2017 [32]	RCT	UTI	*E. coli*		100	22.2	Targeted	Piperacillin-tazobactam, $n = 33$	Ertapenem, $n = 33$	Clinical cure	Crude	31/33 vs. 32/33, NS			H
Seo 2017 [32]	RCT	UTI	*E. coli*		100	22.2	Targeted	Piperacillin-tazobactam, $n = 33$	Ertapenem, $n = 33$	Microbiological cure	Crude	32/33 vs. 32/33			H
Solomkin 2017 [95]	Subgroup analysis of RCT	IAI	Enterobacterales		0		Any	Eravacycline, $n = 21$	Ertapenem, $n = 18$	Clinical cure	Crude	19/21 (90.5%) vs. 15/18 (83.3%), NS			L
Torres 2017 [89]	Subgroup analysis of RCT	HAP/VAP	Enterobacterales		0		Targeted	Ceftazidime-avibactam, $n = 34$	Meropenem, $n = 41$	Clinical cure	Crude	32/34 (94.1%) vs. 33/41 (80.5%), NS			L
Yoon 2017 [33]	Cohort retrospective	UTI	*E. coli*	24.7	100	15.3	Targeted	Piperacillin-tazobactam, $n = 68$	Ertapenem, $n = 82$	Failure	OR adjusted	0.83	0.35	1.97	M

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Table 3 (*continued*)

Author year	Design	Infection/s included	Pathogen	% ICU	% UTI	% BSI	Treatment phase	Group 1	Group 2	Outcome measured	Statistic used	Effect estimate	CI low	CI high	Risk of bias
Kim 2018 [79]	Cohort retrospective	UTI	Enterobacterales	15	100	9.4	Empirical	Cefepime, $n = 17$	Carbapenem, $n = 89$	Clinical failure	Crude unadjusted	0/17 vs. 0/89			H
Kim 2018 [79]	Cohort retrospective	UTI	Enterobacterales	15	100	9.4	Empirical	Cefepime, $n = 17$	Carbapenem, $n = 89$	Microbiological failure	Crude unadjusted	0/17 vs. 0/89			H
Kim 2018 [79]	Cohort retrospective	UTI	Enterobacterales	15	100	9.4	Empirical	Cefepime, $n = 17$	Carbapenem, $n = 89$	Relapse	Crude unadjusted	0/17 vs. 6/89, NS			H
Ko 2018 [37]	Cohort retrospective	BSI	*E. coli* and *Klebsiella*	33	37	100	Empirical	Piperacillin-tazobactam, $n = 40$; quinolones, $n = 9$	Carbapenem, $n = 183$	Mortality	OR adjusted	1.02	0.99	1.06	M
Meini 2018 [38]	Cohort retrospective	BSI	Enterobacterales	57	57	100	Empirical	BLBLI, $n = 13$	Carbapenem, $n = 19$	Mortality	Crude unadjusted	1/13 vs. 3/19, p 0.396			H
Meini 2018 [38]	Cohort retrospective	BSI	Enterobacterales	57	57	100	Empirical	BLBLI, $n = 13$	Carbapenem, $n = 19$	Clinical cure	Crude unadjusted	1/13 vs. 4/19, p 0.211			H
Ray 2018 [40]	Cohort retrospective	Any	Enterobacterales	100			Empirical	BLBLI, $n = 38$	Carbapenem, $n = 38$	Mortality	Crude unadjusted	21/38 vs. 10/38, p 0.01			H
Kaye 2019 [71]	Subgroup analysis of RCT	UTI	Enterobacterales		100	8.6	Empirical	Piperacillin-tazobactam, $n = 55$	IV fosfomycin, $n = 55$	Clinical cure	Crude	51/55 (93%) vs. 52/56 (93%), NS			L
Kaye 2019 [71]	Subgroup analysis of RCT	UTI	Enterobacterales		100	8.6	Empirical	Piperacillin-tazobactam, $n = 57$	IV fosfomycin, $n = 58$	Microbiological Cure	Crude	27/57 (47%) vs. 32/58 (55%), NS			L
Kollef 2019 [90]	Subgroup analysis of RCT	Ventilated HAP/VAP	Enterobacterales	92	0		Empirical	Ceftolozane−tazobactam, $n = 84$	Meropenem, $n = 73$	Clinical cure	Absolute difference	48/84 (57.1%) vs. 45/73 (61.6%), −4.5 (−19.3 to 10.7)			L
Luyt 2019 [256]	Cohort retrospective	Any	Enterobacterales	100	0.06	0.21	Targeted	Non-carbapenems, $n = 40$	Carbapenem, $n = 67$	Mortality	Crude unadjusted	9/40 vs. 30/67, p 0.02			H
Luyt 2019 [256]	Cohort retrospective	Any	Enterobacterales	100	0.06	0.21	Targeted	non-carbapenems, $n = 40$	Carbapenem, $n = 67$	Relapse	Crude unadjusted	10/40 vs. 15/67, p 0.8			H
Meije 2019 [47]	Cohort retrospective	BSI	Enterobacterales		64	100	Targeted	Non-carbapenem oral (mostly SXT-TMP and ciprofloxacin), $n = 42$	Carbapenem, $n = 59$	Clinical failure	OR adjusted	0.27	0.05	1.61	H
Meije 2019 [47]	Cohort retrospective	BSI	Enterobacterales		64	100	Targeted	Non-carbapenem oral (mostly SXT-TMP and ciprofloxacin), $n = 42$	Carbapenem, $n = 59$	Mortality	Crude unadjusted	2/41 vs. 6/59, p 0.46			H
Namikawa 2019 [39]	Cohort retrospective	BSI	Enterobacterales		100	100	Empirical	Piperacillin-tazobactam, $n = 9$	Carbapenem, $n = 23$	Mortality	Crude unadjusted	2/9 vs. 5/23, NS			H
Namikawa 2019 [39]	Cohort retrospective	BSI	Enterobacterales		100	100	Targeted	Piperacillin-tazobactam, $n = 9$	Carbapenem, $n = 36$	Mortality	Crude unadjusted	1/9 vs. 7/36, NS			H
Nasir 2019 [34]	Cohort retrospective	BSI	*E. coli*		65	100	Empirical	BLBLI, $n = 152$	Carbapenem, $n = 53$	Mortality	Adjusted	Reported as NS			H
Nasir 2019 [34]	Cohort retrospective	BSI	*E. coli*		65	100	Targeted	BLBLI, $n = 89$	Carbapenem, $n = 174$	Mortality	Adjusted	Reported as NS			H
Wagenlehner 2019 [74]	Subgroup analysis of RCT	UTI	Enterobacterales		100	12	Empirical	Meropenem, $n = 60$	Plazomicin, N = 51	Microbiological Cure	Risk difference	7.4	−9.6	23.1	L
Xiao 2019 [36]	Cohort retrospective	Any	*E. coli*	8.8	20	100	Empirical	BLBLI, $n = 95$	Carbapenems, $n = 117$	Mortality	Crude unadjusted	17.9% vs. 12.8%, p = 0.384			H
Zohar 2019 [69]	Cohort retrospective	UTI	Enterobacterales	3.1	100	100	Targeted	Aminoglycoside, $n = 108$	Carbapenem or piperacillin-tazobactam, $n = 85$	Mortality	OR adjusted	0.51	0.24	1.06	M
Zohar 2019 [69]	Cohort retrospective	UTI	Enterobacterales	3.1	100	100	Targeted	Aminoglycoside, $n = 108$	Carbapenem or piperacillin-tazobactam, $n = 85$	Relapse	OR adjusted	1.43	0.58	3.54	M
Harris 2019 + Henserson 2020 [16,20]	RCT	BSI	*E. coli* and *Klebsiella*	7	61	100	Targeted	Piperacillin-tazobactam, $n = 187$	Meropenem, $n = 191$	Mortality	1-sided risk difference, 97.5% CI	8.60%	∞	14.50%	M
Harris 2019 + Henserson 2020 [16,20]	RCT	BSI	*E. ccoli* and *Klebsiella*		100	100	Targeted	Piperacillin-tazobactam, $n = 102$	Meropenem, $n = 128$	Mortality	1-sided risk difference, 97.5% CI	3.70%	∞	10.70%	M
Harris 2019 + Henserson 2020 [16,20]	RCT	BSI	*E. coli* and *Klebsiella*		0	100	Targeted	Piperacillin-tazobactam, $n = 63$	Meropenem, $n = 85$	Mortality	1-sided risk difference, 97.5% CI	14.10%	∞	24.50%	M
Harris 2019 + Henserson 2020 [16,20]	RCT	BSI	*E. coli* and *Klebsiella*			100	Targeted	Piperacillin-tazobactam, $n = 134$	Meropenem, $n = 149$	Mortality	2-sided risk different, 95% CI	5.00%	−1	11.00%	M
Senard 2020 [78]	Cohort retrospective	UTI	*E. coli*		100	27	Targeted	Cefoxitin, $n = 23$	Carbapenem, $n = 27$	Clinical cure	OR adjusted	0.90	0.12	6.70	H
Senard 2020 [78]	Cohort retrospective	UTI	*E. coli*		100	27	Targeted	Cefoxitin, $n = 12$	Carbapenem, $n = 19$	Microbiological cure	OR adjusted	0.85	0.05	14	H
Sharara 2020 [35]	Cohort prospective	UTI	Enterobacterales	26	100	0	Targeted	Piperacillin-tazobactam, $n = 45$	Carbapenem, $n = 141$	Mortality	OR adjusted	0.38	0.05	3.06	M

