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EXPERT OPINION

An Evidence-Based Multidisciplinary Approach Focused at Creating Algorithms for Targeted Therapy of BSIs, cUTIs, and cIAIs Caused by *Enterobacterales* in Critically Ill Adult Patients

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Abstract: Prompt implementation of appropriate targeted antibiotic therapy represents a valuable approach in improving clinical and ecological outcome in critically septic patients. This multidisciplinary opinion article focused at developing evidence-based algorithms for targeted antibiotic therapy of bloodstream (BSIs), complicated urinary tract (cUTIs), and complicated intrabdominal infections (cIAIs) caused by *Enterobacterales*. The aim was to provide a guidance for intensive care physicians either in appropriately placing novel antibiotics or in considering strategies for sparing the broadest-spectrum antibiotics. A multidisciplinary team of experts (one intensive care physician, one infectious disease consultant, one clinical microbiologist and one MD clinical pharmacologist), performed several rounds of assessment to reach agreement in developing six different algorithms according to the susceptibility pattern (one each for multi-susceptible, extended-spectrum beta-lactamase-producing, AmpC beta-lactamase-producing, *Klebsiella pneumoniae* carbapenemase (KPC)-producing, OXA-48-producing, and Metallo-beta-lactamase (MBL)-producing *Enterobacterales*). Whenever multiple therapeutic options were feasible, a hierarchical scale was established. Recommendations on antibiotic dosing optimization were also provided. In order to retrieve evidence-based support for the therapeutic choices proposed in the algorithms, a comprehensive literature search was performed by a researcher on PubMed-MEDLINE from inception until March 2021. Quality and strength of evidence was established according to a hierarchical scale of the study design. Only articles published in English were included. It is expected that these algorithms, by allowing prompt revision of antibiotic regimens whenever feasible, appropriate place in therapy of novel beta-lactams, implementation of strategies for sparing the broadest-spectrum antibiotics, and pharmacokinetic/pharmacodynamic optimization of antibiotic dosing regimens, may be helpful either in improving clinical outcome or in containing the spread of antimicrobial resistance.

Keywords: critically ill patients, targeted antibiotic therapy, antimicrobial stewardship, *Enterobacterales*, multidisciplinary taskforce, PK/PD dosing optimization

Introduction

Sepsis is a common occurrence in patients admitted to intensive care unit (ICU), accounting for high mortality and massive antibiotic consumption.[1–3] Bloodstream infections (BSIs), complicated intra abdominal infections (cIAIs) and complicated urinary tract infections (cUTIs) are second only to pneumonia as sources of infections among ICU patients.[4,5] *Enterobacterales* account for the most frequently

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isolated pathogens.[5,6] Beta-lactams represent mainstay of treatment, and may have different roles according to the susceptibility pattern of clinical isolates. Previous antibiotic use, colonization by or ICU acquisition of MDR-*Enterobacterales*, prolonged hospitalisation, severity of acute illness are the major determinants of risk for developing infections caused by multidrug-resistant (MDR) *Enterobacterales*.[7–9] Six different susceptibility patterns to beta-lactams may be identified among *Enterobacterales*: multi-susceptible, extended-spectrum beta-lactamase (ESBL)-producing, AmpC beta-lactamase (AmpC)-producing, *Klebsiella pneumoniae* carbapenemase (KPC)-producing, OXA-48-producing, and metallo-beta-lactamase (MBL)- producing *Enterobacterales*.[7–9]

Early and appropriate antimicrobial treatment represents a cornerstone in the management of critically septic patient.[10,11] The *Surviving Sepsis Campaign* guidelines recommend prompt implementation of targeted antibiotic therapy once that pathogen has been identified and antimicrobial susceptibility has been tested.[12] A multidisciplinary team composed of the intensive care physician, the infectious disease consultant, the clinical microbiologist, and the MD clinical pharmacologist (Figure 1), could be helpful to pursuit this aim. Prompt implementation of appropriate definitive therapy according to the "antimicrobial puzzle" concepts[13] could play a key role in improving clinical and ecological outcome in critical settings.[14,15]

This multidisciplinary opinion article aims to develop evidence-based algorithms for targeted antibiotic therapy of BSIs, cIAIs, and cUTIs caused by *Enterobacterales* in critically ill adult patients.