Sharara 2020 [35]	Cohort prospective	UTI	Enterobacterales	26	100	0	Targeted	Piperacillin-tazobactam, $n = 45$	Carbapenem, $n = 141$	Clinical cure	OR adjusted	1.79	0.5	6.46	M
Sharara 2020 [35]	Cohort prospective	UTI	Enterobacterales	26	100	0	Targeted	Piperacillin-tazobactam, $n = 45$	Carbapenem, $n = 141$	Relapse	OR adjusted	0.75	0.31	1.81	M
Sharara 2020 [35]	Cohort prospective	UTI	Enterobacterales	26	100	0	Targeted	Piperacillin-tazobactam, $n = 45$	Carbapenem, $n = 141$	Resistance selection	OR adjusted	0.16	0.02	1.29	M
Sojo-Dorado 2020 [72] [a]	Subgroup analysis of RCT	UTI	*E. coli*		100	100	Targeted	Meropenem, $n = 42$	IV fosfomycin, $n = 39$	Overall cure	Crude	30/42 (71.4%) vs. 23/39 (59%), NS			L
Sojo-Dorado 2020 [72] [a]	Subgroup analysis of RCT	UTI	*E. coli*		100	100	Targeted	Meropenem, $n = 42$	IV fosfomycin, $n = 39$	Treatment failure	Crude	10/42 (23.8%) vs. 7/39 (17.9%), NS			L
Sojo-Dorado 2020 [72] [a]	Subgroup analysis of RCT	UTI	*E. coli*		100	100	Targeted	Meropenem, $n = 42$	IV fosfomycin, $n = 39$	Mortality	Crude	2/40 (5%) vs. 1/32 (3.1%), NS			M
Delory 2021 [80]	Case–control, matched	UTI	Enterobacterales	7.64	100	32.6	Targeted	Carbapenem, $n = 72$	Temocillin, $n = 72$	Clinical cure	Crude	0.24	0.03	2.20	H
Delory 2021 [80]	Case–control, matched	UTI	Enterobacterales	7.64	100	32.6	Targeted	Carbapenem, $n = 72$	Temocillin, $n = 72$	Mortality	Crude	1.02	0.28	3.67	H
Stewart 2021 [21]	RCT	BSI	Enterobacterales [b]	11.1	19.4	100	Targeted	Piperacillin-tazobactam, $n = 38$	Meropenem, $n = 34$	Mortality	Crude	0/38 (0%) vs. 2/34 (6%), NS			M
Stewart 2021 [21]	RCT	BSI	Enterobacterales [b]	11.1	19.4	100	Targeted	Piperacillin-tazobactam, $n = 38$	Meropenem, $n = 34$	Clinical failure	Crude	8/38 (21%) vs. 4/34 (12%), NS			M
Stewart 2021 [21]	RCT	BSI	Enterobacterales [b]	11.1	19.4	100	Targeted	Piperacillin-tazobactam, $n = 38$	Meropenem, $n = 34$	Microbiological failure	Crude	5/38 (13%) vs. 0/34 (0%), NS			M

Table is sorted by publication year followed by first author alphabetically.
Abbreviations: BLBLI, β-lactam with β-lactamase inhibitor; BSI, bloodstream infections; FQ, fluoroquinolone; GNB, Gram-negative bacteria; HAP, hospital-acquired pneumonia; HR, hazard ratio; ICU, intensive care unit; NS, non-significant; PS, propensity score; Risk of bias H, high; M, moderate; L, low; RR, risk ratio; SXT-TMP, sulfamethoxazole-trimethoprim; UTI, urinary tract infections; VAP, ventilator-associated pneumonia.
[a] Additional data provided by the authors.
[b] Presumed Amp-C β-lactamase-producing Enterobacterales.

variably reporting also secondary outcomes. The largest study included 365 patients for the empirical treatment and 601 patients for targeted treatment [22], but most included a few dozen patients (Table 3). None of the studies showed a significant difference between groups, except for a small study at high risk of bias showing higher unadjusted mortality with BLBLI including all Enterobacterales [41]. None of the studies were at low risk of bias; 13 were classified at moderate risk, when using an adjusted analysis with a minimal sample size allowing some adjustment and seven at high risk, mostly reporting crude associations. Hence, there is a large bulk of observational, real-life, data showing no differences in mortality and other outcomes between BLBLI and carbapenems for the treatment for 3GCephRE BSI. These data are highly limited by small samples sizes that do not allow for full adjustment for indication bias, severity of infection, different bacteria and ESBL types, sources of infection and the interaction between types of bacteria and source of infection. Different susceptibility testing methods and definitions of 3GCephRE were used in different studies. The overall certainty of the evidence for the lack of advantage for carbapenems from observational studies was judged as low for low-risk BSI, and very low for high-risk BSI.

Carbapenems versus non-carbapenems and BLBLI versus non-BLBLI. Nine retrospective observational studies compared carbapenems with any other non-carbapenem antibiotic (carbapenem-sparing regimen); two addressed empirical treatments and all but one analysed the targeted treatment phase [30,42–49]. The carbapenem-sparing regimens included mainly BLBLI, quinolones and aminoglycosides. Four studies reported an adjusted association and none of these found a significant outcome difference between carbapenems and non-carbapenems, but the sample sizes were small and residual differences between groups remained despite adjustment (moderate-risk to high-risk bias) [43,47–49]. Odds ratios for mortality tended in favour of carbapenems in two studies [43,49], clinical failure was in favour of non-intravenous carbapenem-sparing antibiotics in one [47] and in the largest study (249 patients receiving empirical carbapenems compared with 86 patients receiving mainly aminoglycosides), there was no significant difference between groups with respect to mortality and clinical failure [48].

Three studies compared old BLBLI with a comparator regimen [27,42,46]. A single study using propensity score matching showed numerically better outcomes with a carbapenem or cefepime compared with piperacillin-tazobactam as targeted treatment for AmpC-β-lactamase-producing Enterobacterales, but with a small sample and no statistically significant difference between groups [27]. All studies were at high risk of bias precluding inferences for this comparison.

This is a small body of observational evidence further supporting no significant advantage to carbapenems in the real-life treatment of 3GCephRE BSI, but the certainty of this evidence is very low.

Ertapenem versus imipenem/meropenem. Four observational studies [50–53] and one small RCT [54] compared ertapenem with imipenem or meropenem, mostly as targeted therapy for BSI caused by any Enterobacterales. The studies included BSI of different sources, with UTI comprising 40%–47% of the patients in all studies. The RCT included also non-bacteraemic infections and found significantly lower mortality with ertapenem [54]. The other studies did not find a significant difference between the different carbapenems. Although most reported an adjusted analysis, the risk of bias was moderate to high because there was a large difference between groups at baseline, with ertapenem used for less severe infections or prescribed as de-escalation therapy after clinical improvement in studies evaluating targeted therapy. The overall certainty of the evidence showing similar or better

outcomes for ertapenem and imipenem/meropenem for 3GCephRE BSI was moderate.

Cephamycins and cefepime. Cephamycins may be active against ESBL-producing 3GcephRE. Five retrospective observational cohort studies evaluated cefmetazole or flomoxef versus carbapenems for 3GCephRE BSI (27 to 389 patients per study) [55–59]. All evaluated mortality. In the largest study including 389 patients, overall, no association was found between targeted flomoxef therapy and mortality; but when flomoxef's MIC were elevated within the susceptible range (2–8 mg/L), flomoxef was associated with mortality compared with carbapenems (adjusted OR 5.7; 95% CI 1.9–16.8) [57]. Another small study of 42 patients with dialysis access-related ESBL-*Klebsiella* spp. BSI showed higher mortality with targeted flomoxef compared with carbapenems, but most patients did not receive *in vitro* covering therapy in the first 5 days and appropriate adjustment was not possible considering the sample size [56]. The overall certainty of the evidence for a possible advantage of carbapenems over cephamycins was very low.

Cefepime may be active against AmpC-producing 3GcephRE. Seven retrospective observational cohort studies evaluated cefepime versus carbapenems [60–65] or a non-cefepime regimen [43]. Variation in results depending on resistance mechanism was found, with higher mortality sometimes reported with cefepime for ESBL infections and no difference in outcomes in studies specifically addressing AmpC producers. Two studies from the same group in Taiwan found an association between cefepime treatment and mortality [60,63]. In a study including 144 patients with cephalosporin-resistant *Enterobacter* spp. infections, overall there was no significant association, but in a very small subgroup of patients with higher cefepime MIC in the susceptible dose-dependent category, mortality was higher with cefepime (5 of 7 versus 2 of 11, p 0.045) [63]. In a study of 178 patients with ESBL-producing Enterobacterales BSI, definitive treatment with cefepime administered only to 17 patients was associated with higher mortality both in multivariate analysis and a propensity-score matched analysis [60]. The other studies were smaller and found no significant difference between cefepime and carbapenems or comparator antibiotics. Most studies were at high risk of bias and, considering serious inconsistency, there was very low certainty of evidence for no difference between cefepime and carbapenems or inferiority of cefepime with high MIC compared with carbapenems.

Other antibiotics. Quinolones were examined individually [42,66,67] or as part of a general comparator group [45] in five retrospective cohort studies. In a single study reporting an adjusted analysis for mortality with targeted quinolone treatment (24 patients) compared with carbapenems, quinolone treatment was associated with lower mortality [67]. The quinolone group in all studies was very small (4–24 patients) and this analysis is a priori very difficult to analyse in an observational design, because quinolones, administered orally with good bioavailability, were given as stepdown therapy to stable patients. As a result, there is no direct evidence on targeted quinolone therapy for 3GcephRE BSI, but favourable effects were observed in studies assessing Gram-negative bacteraemia in general, where a proportion of patients is expected to have had 3GcephRE BSI [68].

Aminoglycosides were examined specifically in a single study [69] and as part of a general comparator group in two studies [42,70]. In the single study reporting an adjusted analysis (moderate risk of bias), aminoglycosides as targeted therapy for BSI of urinary tract source were not significantly different from carbapenems or piperacillin-tazobactam, but with large confidence intervals [69]. Given the paucity of data and observational design, there is very-low-certainty evidence for aminoglycoside treatment for bacteraemic UTI.

Complicated urinary tract infections with or without bacteraemia. Intravenous fosfomycin was compared with piperacillin-tazobactam (ZEUS [71]) or meropenem (FOREST [72]) in two RCT. The ZEUS trial included patients with cUTI or acute pyelonephritis, including few patients with BSI, and the FOREST trial included patients with bacteraemic cUTI caused by *E. coli*. Both trials showed no significant differences in clinical or microbiological cure between intravenous fosfomycin and comparators in the subgroup of patients with cephalosporin-resistant or ESBL-producing Enterobacterales. In the FOREST trial, 6/70 (8.6%) patients in the intravenous fosfomycin arm developed heart failure (compared with 1/73 with meropenem). The trials were not powered to show non-inferiority in this subgroup, but together provide high-certainty evidence for treatment of cUTI with intravenous fosfomycin, in patients without septic shock, with or without bacteraemia. Safety should be considered among patients at risk for heart failure. Oral fosfomycin was compared with ertapenem for oral stepdown or outpatient therapy in an observational study in patients with mostly complicated non-bacteraemic UTI caused by ESBL-producing Enterobacterales [73]. The study was at high risk of bias due to the large baseline differences between groups and did not reveal a significant difference between 89 patients treated with fosfomycin and 89 treated with ertapenem (very low certainty of evidence).

Plazomicin was not significantly different from meropenem in a subgroup analysis of an RCT including cUTI caused by 3GCephRE Enterobacterales and reporting on microbiological cure, but with broad confidence intervals (risk difference 7.4, 95% CI −9.6 to 23.1, low risk of bias) [74]. Together with the retrospective cohort study finding no significant advantage in mortality or relapse for carbapenem or piperacillin-tazobactam over aminoglycosides given as targeted treatment for bacteraemic UTI (moderate risk of bias) [69], there was moderate-certainty evidence for aminoglycoside treatment of cUTI. The risk for nephrotoxicity increases after 7 days of aminoglycoside therapy [75], so shorter durations are recommended.

Other carbapenem-sparing treatments were evaluated in several studies. Carbapenems versus BLBLI were evaluated in one RCT [32] at high risk of bias due to small sample size and baseline differences between groups and several observational studies (moderate to high risk of bias) [28,33,35]. All studies evaluated the targeted treatment of pyelonephritis and assessed variable clinical and microbiological cure and mortality; one study assessed relapse and resistance selection [35]. None of the studies found statistically significant differences between BLBLI and carbapenems, supporting moderate-certainty evidence for BLBLI in the treatment of pyelonephritis caused by 3GCephRE.

Cephamycins and cefepime were compared with carbapenems in several retrospective cohort studies [76–79]. None found statistically significant differences between groups, in very small sample sizes (the cephalosporin group ranging from 10 to 23 patients). All studies were at high risk of bias, together providing low-certainty evidence for cephamycins and cefepime for the treatment of pyelonephritis caused by 3GCephRE.

Temocillin provided for more than 50% of the time of effective antibiotic therapy duration was compared with carbapenems in a matched case–control study (144 patients) [80]. The study showed no significant difference between treatment groups in clinical cure, relapse and mortality, but despite matching there were significant differences between groups that were not adjusted for, and the confidence intervals were large, providing very low-certainty evidence for temocillin in cUTI.

Finally, two retrospective studies did not reveal significant differences in clinical cure and microbiological outcomes between carbapenems and any non-carbapenem antibiotic, with high risk of

bias [81,82]. Different carbapenem-sparing options, mainly BLBLI, were found to achieve similar outcomes to carbapenems in the treatment of complicated UTI (moderate-certainty evidence).

Antibiotic approval RCT compared ceftazidime-avibactam with carbapenems or best available therapy in subgroup analyses of 3GCephRE UTI [83–85]. They showed no significant differences between groups in clinical failure, with an advantage to ceftazidime-avibactam in microbiological cure in one trial (high certainty of evidence) [84]. Ceftolozane-tazobactam was evaluated in a subgroup analysis of an RCT compared with levofloxacin (118 patients) [86]. An advantage to ceftolozane-tazobactam in clinical cure was observed but was at high risk of bias because resistance to levofloxacin was high (26.7% (195/731) of all Gram-negatives in the trial). However, ceftazidime-avibactam and ceftolozane-tazobactam are not antibiotics of primary interest for the management of UTI and their use should be reserved for extremely drug resistant (XDR) infections such as CR-GNB.

Hospital-acquired and ventilator-associated pneumonia. Several RCT that included patients with hospital-acquired/ventilator-associated pneumonia (HAP/VAP) reported on subgroup analyses of patients with pneumonia caused by 3GCephRE, comparing imipenem and tigecycline (41 patients overall) [87], imipenem and cefepime (23 patients) [88], meropenem and ceftazidime-avibactam (75 patients) [89], and meropenem and ceftolozane-tazobactam (157 patients) [90]. An additional small retrospective cohort study reporting unadjusted results compared imipenem and cefepime [91]. The FDA warns against tigecycline for HAP/VAP, although not addressing specifically 3GCephRE [92]. The evidence was of very low certainty for tigecycline and cefepime, low certainty for ceftazidime-avibactam compared with carbapenems and high certainty for non-inferiority of ceftolozane-tazobactam versus meropenem in the treatment of HAP/VAP caused by 3GCephRE.

Intra-abdominal infections. Some of the syndrome-directed IAI antibiotic-approval RCT reported on the subgroup of patients with infections caused by 3GCephRE. Ceftazidime-avibactam was compared with meropenem (overall 106 patients with 3GCephRE) [93] and with best-available therapy (mostly carbapenem, overall 19 patients with 3GCephRE) [84]; ceftolozane-tazobactam (with metronidazole) was compared with meropenem (50 patients with ESBL-producing Enterobacterales) [94]; and eravacycline was compared with ertapenem (39 patients with ESBL-producing Enterobacterales) [95]. Clinical or microbiological outcomes were similar between groups in all studies. These trials, showing non-inferiority of the new antibiotics compared with carbapenems, were not powered to prove non-inferiority in the subgroups of patients with 3GCephRE. Hence, there is moderate certainty for ceftazidime-avibactam in the treatment of IAI caused by 3GCephRE and very low certainty of evidence for eravacycline and ceftolozane-tazobactam.

2. Carbapenem-resistant Enterobacterales

Question 2.1: What is the antibiotic of choice for CRE

Recommendations

- For patients with severe infections due to CRE, we suggest meropenem-vaborbactam or ceftazidime-avibactam if active *in vitro* (**conditional recommendation for use, moderate and low certainty of evidence, respectively**).
- For patients with severe infections due to CRE-carrying metallo-β-lactamases (MBL) and/or resistant to all other antibiotics, including ceftazidime-avibactam and meropenem-vaborbactam, we conditionally recommend treatment with cefiderocol (**conditional recommendation for use, low certainty of evidence**).
- For patients with non-severe infections due to CRE, under the consideration of antibiotic stewardship, we consider the use of an old antibiotic, chosen from among the *in vitro* active on an individual basis and according to the source of infection, as good clinical practice (**good practice statement**). For patients with cUTI, we suggest aminoglycosides, including plazomicin, over tigecycline (**conditional recommendation for use, low certainty of evidence**).
- We suggest that tigecycline not be used for BSI and HAP/VAP; if necessary, in patients with pneumonia, clinicians may use high-dose tigecycline (**conditional recommendation against use, low certainty of evidence**).
- There is no evidence to recommend for or against the use of imipenem-relebactam and fosfomycin monotherapies for CRE at the time of writing.

Review of the evidence

Evidence on antibiotic treatment of CRE derives mostly from observational retrospective studies including patients with mixed type of infections, mostly BSI with heterogeneous sources and various degrees of clinical severity. Combination treatments were rarely reported in terms of individual antibiotics, dosage and duration. Criteria for patient enrolment included both phenotypic and genotypic testing, thus leading to the inclusion of strains with various patterns of antimicrobial resistance, ranging from residual susceptibility to carbapenems to pan-resistant strains. Most of the studies included infections caused by KPC-producing *K. pneumoniae* and very few data were available for OXA-48 producers, MBL non-carbapenemase producers and CRE other than *K. pneumoniae*.

Ceftazidime-avibactam. Ceftazidime-avibactam is active *in vitro* against Ambler class A (KPC) and certain class D (OXA-48) carbapenemases but is inactive against MBL producers. Evidence for recommending the use of ceftazidime-avibactam over other antibiotics for the treatment of CRE infections relies only on observational studies [96–100]. In a study using inverse probability of treatment weighting for adjustment of the comparison between patients treated with ceftazidime-avibactam versus those treated with colistin (before ceftazidime-avibactam was available) for CRE infections there was an overall probability for a better outcome with ceftazidime-avibactam of 64% (95% CI 57%–71%) [96]. The study included mainly CR-*K. pneumoniae* infections, 46% with BSI, and used an ordinal outcomes analysis (DOOR and partial credit) considering survival, discharge to home and renal failure. Concordant results were shown in another cohort of KPC-producing *K. pneumoniae* BSI from Italy, where patients failing previous treatment were treated with ceftazidime-avibactam-containing regimens, showing higher survival in a propensity-score-adjusted analysis compared with non-ceftazidime-avibactam-based regimens [99]. Most of patients in both studies received ceftazidime-avibactam in combination with other agents. One study from Saudi Arabia retrospectively collected patients with infections caused by OXA-48 producers, showing no difference in mortality among inpatients treated with ceftazidime-avibactam compared with polymyxin- or tigecycline-containing regimens [100].