The aim was to provide a useful guidance for intensive care physicians either in appropriately placing novel antimicrobial agents in lack of definitive evidence or in considering antimicrobial stewardship strategies for sparing the broadest-spectrum antibiotics.

Materials and Methods

A multidisciplinary team composed by one intensive care physician (B.V.), one infectious disease consultant (P.V.), one clinical microbiologist (G.M.R.), and one MD clinical pharmacologist (F.P.) met virtually on several occasions to reach agreement in developing algorithms and specific recommendations for targeted antimicrobial therapy of BSIs, cIAIs, and cUTIs caused by *Enterobacterales* in ICU critically ill patients. The definitive agreement for each therapeutic algorithm was reached by the multidisciplinary team after thoroughly discussion based on specific long-standing experience and on the specific expertise of each single member. The rationale for considering common algorithms for these infection sites is based on the fact that cIAIs and cUTIs were investigated together in the last pivotal trials concerning novel antibiotics.[16] Additionally, bacteraemic and non-bacteraemic cUTIs and cIAIs are commonly considered as relatively benign infection sources showing no high-inoculum effect, differently from that occurs in severe nosocomial pneumonia.[17,18] Consequently, we believe that algorithms for targeted therapy of infection-related ventilator associated complications (IVACs) must be considered apart. Six different scenarios were structured according to the pattern of antibiotic susceptibility of the pathogens and/or of the genotype of

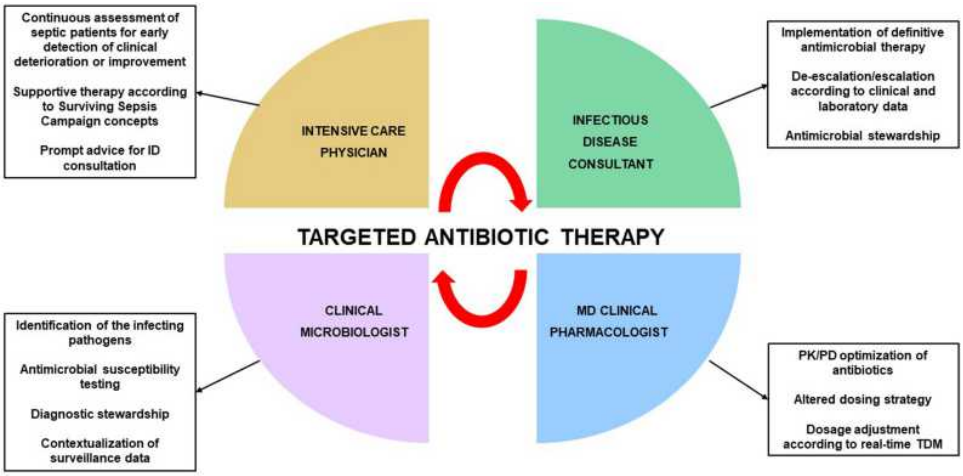

Figure 1 Features of multidisciplinary taskforce involved in implementation of targeted antimicrobial therapy in critically ill patients.
Abbreviations: ID, infectious disease; PCR, polymerase chain reaction; PK/PD; pharmacokinetic/pharmacodynamic; TDM, therapeutic drug monitoring.

resistance. Whenever multiple therapeutic options were feasible, a hierarchical scale was established. Recommendations on antibiotic dosing optimization were also provided.

Scientific evidence supporting the specific choices included in the algorithms was retrieved by means of a literature search conducted by a researcher (M.G.) on PubMed-MEDLINE (from inception until March 2021). Key terms for search included selected antibiotics, site of infections, and genotype of resistance and/or pattern of susceptibility of bacterial pathogens. Quality of evidence was established according to a hierarchical scale of the study design, as reported in the evidence pyramid:[19] randomized controlled trials (RCTs); prospective observational studies; retrospective observational studies; case series; case reports; in vitro studies. International guidelines issued by the Infectious Disease Society of America and/or by the European Society of Clinical Microbiology and Infectious Diseases, systematic reviews and meta-analyses were also consulted. Consistence between retrieved studies was also considered, by assessing the concordance in clinical outcome of the included studies at each level of the evidence pyramid. Only articles published in English were included, and search was focused mainly on the last ten years in order to provide an up-to-date overview on the scientific evidence that may support the therapeutic algorithms.