Resistance to ceftazidime-avibactam in bla_{KPC-2} and bla_{KPC-3} isolates, retaining the MDR phenotype, has been described regardless of previous exposure to ceftazidime-avibactam or during treatment [101–105]. The mechanisms described include increased hydrolysis of ceftazidime and amino acid insertion, substitution or deletion in the Ω loop of the KPC protein, disrupting the ability of ceftazidime-avibactam to bind at the active site [103,106,107]. In different studies, emergence of resistance during or following

therapy occurred in up to 3.7%–8.1% of ceftazidime-avibactam-treated patients [101,108]. More recently in Greece, a novel plasmid-borne Vietnamese extended-spectrum β-lactamase (VEB)-25 has been described in ceftazidime-avibactam-resistant CR-*K. pneumoniae* strains, independent of ceftazidime-avibactam exposure [109]. VEB-25 seemed to decrease avibactam's ability to reduce ceftazidime's MIC. In an outbreak including eight patients with ceftazidime-avibactam-resistant KPC-2-producing *K. pneumoniae* ST-147 in two Greek intensive care units (ICU), horizontal transmission was suspected [110].

Given the observational study designs, the focus on *K. pneumoniae* and the combination treatments used, there is low-certainty evidence of an advantage of ceftazidime-avibactam over polymyxins for CRE susceptible to ceftazidime-avibactam.

Meropenem-vaborbactam. Vaborbactam is a novel cyclic boronic acid inhibitor that restores meropenem activity against producers of numerous class A and C β-lactamases, but it is inactive against MBL and OXA-48 producers [111]. Clinical efficacy of meropenem-vaborbactam in patients with infections due to CRE was tested in an RCT (Tango-II) in comparison with best available treatment (BAT) monotherapy or combinations of polymyxins, carbapenems, aminoglycosides or tigecycline; or monotherapy with ceftazidime-avibactam. Forty-seven patients (randomized 2:1) were included in the final analysis and significantly improved cure rates at the end of treatment were found in the meropenem-vaborbactam group (65.6% versus 33.3%, p 0.03) with non-significantly lower 28-day mortality (15.6% (5/32) versus 33.3% (5/15), p 0.2) and lower rates of renal-related adverse events [112]. Based on this small study, there is moderate-certainty evidence for an advantage of meropenem-vaborbactam for susceptible CRE compared with the old antibiotics.

Imipenem-relebactam. Relebactam produces a dose-dependent synergy with imipenem against CRE producing KPC or combining AmpC or ESBL with reduced permeability, but it is poorly active against OXA-48 producers [113]. Efficacy and safety of imipenem-relebactam have been proven to be comparable to those of imipenem or piperacillin-tazobactam in RCT enrolling patients with cUTI, cIAI and HAP/VAP; few patients with CR-GNB infections were included in these studies but comparative clinical outcome data for CRE are not available and the numbers are too small for a meaningful analysis [114–117]. A small RCT including 31 patients with CR-GNB infections (RESTORE-IMI 1) compared the efficacy of imipenem-relebactam with the combination of imipenem and colistin; however, only seven patients with CRE infections were included [118]. Given the paucity of data available for imipenem-relebactam against CRE, we cannot make recommendations on imipenem-relebactam for CRE at this time.

Cefiderocol. Although non-inferior to carbapenems for UTI and HAP/VAP caused by carbapenem-susceptible GNB [119,120], conflicting results were observed in an open-label RCT designed to assess the efficacy of cefiderocol for CR-GNB (CREDIBLE-CR). A total of 150 patients with proven/suspected CR-GNB infections were randomized 2:1 to receive cefiderocol versus BAT (mostly polymyxin-based combination). The trial included mainly patients with HAP/VAP and BSI and was not powered to conduct specific hypothesis testing. Mortality was higher in the cefiderocol arm at 28 days (25/101, 24.8% with cefiderocol versus 9/49, 18.4% with BAT) and at end of follow up (34/101, 33.7% versus 9/49, 18.4%, respectively). Clinical and microbiological efficacies of cefiderocol versus BAT were similar. A subgroup analysis of patients with MBL-producing CR-GNB infections showed statistically non-significant higher cure and microbiological eradication rates for cefiderocol (16 patients) versus BAT (seven patients), but mortality was not shown, and the analysis did not separate CRE from other CR-GNB. A post-hoc analysis by baseline pathogen revealed that the mortality difference was observed among patients with CRAB infections, but among patients with CR-*K. pneumoniae*, mortality at end of follow up was 6/28 (21.4%) with cefiderocol versus 4/15 (26.7%) for BAT (and 1/6 versus 0/3 for CR-*E. coli*, respectively) [121]. Based on these small subgroup analyses, we conclude on low-certainty evidence for non-inferiority of cefiderocol compared with other antibiotics for MBL-producing CRE.

Aztreonam. There is no clinical experience evaluating the use of aztreonam monotherapy in the treatment of CRE infections. Aztreonam is uniquely active against MBL-producing CRE [122], but as monotherapy it does not cover other broad-spectrum β-lactamases or carbapenemases, frequently co-produced by such strains. Aztreonam-avibactam is being tested in phase 3 trials and is not currently considered in our guideline because it has not been FDA/EMA approved.

Polymyxin. Comparative data on efficacy of polymyxins versus other antibiotics for the treatment of CRE are difficult to evaluate because of the lack of active comparators, concomitant use of other active agents and the frequently suboptimal dosing strategy adopted in the existing studies. Higher mortality among patients with CRE infections was observed with colistin compared with ceftazidime-avibactam in a small retrospective study using inverse probability of treatment weighting adjustment [96]. Conversely, lower 30-day mortality was shown in critically ill patients with KPC-producing *K. pneumoniae* infections and septic shock treated with a colistin-containing regimen, compared with colistin-free schemes (hazard ratio (0.21) 95% CI 0.05–0.72) [123]. However, colistin was administered as part of combination therapy regimens in both studies. Hence, there is no evidence on the comparative efficacy of colistin versus other antibiotics for CRE.

Aminoglycosides. Two studies from the prospective CRaCKle cohort suggest better clinical outcomes with aminoglycoside-containing regimens compared with tigecycline-containing regimens [124,125]. Van Duin et al. analysed the results from 157 CR-*K. pneumoniae* infections with a urinary source (20% severe infections) and recorded better clinical cure when compared with tigecycline-based regimens (adjusted HR 5.19, 95% CI 2.03–14.13), whereas no benefit was observed when compared with colistin-containing regimens (adjusted HR 1.92, 95% CI 0.63–5.76) [125]. Similarly, Messina et al. observed a higher rate of hospital readmission at 90 days in patients treated with tigecycline-based combinations when compared with aminoglycoside-containing combinations (adjusted HR 4.33, 95% CI 1.67–11.6), in a study where cUTI was the most common source (67% of patients) and 8% of patients were bacteraemic [124]. Microbiological cure was better with aminoglycosides compared with tigecycline for cUTI in the USA [126]. Another cohort from Spain describes 50 patients with sepsis due to carbapenem and colistin-resistant *K. pneumoniae* with a prevalent respiratory source where the use of gentamicin in fully susceptible isolates (MIC $\leq$4 mg/L) alone or with tigecycline was associated with significantly higher survival at 30 days (adjusted HR 0.30, 95% CI 0.11–0.84) compared with non-aminoglycoside regimens [127]. Moreover, in a retrospective cohort of kidney transplant patients, amikacin-containing schemes were associated with clinical success for treatment of mixed infections caused by carbapenem- and polymyxin-resistant Enterobacterales (adjusted OR 0.12, 95% CI 0.02–0.64) [128]. The certainty of the evidence for an advantage of aminoglycosides over tigecycline for cUTI was judged as moderate, with insufficient evidence for other comparisons and other sources of infection.

Tigecycline. Three studies showed that tigecycline was inferior to aminoglycosides for cUTI caused by CRE (moderate certainty of the evidence) [124–126]. Two small studies at high risk of bias showed an advantage to polymyxin-based regimens compared with tigecycline-based regimens for CRE BSI [129,130]. Finally, out of three additional studies assessing tigecycline or eravacycline for CRE infections of any source [131–133], a single study showed survival advantage to tigecycline compared with colistin-based therapy for CRE and/or CRAB, explained by the higher severity of patients receiving colistin [132]. Among critically ill patients with MDR-GNB infections treated with different dosages of tigecycline, the only independent predictor of clinical cure was the use of high tigecycline dose in the subgroup of patients with VAP [134]. However, more than 80% of patients in this study received concomitant active antibiotics. A higher dosage of tigecycline (200 mg loading dose followed by 100 mg twice a day) in combination with other drugs was associated with non-significantly higher survival rates also in a cohort of 40 KPC-BSI compared with the standard dosage (100 mg loading dose following by 50 mg twice a day) [135]. Overall, there was low-certainty evidence for the inferiority of tigecycline compared with other antibiotics for cUTI and BSI caused by CRE. There are no studies comparing tigecycline with other antibiotics for HAP/VAP and IAI caused by CRE. If used, high-dosing regimens should be used for HAP/VAP.

Fosfomycin. Potential efficacy of intravenous fosfomycin for CRE has been described in *in vitro* studies and small case series with variable clinical response [136–138]. In a study from China the use of fosfomycin in combination with other antibiotics for treating CRE-BSI was associated with non-significantly higher survival compared with non-fosfomycin-based schemes in an adjusted analysis [139]. There is no evidence for fosfomycin monotherapy for CRE.