Targeted Treatment of BSIs, cUTIs, and cIAIs Caused by *Enterobacterales* in Critically Ill Adult Patients

Six different algorithms for targeted treatment of BSIs, cUTIs, cIAIs are depicted in Figure 2, one each for infections caused by multi-susceptible, ESBL-, AmpC-, KPC-, OXA-48-, and MBL-producing *Enterobacterales*.

Multi-Susceptible Enterobacterales

Recommendations are depicted in Figure 2, panel A.1. Ampicillin-sulbactam [3g q6h over 6h by continuous infusion (CI) after 3g loading dose [LD]] or ceftriaxone (2g q24h) are recommended for BSIs, cUTIs, and cIAIs caused by multi-susceptible *Enterobacterales*. Evidences supporting these choices are summarized in Table 1. Both the European[20] and the American[21] guidelines recommended the use of ampicillin-sulbactam or ceftriaxone for the management of mild-to-moderate cIAIs/peritonitis. In regard to ampicillin-sulbactam, an RCT[22] found no significant difference in clinical response rate between

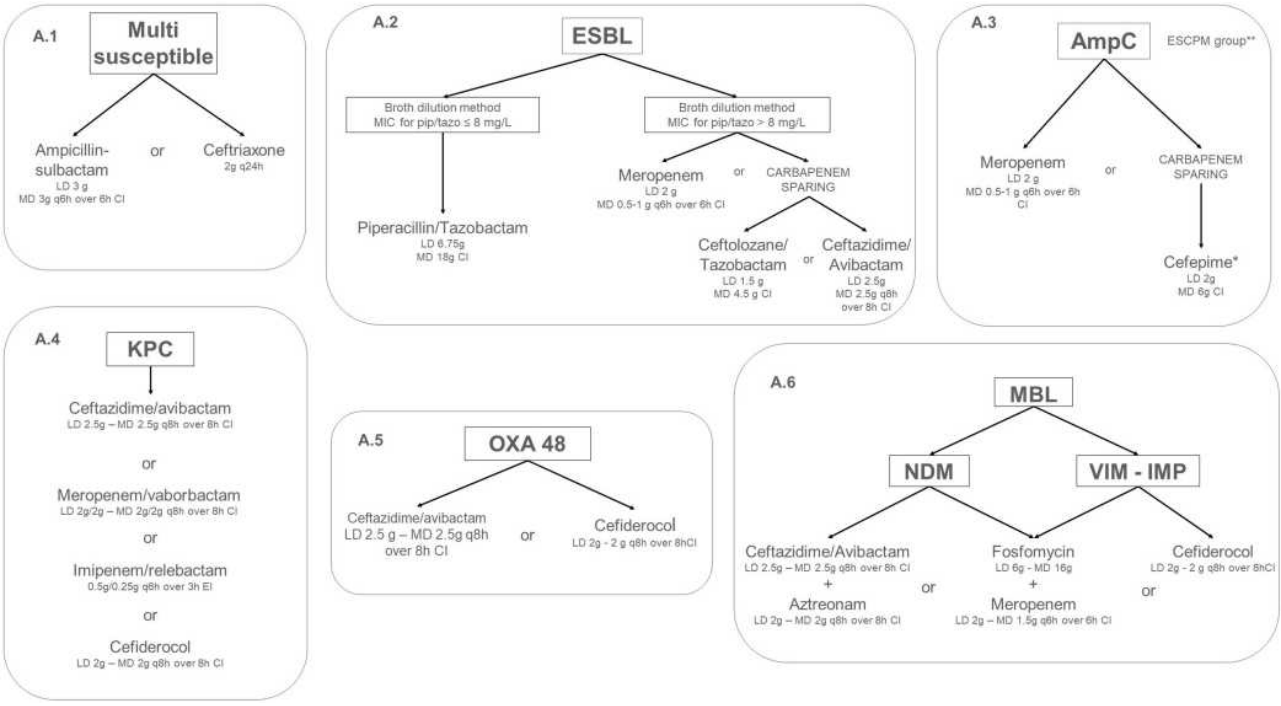

Figure 2 Algorithms for targeted treatment of BSI, cUTI and cIAI, caused by Enterobacterales with different pattern of susceptibility in the ICU setting. *if MIC for cefepime ≤1 mg/L. ** ESCPM group includes: Enterobacter (E. cloacae complex, E. aerogenes), Serratia marcescens, Citrobacter freundii, Providencia stuartii, and Morganella morganii. **Abbreviations:** CI, continuous infusion; MIC, minimum inhibitory concentration.