Trimethoprim-sulfamethoxazole. Within the already mentioned CRaCKle prospective cohort, a small subgroup of patients with trimethoprim-sulfamethoxazole-susceptible CRE infections received trimethoprim-sulfamethoxazole-based schemes with mortality rates comparable to other treatments. However, in three out of four available follow-up cultures, subsequent isolates were found to be resistant to trimethoprim-sulfamethoxazole [140] trimethoprim-sulfamethoxazole (no evidence for trimethoprim-sulfamethoxazole).

Eravacycline. Eravacycline has an observed two-fold *in vitro* higher activity compared with tigecycline against Gram-negative bacteria; however no patients with CRE were included in the trials that brought to its approval [95,141] (no evidence for eravacycline).

Plazomicin. Efficacy of plazomicin for the treatment of CRE infections was planned to be tested in the CARE-RCT in comparison with colistin (in combination with meropenem or tigecycline, NCT01970371). The sponsor decided to suspend the study after 2 years because of enrolment difficulties. Available results showed that all-cause mortality at 28 days was 8/20 with colistin combination therapy (6/15 with BSI) versus 2/17 with plazomicin combination therapy (1/14 with BSI) [142]. Currently, there is insufficient evidence on plazomicin compared to colistin for CRE.

Question 2.2: Should combination therapy be used for the treatment of CRE?

Recommendations

- For patients with CRE infections susceptible to and treated with ceftazidime-avibactam, meropenem-vaborbactam or cefiderocol, we do not recommend combination therapy (**strong recommendation against use, low certainty of evidence**)
- For patients with severe infections caused by CRE carrying MBL and/or resistant to new antibiotic monotherapies, we suggest aztreonam and ceftazidime-avibactam combination therapy (**conditional recommendation for use, moderate certainty of evidence**).
- For patients with severe infections caused by CRE susceptible *in vitro* only to polymyxins, aminoglycosides, tigecycline or fosfomycin, or in the case of non-availability of new BLBLI, we suggest treatment with more than one drug active *in vitro* (**conditional recommendation for use, moderate certainty of evidence**). No recommendation for or against specific combinations can be provided.
- We suggest that clinicians avoid carbapenem-based combination therapy for CRE infections (**conditional recommendation against use, low certainty of evidence**), unless the meropenem MIC is $\leq$ 8 mg/L, where high-dose extended-infusion meropenem may be used as part of combination therapy if the new BLBLI are not used (**conditional recommendation for use, low certainty of evidence**).
- In patients with non-severe infections or among patients with low-risk infections, under the consideration of antibiotic stewardship, we consider the use of monotherapy chosen from among the *in vitro* active old drugs, on an individual basis and according to the source of infection as good clinical practice (**good practice statement**).

Review of the evidence

Thirty-five studies assessed mortality (all-cause at any timepoint) in patients with CRE infections receiving antibiotic combination versus monotherapy and the results are conflicting [97,123,128,130,139,140,143–171]. Certainty of the evidence was very low because of the observational nature of most of the studies (34 out of 35 studies) and the considerable risk of bias (high in 12 studies; moderate in 14; and low in 9). Most importantly, the study definitions of 'combination therapy' were highly variable, including poorly specified treatment schemes, comprising from two up to five antibiotics with variable *in vitro* activity and different dosages and durations. Adjustment for relevant confounders was seldom available, mostly because of the very small sample sizes.

Single versus multiple-covering therapy. In the few available studies with adequate sample size and adjustment for confounders, the evidence seems to favour combination over monotherapy in terms of better clinical outcomes [123,147,152,159,163,164,172,173]. This advantage emerges mainly in subgroups of patients with more severe disease and when combination is defined as regimens including more than one *in vitro* active antimicrobial. In a large retrospective cohort study including patients with BSI (N = 447) and non-bacteraemic infections (n = 214) caused by KPC-producing *K.*

pneumoniae in Italy, treatment including two or more *in vitro* active antibiotics was associated with lower 14-day mortality (OR 0.52, 95% CI 0.35–0.77) [164]. In the retrospective INCREMENT cohort such combination therapy was associated with lower 30-day mortality among patients with CRE BSI at high risk for death, with an INCREMENT score of 8–15 (n = 166; adjusted HR 0.56, 95% CI 0.34–0.91). Among patients with lower INCREMENT scores (n = 177), combination therapy was not associated with survival (adjusted OR 1.21) 95% CI 0.56–2.56) [152]. Use of two or more *in vitro* active antibiotics (including colistin, tigecycline, gentamicin, carbapenems, rifampin) was independently associated with 30-day survival in retrospective study including 111 critically ill patients with KPC-producing *K. pneumoniae* infections and septic shock [123]. Lower efficacy of a single drug regimen with these drugs has been attributed to the often suboptimal dosage and the unsuitable pharmacokinetics–-pharmacodynamics profile for some infection sites [174–176]. Unfortunately, none of these studies focused on specific antibiotic combinations, so information on which antimicrobials should be included in the treatment scheme cannot be derived even from higher-certainty evidence. When looking at smaller studies analysing specific drugs, polymyxin and tigecycline seemed the antimicrobials for which the addition of a companion drug seems more advisable [143,146,147,151–153,155–157,160,161,164,167,177,178]. Due to the high heterogeneity of treatment included, even in smaller studies, no firm conclusions can be drawn on which companion drug should be preferred when prescribing polymyxin and tigecycline, but treatment with more than one *in vitro* active antibiotic might be beneficial (moderate-certainty evidence).

Carbapenem combination therapy. The inclusion of a carbapenem in the combination scheme for treating carbapenem-resistant infections has been a long-standing matter of debate. Two investigator-initiated RCT, the AIDA and OVERCOME trials, evaluated the efficacy of colistin monotherapy versus colistin-meropenem combination therapy in patients with severe infections caused by CR-GNB, mainly HAP/VAP and BSI [160,179]. Subgroup analysis of patients with CRE infections did not show statistically significant differences in 28-day mortality between colistin monotherapy and colistin-carbapenem combination therapy in both trials: 12/34 (35%) versus 8/39 (21%) (p 0.24) in AIDA [160] and 11/35 (31%) versus 7/36 (19%) (p 0.25) in OVERCOME [179], respectively.

In the retrospective Italian cohort study of patients' BSI and non-bacteraemic infections due to KPC-producing *K. pneumoniae*, combination therapy including a carbapenem was associated with lower 14-day mortality when the meropenem MIC were ≤8 mg/L [164]. A continuation and re-analysis of the same cohort showed a similar association between high-dose carbapenem-containing combinations (6 g/day, 3 hours infusion) and 14-day survival compared with non-carbapenem containing combinations, even when the MICs were higher (≥16 mg/L) [180].

We concluded low-certainty evidence for an advantage of high-dose extended-infusion meropenem-polymyxin combination therapy over polymyxin monotherapy in the treatment of severe infections caused by CRE, mainly KPC-producing *K. pneumoniae*.

Double-carbapenem combination therapy. The rationale for using double-carbapenem therapy for treating CRE infections is based on the higher affinity of ertapenem for carbapenemases and a hypothesis that consumption of the carbapnemases by ertapenem will allow for the action of the other carbapenem. In vitro data for synergistic interactions are conflicting [181,182]. Two observational studies from Italy and one from the USA suggested better survival in patients with invasive KPC infections treated with a double carbapenem regimen when compared with other regimens, even with high carbapenem MICs [183–185]. Lack of adjustment for confounders, small sample size and use of other drugs in the combinations made the authors of these studies conclude that, although promising, this option requires further evaluation (Insufficient evidence).

New antibiotic combination therapies. Five retrospective cohorts enrolled a total of 824 patients from three countries (USA, Spain and Italy) and compared ceftazidime-avibactam in combination with other antibiotics versus ceftazidime-avibactam monotherapy, showing no difference in mortality and clinical failure in mixed infections caused by KPC and OXA-48 producers [99,154,186–188]. The largest study included 577 patients with KPC-producing *K. pneumoniae* infections, mostly BSI, in Italy and showed also that prolonged infusion (≥3 hours) of ceftazidime-avibactam and appropriate renal adjustment were associated with 30-day survival [188], supporting our good practice statement for optimal antibiotic administration schedules.

Ceftazidime-avibactam in combination with aztreonam is active in vitro against a substantial proportion of MBL producers, for which treatment options are lacking [189,190]. Following a small case series reporting on patients with MBL-producing CRE treated with ceftazidime-avibactam-aztreonam [191], an observational prospective study was conducted including 102 patients with MBL-producing CRE bacteraemia (82 NDM-producing strains and 20 VIM-producing strains) treated with ceftazidime-avibactam in combination with aztreonam compared with other *in vitro* covering therapies, mostly combinations [192]. The isolates were mostly non-susceptible to aztreonam alone. Using propensity-score-adjusted multivariable regression, the study showed a significant independent association between ceftazidime-avibactam-aztreonam and lower 30-day mortality (HR 0.37, 95% CI 0.13–0.74), clinical failure and length of hospital stay, providing moderate-certainty evidence for ceftazidime-avibactam in combination with aztreonam against BSI caused by MBL-producing CRE susceptible to the combination. There are currently no standardized antimicrobial susceptibility testing methods recommended or clinical interpretative breakpoints approved for the combination.

In the CREDIBLE RCT [121], an observational post-hoc comparison between patients receiving cefiderocol monotherapy versus cefiderocol combination therapy, clinical and microbiological cure rates were similar, but results were not presented separately for CRE and mortality data were not available. There are no studies addressing the clinical use in monotherapy versus combination of recently marketed antibiotics with activity against CRE (imipenem-relebactam, meropenem-vaborbactam, eravacycline and plazomicin).