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Table 1 Summary of the Studies Investigating the Treatment of Full-Sensitive *Enterobacterales* Bloodstream Infections (BSIs), Complicated Intraabdominal (cIAIs) and Urinary Tract Infections (cUTIs) with Ampicillin or Ceftriaxone

Author, Year and Reference	Study Design	No. of Patients	Antibiotic and Dosing	Source of Infection	Isolates	Severity	Clinical Outcomes	Relapse Rate – Resistance Development	Comments
Ampicillin									
Eckmann et al, 2011[20]	Guidelines	Ampicillin-sulbactam 3 g q6h recommended for community-acquired localized peritonitis (Strength of recommendation: Grade A – Quality of evidence: Level I)							
Walker et al, 1993[22]	Prospective randomized, double-blind, multicenter	385 (194 AMP-SUL vs 191 cefoxitin)	AMP-SUL 3 g q6h vs Cefoxitin 2 g q6h	cIAI	*E. coli* most frequent	NA	Clinical response rate: 86% vs 78%	Persistent or recurrent infections: 14% vs 22%	AMP-SUL demonstrated no difference in efficacy when compared with cefoxitin in the treatment of serious bacterial cIAI
McKinnon et al, 1999[23]	Retrospective open-label, multicenter	890 (664 AMP-SUL vs 226 TIC-CVL)	AMP-SUL 1.5–3 g q6h vs TIC-CVL 3.1 g q6h	258 SSTI 257 cIAI 200 respiratory 67 cUTI 67 gynaecologic 41 other	*E. coli* and *Klebsiella spp* most frequent (frequencies not provided)	NA	Clinical response rate: 84.3% vs 77.5% Clinical response rate in cIAI: 88% vs 73% Clinical response rate in cUTI: 83.3% vs 84%	NA	AMP-SUL had efficacy comparable with that of TIC-CVL in a variety of infections in hospitalized patients
Ceftriaxone									
Eckmann et al, 2011[20]	Guidelines	Ceftriaxone 2 g/day + Metronidazole 500 mg q8h recommended for community-acquired localized peritonitis (Strength of recommendation: Grade A – Quality of evidence: Level I)							
Solomkin et al, 2010[21]	Guidelines	Ceftriaxone 2 g/day + Metronidazole 500 mg q8h recommended for mild-moderate community-acquired cIAI (Strength of recommendation: Grade A – Quality of evidence: Level I)							
Wells et al, 2004[27]	Prospective randomized, double-blind, multicenter	850 (377 ceftriaxone vs 473 ertapenem)	Ceftriaxone 1 g/day vs Ertapenem 1 g/day	cUTI	64.7% *E. coli* 9.8% *K. pneumoniae*	Severe disease 41.3%	Overall microbiological response rate: 91.1% vs 89.5%	Bacterial recurrence: 7.6% vs 8.9%	No significant difference in efficacy between ceftriaxone and ertapenem in cUTI

Tomera et al, 2002[25]	Prospective randomized, double-blind, multicenter	592 (294 ceftriaxone vs 298 ertapenem)	Ceftriaxone 1 g/day vs Ertapenem 1 g/day	cUTI 5.9% bacteraemic	69.1% *E. coli* 13.1% *K. pneumoniae*	Severe disease 42.2%	Overall microbiological response rate: 93% vs 91.8%	Relapse and superinfection: 8.4%	No significant difference in efficacy between ceftriaxone and ertapenem in cUTI
Rubinstein et al, 1995[24]	Prospective randomized controlled, multicenter	580 (274 ceftriaxone + tobramycin vs 306 ceftazidime)	Ceftriaxone 2 g/day + Tobramycin 3–5 mg/kg vs Ceftazidime 2 g q12h	Serious hospital-acquired Gram-negative infections 297 pneumonia 184 sepsis 99 cUTI	23.8% *P. aeruginosa* 20.6% *Klebsiella spp* 20.1 *E. coli*	ICU admission 43.3% Mechanical ventilation 27.9%	Clinical response rate: pneumonia 65% vs 73% sepsis 59% vs 73% cUTI 76% vs 80%	Relapse and superinfection: 7.3% vs 4.6% (p=NS)	No significant difference in efficacy between the two groups in severe hospital-acquired gram-negative infections
Park et al, 2012[28]	Prospective randomized, double-blind, multicenter	271 (136 ceftriaxone vs 135 ertapenem)	Ceftriaxone 1 g/day vs Ertapenem 2 g/day	cUTI 33.6% bacteraemic	85.3% *E. coli* 4.6% *K. pneumoniae* 4.4% ESBL+	NA	Overall microbiological response rate: 88.7% vs 87.9%	NA	No significant difference in efficacy between ceftriaxone and ertapenem in cUTI
Jimenez-Cruz et al, 2002[26]	Prospective randomized, double-blind, multicenter	258 (83 ceftriaxone vs 175 ertapenem)	Ceftriaxone 1 g/day vs Ertapenem 1 g/day	cUTI	77.6% *E. coli* 6.6% *K. pneumoniae*	Severe infection 39.1%	Overall microbiological response rate: 84.9% vs 85.6%	Relapse and superinfection: 7.4%	No significant difference in efficacy between ceftriaxone and ertapenem in cUTI