Despite numerous results of *in vitro* studies showing reduction in resistance development when polymyxin [7] and ceftazidime-avibactam [193] are combined with other antibiotics, these results are not confirmed in clinical studies. In two retrospective cohort studies of 77 and 577 patients with KPC-producing CRE infections treated with ceftazidime-avibactam, development of resistance to ceftazidime-avibactam occurred in 10.4% and 3.8%, respectively, and was not associated with its use as monotherapy or in combination regimens [186].

3. Carbapenem-resistant *Pseudomonas aeruginosa*

Question 3.1: What is the antibiotic of choice for CRPA

Recommendations

- In patients with severe infections due to DTR-CRPA, we suggest therapy with ceftolozane-tazobactam if active *in vitro* (**conditional recommendation for use, very low certainty of**

evidence). Insufficient evidence is available for imipenem-relebactam, cefiderocol and ceftazidime-avibactam at this time.
- In patients with non-severe or low-risk CRPA infections, under the consideration of antibiotic stewardship, we consider it good clinical practice to use the old antibiotics, chosen from among the *in vitro* active antibiotics on an individual basis and according to the source of infection (**good practice statement**).

Review of the evidence

The clinical evidence on management of DTR-CRPA is highly limited. Data from RCT for the new BLBLI are limited to small subgroup analyses of the registration trials, some of which are based on single patients There are no comparative RCT data on the effect of ceftolozane-tazobactam on CRPA infections, although this is the intended use of the drug. Overall, there is no high-certainty evidence pointing to a preferred antibiotic treatment for CRPA.

New BLBLI. Of the potentially active new BLBLI, only imipenem-relebactam has been tested against CR-GNB in an RCT, in the RESTORE-IMI 1 trial. The trial included patients with HAP, VAP, UTI and IAI caused by CR-GNB, of which CRPA was the most common (16/21 patients allocated to imipenem-relebactam and 8/10 allocated to colistin with imipenem). A favourable overall response to treatment at 28 days, with a definition tailored per infection source, was observed in 13/16 with imipenem-relebactam compared with 5/8 with colistin and imipenem, adjusted difference 3.1 (95% CI −19.8 to 38.2) [118].

Of the RCT evaluating ceftolozane-tazobactam, the trial including patients with nosocomial pneumonia (ASPECT-NP) reported clinical cure among 4/10 versus 2/5 patients with XDR-PA treated with ceftolozane-tazobactam versus meropenem, respectively [90]. Data on CRPA, however, are not available. Treatment with ceftolozane-tazobactam (100 patients) was compared with polymyxins or aminoglycosides (100 patients), among patients with MDR/XDR *P. aeruginosa* mixed infections (mostly pneumonia) in a retrospective cohort study [194]. Clinical cure was higher (adjusted OR 2.63, 95% CI 1.31–5.30) and nephrotoxicity was lower (adjusted OR 0.08, 95% CI 0.03–0.22) with ceftolozane-tazobactam. Aminoglycoside/polymyxins were given mostly in combination therapies, patient selection was unclear, baseline difference between groups could not be fully adjusted and data on carbapenem resistance was not provided (high risk of bias).

Overall, given the paucity of data on effects against CRPA, we conclude on very-low-certainty evidence for non-inferiority of imipenem-relebactam compared with colistin-meropenem combination therapy and superiority of ceftolozane-tazobactam compared with aminoglycoside/polymyxin combination therapies for CRPA infections with no evidence for other new BLBLI.

Other antibiotics. In the CREDIBLE RCT, mortality at the end of the study was similar for patients with baseline monomicrobial CRPA infections for cefiderocol (2/11 patients) compared with BAT (2/11 patients). Clinical cure (7/12 versus 5/10 patients, respectively) and microbiological persistence (4/12 versus 2/10 patients, respectively) were not different, in very small numbers (very-low-certainty evidence for non-inferiority of cefidrocol compared with BAT).

A small, retrospective cohort of 49 patients with nosocomial pneumonia, mostly VAP, caused by CRPA intermediately susceptible to doripenem (MIC 4–8 mg/L), in Thailand compared high-dose, 4-hour infusion of doripenem versus colistin, both combined with fosfomycin. Unadjusted all-cause 30-day mortality was not different; 10/24 versus 10/25, respectively, as were clinical and microbiological cure rates [195]. No clinical comparative studies were found for intravenous fosfomycin or eravacycline.

A before–after retrospective study compared the nephrotoxicity of colistin and polymyxin B among critically ill patients with severe, at-risk infections, caused by MDR *P. aeruginosa* (46 patients) and *A. baumannii* (107 patients), showing higher RIFLE-defined nephrotoxicity with colistin (adjusted HR 2.27, 95% CI 1.35–3.82) [196].

Question 3.2: Should combination therapy be used for the treatment of CRPA?

Recommendations

- Lacking evidence, we cannot recommend for or against the use of combination therapy with the new BLBLI (ceftazidime-avibactam and ceftolozane-tazobactam) or cefiderocol for CRPA infections.
- When treating severe infections caused by CRPA with polymyxins, aminoglycosides, or fosfomycin, we suggest treatment with two *in vitro* active drugs (**conditional recommendation for use, very low certainty of evidence**). No recommendation for or against specific combinations can be provided.
- In patients with non-severe infections or low-risk CRPA infections, under the consideration of antibiotic stewardship, we consider it good clinical practice to use monotherapy chosen from among the drugs active *in vitro*, on an individual basis and according to the source of infection **(good practice statement).**

Review of the evidence

Similar to the choice of monotherapy, there is a paucity of data on combination therapy for DTR-CRPA.

Polymyxin-based combination therapy. Both in the AIDA and OVERCOME RCT comparing colistin with colistin-carbapenem therapy for severe infections caused by CR-GNB there were no significant differences in 28-day mortality in the subgroup of patients with *P. aeruginosa* infections (21 patients in AIDA and 43 in OVERCOME) [160,179]. In a retrospective study evaluating 114 patients with nosocomial pneumonia, including ventilator-associated pneumonia, with isolation of XDR-*P. aeruginosa*, colistin given alone or with a non-active antibiotic was associated with higher mortality than colistin combined with another active antibiotic (adjusted OR 6.63, 95% CI 1.99–22.05) [197]. From other observational studies, the results for the subgroup of patients with CRPA were non-adjusted. In a retrospective study evaluating critically ill patients with mixed infections caused by *P. aeruginosa* there was no difference in 30-day mortality among patients treated with polymyxin compared with polymyxin and a second *in vitro* inactive agent, overall; in a small subgroup of patients with XDR-*P. aeruginosa*, mortality was lower when combinations were used (14/15 dead with monotherapy versus 0/3 with combinations) [198]. In another retrospective analysis, Falagas et al. assessed clinical cure rates comparing colistin monotherapy with different combinations for mixed infections due to MDR-GN. There was no significant difference in outcomes in a small subgroup of patients with MDR-*P. aeruginosa* (9/12 were cured with colistin monotherapy compared with 42/56 with combinations) [199].

There was very low-certainty evidence for an advantage of polymyxin combined with another active antibiotic over polymyxin alone or combined with inactive antibiotics. There was low-certainty evidence on the lack of advantage of carbapenem-polymyxin combination therapy compared with polymyxin monotherapy for CRPA.

Other combination therapy. A cohort study summarized retrospectively outcomes for patients treated with ceftolozane-tazobactam for MDR- or XDR-*P. aeruginosa* infections. There was no difference

in cure, defined as clinical and microbiological cure at day 7, between patients given ceftolozane-tazobactam monotherapy (14/21, 66.7%) and those treated with ceftolozane-tazobactam in combination with colistin or an aminoglycoside (21/35, 60%), without adjustment [200]. The study found no significant difference in development of resistance to ceftolozane-tazobactam during therapy between monotherapy and combination therapy. Overall, there was no evidence for other combination therapy for CRPA.

4. Carbapenem-resistant *Acinetobacter baumannii*

Question 4.1: What is the antibiotic of choice for CRAB?

Recommendations

- For patients with CRAB susceptible to sulbactam and HAP/VAP, we suggest ampicillin-sulbactam (**conditional recommendation, low certainty of evidence**).
- For patients with CRAB resistant to sulbactam, a polymyxin or high-dose tigecycline can be used if active *in vitro*. Lacking evidence, we cannot recommend on the preferred antibiotic.
- We conditionally recommend against cefiderocol for the treatment of infections caused by CRAB (**conditional recommendations against use, low certainty of evidence**).

Review of the evidence

Antibiotics active *in vitro* against CRAB have been directly compared, mostly in retrospective observational studies. The studies generally addressed all species within the *A. baumannii* complex, not specifically *A. baumannii* (genospecies 2 of the *Acinetobacter calcoaceticus-A. baumannii* complex), because automated detection tests do not discriminate between the different genospecies included in the *A. baumannii* complex (*A. calcoaceticus*, *A. baumannii*, genospecies 3 and genospecies 13TU). The most common infection described with CRAB is pneumonia, frequently VAP. As colistin's concentrations in epithelial lining fluid after intravenous administration are negligible [201,202], we were interested in separate assessment of pneumonia and other sources of infection, but the data were insufficient to provide recommendations by source of infection. Of the antibiotics that have been considered to date, EUCAST does not provide breakpoints for sulbactam and tigecycline, for *Acinetobacter*.

Polymyxin versus ampicillin-sulbactam. Several small studies compared polymyxins, mostly colistin, with ampicillin-sulbactam. A small RCT using alternation as the randomization method (not true randomization) included 28 patients in ICU with VAP caused by CRAB susceptible to ampicillin-sulbactam and did not find a difference between ampicillin-sulbactam and colistin in mortality, or clinical or microbiological failure [203]. Nephrotoxicity was more common with colistin without statistical significance. An RCT evaluating 47 ICU patients diagnosed with CRAB VAP compared colistin and sulbactam, both combined with meropenem, with similar results [204]. A retrospective study including 167 patients with different CRAB infections, mostly in ICU and mostly with primary BSI or pneumonia, compared colistin or polymyxin B with ampicillin-sulbactam, with additional antibiotics not active *in vitro* in both groups [205]. Mortality at end of treatment (but not in-hospital mortality) was significantly higher in the polymyxin group (adjusted OR 2.07, 95% CI 1.03–4.16). A retrospective cohort study of 98 patients in ICU with CRAB VAP compared low-dose colistin (6 MIU/day) with ampicillin-sulbactam, showing significantly higher all-cause mortality with colistin, higher microbiological failure and no difference in clinical failure [206]. A small RCT, presented as an interim study, compared colistin with extended infusion ampicillin-sulbactam (6 g intravenous ampicillin-sulbactam 2:1 four times a day) both combined with high-dose levofloxacin for the treatment of *A. baumannii* VAP in an ICU where all *A. baumannii* are carbapenem-resistant [207]. The study showed a large advantage to ampicillin-sulbactam in 14-day and 28-day mortality, clinical response and renal failure (28-day mortality 9/11 with colistin versus 5/12 with ampicillin-sulbactam). None of the studies addressed the comparative rates of resistance development during therapy. Most studies considered isolates with MIC $\leq$8/4 mg/L as susceptible to sulbactam. Dosing of ampicillin-sulbactam was quite heterogeneous across studies, ranging from 3 to 16 g/8 h (for ampicillin-sulbactam 2:1). The data support an advantage to ampicillin-sulbactam over polymyxins for CRAB, but the evidence is of low certainty.

Polymyxin versus tigecycline. Colistin has been compared with tigecycline in four retrospective observational studies. Most included patients in ICU, mainly with pneumonia, and colistin and tigecycline were commonly combined with other antibiotics [132,208–210]. All studies, except one [132], demonstrated higher mortality and lower clinical response with tigecycline monotherapy, although without statistical significance. In one study, microbiological success was significantly better with colistin [210]. In three studies, nephrotoxicity was more frequent with colistin [208–210]. Low doses of tigecycline were commonly used (50 mg twice a day), while double dosing may be more appropriate [211]. From these data, no conclusion can be drawn (no evidence).

Tigecycline versus sulbactam-based therapy. A comparison between tigecycline and sulbactam has been included in five retrospective cohort studies. A single-centre, hospital-wide, retrospective study in Taiwan included 386 patients and compared tigecycline-based therapy with sulbactam-based therapy for hospital-acquired infections caused by tigecycline and sulbactam-susceptible CRAB, respectively [212]. Sulbactam was combined with imipenem, and tigecycline was prescribed variably alone or with a carbapenem or another β-lactam. There was no significant difference in 30-day mortality or length of stay, but there was a significantly lower rate of clinical or microbiological failure in the tigecycline-based group. Another single-centre retrospective study in Taiwan included 84 patients with CRAB pneumonia that were matched to a historical cohort of 84 patients treated with sulbactam or ampicillin-sulbactam, mostly given in combination therapies [213]. Patients with BSI were excluded. There was no statistically significant difference between groups with respect to 30-day mortality or clinical failure, but there was a significant advantage to sulbactam-based therapy in microbiological cure. A multicentre study in Taiwan comparing retrospectively treatment strategies among critically ill patients hospitalized in ICU with CRAB pneumonia, included a comparison between sulbactam-based combination or monotherapy (12 patients) and tigecycline monotherapy (84 patients) [214]. ICU mortality (adjusted OR 0.12, 95% CI 0.01–1.02) and treatment failure (adjusted OR 0.14, 95% CI 0.04–0.55) were less frequent with sulbactam-based therapy. A single-centrer retrospective study in China included 210 patients with CRAB-BSI, mostly in ICU, comparing cefoperazone-sulbactam to tigecycline, both given mostly in combination with other antibiotics [215]. The study demonstrated significantly lower 28-day mortality with sulbactam-based treatment (adjusted HR 0.57, 95% CI 0.34–0.94), despite the fact that 80% of the isolates were resistant to sulbactam [215]. The last study, retrospectively evaluated 274 episodes of MDR-AB-BSI hospital-wide in one centre in China, showing unadjusted lower mortality with cefoperazone-sulbactam-containing regimens compared with tigecycline-based therapy, although non-

susceptibility rates to sulbactam were high [216]. An increased risk of death with tigecycline for HAP, VAP and bacteraemia has been reported, in general, not specifically for CR-GNB [92]. The data support low-certainty evidence for an advantage of sulbactam-based therapy over tigecycline.

Cefiderocol. Cefiderocol is a novel siderophore cephalosporin whose MIC_{90} for *A. baumannii* is in the range of 1–8 mg. Cefiderocol was compared with BAT for CR-GNB infections in the previously described CREDIBLE RCT [121,217] Among patients with CRAB infections in the CREDIBLE trial, the 28-day mortality rates were 19/39 (49%) in the cefiderocol group (21/42, 50% with CR-*Acinetobacter* sp.) versus 3/17 (18%) in the BAT group. Overall, in the trial, there was no advantage to cefiderocol with respect to clinical or microbiological eradication. In the APEKS-NP RCT, similar mortality, clinical and microbiological outcomes were documented for cefiderocol versus high-dose extended-infusion meropenem, in the subgroup of 36 patients with pneumonia and *A. baumannii* species with meropenem MIC >8 μg/mL, evaluated before switching to *in vitro* covering therapy in the meropenem arm. Given the limited information available to date, we conclude on low-certainty evidence against cefiderocol treatment of CRAB infections.

Eravacycline. Eravacycline is a novel synthetic tetracycline (fluorocycline) that has two-to eight-fold lower MICs than tigecycline against CRAB. It was evaluated in two RCT compared with ertapenem and meropenem for cIAI [95,141] Although potentially active *in vitro*, no data are available on its clinical efficacy against CRAB infections.

Other antibiotics. Small retrospective studies evaluated treatment with aminoglycosides [218,219] and tetracyclines other than tigecycline [218,220] for infections caused by MDR-GNB and CRAB. These studies are small and show inconclusive data (no evidence).

Question 4.2: Should combination therapy be used for the treatment of CRAB?

Recommendations

- For all patients with CRAB infections, we do not recommend polymyxin-meropenem combination therapy (**strong recommendation against use; high certainty of evidence**) or polymyxin-rifampin combination therapy (**strong recommendation against use, moderate certainty of evidence**).
- For patients with severe and high-risk CRAB infections, we suggest combination therapy including two *in vitro* active antibiotics among the available antibiotics (polymyxin, aminoglycoside, tigecycline, sulbactam combinations) (**conditional recommendation for use, very low certainty of evidence**).
- For patients with CRAB infections with a meropenem MIC <8 mg/L, we consider carbapenem combination therapy, using high-dose extended-infusion carbapenem dosing, as good clinical practice (**good practice statement**).

Review of the evidence

Combination therapy for CRAB has been suggested based on *in vitro* studies showing synergistic interactions between polymyxins and meropenem, imipenem, doripenem [7], rifampicin [4,221], vancomycin [222] and many antibiotics [223] and non-antibiotics [224]. Synergistic combinations might be associated with better survival [225], but for clinical adoption specific combination therapies need to be assessed in clinical studies. Most of the data on CRAB rely on low-certainty observational studies, assessing a large number of antibiotic regimens, many times grouped to 'combination therapy' that does not allow the appraisal of specific antibiotics regimens with biological plausibility of a beneficial interaction. We identified 29 studies comparing monotherapy with combination therapy [160,198,199,209,214,215,226–248]; six of which were RCT [160,228,236,238,240,245].

Colistin-carbapenem combination therapy. The combination of colistin with meropenem was assessed in the previously described AIDA RCT, including 406 patients with CR-GNB overall and among them 312 with CRAB bacteraemia, VAP or hospital-acquired pneumonia [160]. There was no significant difference between colistin monotherapy and colistin-meropenem with respect to a primary composite outcome of clinical failure at day 14 or 14-day mortality overall in the randomized trial population (relative risk (RR) 0.93, 95% CI 0.83–1.03 for failure and RR 1.03, 95% CI 0.84–1.28 for mortality with colistin monotherapy) and among patients with CRAB (RR 0.97, 95% CI 0.87–1.09 and RR 1.11, 95% CI 0.82–1.52, respectively). A post-hoc analysis of this trial addressed the subgroup of patients with infections caused by CRAB resistant also to colistin by broth microdilution, showing no benefit to the combination over colistin among patients with colistin-resistant CRAB [237]. The OVERCOME trial was a double-blind RCT comparing colistin monotherapy with colistin-meropenem combination for HAP/VAP and BSI caused by CR-GNB that similarly included mostly patients with CRAB of infections [179]. Mortality at 28 days was similar for colistin monotherapy 76/165 (46%) and colistin-meropenem 69/163 (42%) (p 0.5).

Several observational studies, assessing the combination of polymyxins and carbapanems specifically, showed a significant association between use of the combination and survival or clinical cure [198,235,247] whereas others did not [199,244]. Many observational studies included patients treated with a polymyxin-carbapenem combination in a larger group of patients treated with different combination therapies. These studies mostly showed an association between combination therapy and survival, compared with polymyxin monotherapy. However, from these studies the effects of a specific combination regimen cannot be assessed.

The RCT, including a considerable sample of patients with severe, high-risk, infections caused by CRAB, contribute to high-certainty evidence against carbapenem-polymyxin combination therapies for CRAB infections [160,179]. *Acinetobacter baumannii* when resistant to carbapenems is typically highly resistant, with MICs >16 mg/L. If isolates with lower MICs to a carbapenem are identified, or should these become prevalent, combination therapy with high-dose carbapenem may be considered, preferably administered through extended or continuous infusion.

Colistin-rifampin combination therapy. The combination of colistin with rifampin has been assessed in three RCT [238,240,245]. In the only powered RCT, including 209 patients with CRAB infections, mostly pneumonia, there was no advantage to colistin-rifampin over colistin monotherapy with respect to 30-day mortality [238] Microbiological cure was higher with combination therapy, but surveillance for continued carriage of CRAB was not conducted. Another small trial included 43 patients in ICU with VAP caused by CRAB, showing no difference between colistin-rifampin and colistin monotherapy with respect to in-hospital mortality and microbiological failure [245]. The third RCT included only nine patients assessing death, and clinical and microbiological response, but the lack of differences between the groups are not informative in this small sample [240]. Rifampin was included in a few patients treated with combination therapy in an observational study comparing mixed combinations with polymyxin monotherapy [248], showing no significant survival advantage to the combination. Overall, there

was moderate certainty evidence against rifampin-colistin combination therapy for CRAB.

Other combinations. Other combinations have been tested in single studies. Colistin-vancomycin has been assessed in a retrospective observational study among 57 patients in ICU mostly with CRAB pneumonia, compared with colistin monotherapy [239]. No difference in mortality or length of stay was observed, but there was a significantly higher rate of nephrotoxicity with the combination. In a retrospective study including critically ill patients in ICU treated with colistin-based regimens, colistin-glycopeptide combination therapy in 42 patients was not significantly different from colistin monotherapy administered to 61 patients with respect to 30-day mortality, ICU stay and hospital stay [241]. The study included a mix of MDR Gram-negative infections, most (59/103) with MDR *A. baumannii*. Colistin-fosfomycin was compared with colistin monotherapy in a small RCT including 94 patients with infections caused by CRAB, usually resistant to fosfomycin [228]. There was no significant difference between groups in 30-day mortality or adverse events, but combination resulted in lower microbiological failure. Other observational studies comparing monotherapy (usually colistin) with combination therapy (usually mixed) show conflicting results [198,199,209,214,215,226,227,229–235,243,244,246,247,249,250]; however, the bulk of the data seem to show no advantage to combination therapy (very-low-certainty evidence).

Double covering therapy might be considered, provided that the CRAB is susceptible to more than one antibiotic. The combination of colistin and ampicillin-sulbactam versus colistin alone has been assessed in a small RCT including 49 patients in ICU with VAP caused by CRAB susceptible to ampicillin-sulbactam [236]. There was an advantage to combination therapy with respect to clinical failure, but no difference in 28-day mortality. A systematic review of observational studies showed an association between colistin monotherapy and mortality when compared with potentially double-covering antibiotic combinations (polymyxin, aminoglycoside, tigecycline, sulbactam combinations) [172]. Very-low-certainty evidence exists for double covering combination therapy for CRAB.

General practice recommendations and antibiotic stewardship considerations

Optimal antibiotic dosing schemes should be used, with attention to adverse effects, especially with the old antibiotics—polymyxins and aminoglycosides **(good practice statement)**. Dosing and mode of administration should be optimized by pathogen and indication, with use of therapeutic drug monitoring whenever available (**good practice statement**). We recommend referring to EUCAST's recommended dosing (https://www.eucast.org/clinical_breakpoints/). Source control should always be a priority, to optimize outcomes and shorten antibiotic treatment durations. The guidelines do not address allergies to the recommended antibiotics that should be considered before antibiotic prescription. Nebulized antibiotics were not considered in the current guideline but were addressed by an ESCMID position statement [251]. Testing against the new BLBLI and polymyxins is recommended for CR-GNB that are resistant to all β-lactams. Follow-up cultures are recommended in case of treatment failure, especially for CR-GNB, to detect resistance development **(good practice statement)**. For pan-resistant CR-GNB, the panel recommends selection of antibiotic treatment with the least resistant antibiotic/s based on MICs relative to the breakpoints, but mainly optimal source control (**good practice statement)**.

Throughout the current guideline, antibiotic stewardship considerations have been introduced. The most important concern the use of carbapenems for infections caused by 3GcephRE. In different epidemiological settings of cephalosporin resistance in Enterobacterales and prevalence of CR-GNB, the implications of adopting a sweeping practice of carbapenems for all 3GcephRE are variable. We addressed this recommendation by sepsis severity and source of infection, allowing the option of carbapenem-sparing therapy for non-severe infections and low-risk sources of infection, and addressing stepdown therapy. We support antibiotic stewardship considerations when using colistin (a last resort antibiotic for CRAB and MBL-producing Enterobacterales) and the new BLBLI. Many good practice statements are provided in the guidelines, when no evidence is available and clinical practice mandates decision-making. Many of them place a high value on antibiotic stewardship considerations and can be tailored locally.

The current guidelines address antibiotic treatment targeted to specific pathogens. Empirically, before pathogen identification, these pathogens should be targeted among patients considered at high risk for CR-GNB infections. A difficult antibiotic stewardship balance exists between achieving appropriate empirical antibiotic therapy for patients with infections due to CR-GNB and the need to conserve last resort therapies for these bacteria. The empirical treatment phase is relevant to a much larger population than targeted treatment. Local guidelines, guided by the local epidemiology, should address the empirical treatment phase.

The Infectious Diseases Society of America recently published guidance documents on the treatment of 3GcephRE, CRE, DTR *P. aeruginosa* and CRAB [252,253]. The guidance format, intended to address rapidly evolving topics, does not include a systematic review of the literature and does not use the formal GRADE process to appraise the evidence. Recommendations were developed by six infectious diseases specialists and were made also where evidence was lacking, thus addressing more specific scenarios. The paucity of the evidence on the effects of the new BLBLI against MDR-GNB, mainly CR-GNB, as well as antibiotic stewardship considerations (including also settings in which the new BLBLIs are not available) underly the main differences between our guidelines and the Infectious Diseases Society of America guidance. Our guidelines stress the situations where alternatives to carbapenems and the new BLBLI are possible, stratifying patients by sepsis severity and hence the urgency of sepsis control: piperacillin-tazobactam or amoxicillin-clavulanate are considered in the treatment of 3GcephRE in our guidelines; aminoglycosides are considered for cUTI; and the scenarios in which sparing of the new BLBLI is possible are presented. Combination therapies are less strongly recommended in our guidelines that address the certainty of the evidence with respect to clinical outcomes.

Considering costs and equity

Antibiotics, both old and new, are not equally available worldwide. In low-resource settings, costs of the new antibiotics might prohibit their use; and even in other settings costs of the new antibiotics enter the consideration for use. Antibiotics critical to management of the priority pathogens should be defined and more efforts should be implemented to ensure the universal availability of these antibiotics. Differential costs of the new antibiotics for different socio-economic settings will allow better equity of patient management.

Research needs

Recommendations for further research were not developed formally and were not graded. Most recommendations in the guideline are based on very-low-certainty evidence or no evidence. Only RCT provided high-certainty evidence. RCT are needed that assess patients with infections due to 3GCephRE and CR-GNB; most

antibiotic approval trials of the new antibiotics were syndrome-based and included only a few patients with the MDR bacteria for which these antibiotics were developed. Although we intended by protocol to obtain data by source of infection, this was possible only for 3GCephRE and as a result infection source-specific guidance is mostly lacking. Investigator-initiated RCT are needed addressing these gaps. Concomitantly, observational studies can include a broader and larger patient population and with improved methods to reduce bias can portray the real life and support decision-making. Antibiotic treatments addressed as the exposures in existing studies were frequently combined with other antibiotics, switched and crossed; study designs allowing a cleaner assessment of individual antibiotics or specific combinations are needed. Studies addressing targeted treatment should address the empirical antibiotic treatment and report the phenotypic and genetic characterization of the isolated bacteria to direct more individualized treatment. The ecological impact of different treatment strategies should be evaluated.

Evidence is lacking on the efficacy and safety of oral antibiotics (e.g. pivmecillinam, fosfomycin, amoxicillin/clavulanic acid), for initial treatment of clinically stable patients with UTI or as oral follow up, compared with continued definitive intravenous therapy. Furthermore, more studies are needed to establish optimal dosing regimens (dose, frequency, intermittent or prolonged administration) and treatment durations especially when using β-lactam antibiotics.

Transparency declaration

MP has received research grants from Pfizer. PR has sat on the advisory board of Shionogi. RAB has received research grants from Merck, Wockhardt, Entasis and Shionogi. Jan de Waele has received honoraria for educational activities from MSD and Pfizer. GLD has received honoraria for educational activities from, consulted for and sat on the advisory board of Pfizer, MSD and Shionogi. MA has received honoraria for educational activities from Pfizer, MSD, Gilead and Genentech, and received research support from Pfizer and Gilead. SH has sat on advisory boards for Sandoz and Bode. JG-M has received honoraria for educational activities from Shionogi and Pfizer. MT has sat on advisory boards for Menarini, MSD and Shionogi, and received honoraria from Pfizer. MB has received honoraria and sat on advisory boards for Angelini, Astellas, Bayer, Biomérieux, Cidara, Gilead, Menarini, MSD, Nabriva, Pfizer and Shionogi. EC, TT, RB, CP, BB, KS, PCL, SG, YY, JWM, ET and JRB have no conflicts of interest to declare.

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Updating the guideline

The guidelines will be updated according to ESCMID recommendations.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.cmi.2021.11.025.

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