Abbreviations: AMP-SUL, ampicillin-sulbactam; BSIs, bloodstream infections; cIAI, complicated intra abdominal infections; cUTI, complicated urinary tract infection; ESBL, extended-spectrum beta-lactamase; ICU, intensive care unit; NA, not available; NS, not significant; SSTI, skin and soft tissue infections; TIC-CVL, ticarcillin-clavulanate

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ampicillin-sulbactam and cefoxitin (86% vs 78%) in patients affected by cIAIs mainly due to *Escherichia coli*, although features concerning infection severity were not provided. A retrospective observational study found comparable clinical response rate between ampicillin-sulbactam and ticarcillin-clavulanate (84.3% vs 77.5%) among hospitalized patients with infections including cIAIs and cUTIs.[23] Data on ICU admission and severity of infection were unavailable.

In regard to ceftriaxone, an RCT comparing ceftriaxone plus tobramycin versus ceftazidime in the treatment of severe hospital-acquired Gram-negative infections (including BSIs and cUTIs) showed no significant difference in clinical response rate among patients who required ICU admission in 43.3% of cases.[24] Several RCTs[25–28] showed no significant difference in terms of microbiological response rate between ceftriaxone and ertapenem for the management of cUTIs caused mainly by *E. coli* and *K. pneumoniae*. Almost 40% of patients had severe infection and relapse rate was <10%. cUTI were bacteraemic in 5.9–33.6% of cases may provide, and this may support the efficacy of ceftriaxone in BSIs as well.

Extended-Spectrum Beta-Lactamase (ESBL)-Producing Enterobacterales

Recommentations are depicted in Figure 2, panel A.2. Piperacillin-tazobactam (18g CI after 6.75g LD) is recommended for the management of infections caused by ESBL-producing *Enterobacterales* with a piperacillin-tazobactam MIC ≤8 mg/L (according to the EUCAST breakpoint) tested by broth microdilution (the reference method for piperacillin-tazobactam susceptibility testing). Conversely, meropenem (0.5–1g q6h over 6h CI after 2g LD) should be preferred whenever piperacillin/tazobactam MIC is >8 mg/L. Ceftolozane-tazobactam (1.5g LD followed by 4.5g CI) and ceftazidime-avibactam (2.5g LD followed by 2.5g q8h over 8h CI) may represent alternative options when focusing at a "carbapenem-sparing" approach.[29] In settings with high prevalence of carbapenem-resistant *Enterobacterales* (CRE), ceftazidime-avibactam should be reserved for CRE treatment to avoid epidemiological shift of carbapenemase producers to metallo-beta-lactamases (MBLs).[29,30] Evidences supporting these choices are summarized in Table 2. Several studies compared piperacillin-tazobactam with carbapenems in the treatment of BSIs, cUTIs, and cIAIs caused by ESBL-producing *Enterobacterales*. Overall, an inconsistence emerged from the available evidence. The MERINO trial[31] was the first large RCT that assessed the efficacy of a carbapenem-sparing strategy by comparing piperacillin-tazobactam vs meropenem in the treatment of ceftriaxone-resistant *Escherichia coli* or *Klebsiella pneumoniae* BSIs. Non-inferiority was not achieved in the piperacillin-tazobactam arm, as an overall 30-day all-cause mortality rate 3-fold higher than in the meropenem arm was observed (12.3% vs 3.7%, p=0.90). This arose concerns regarding the use of piperacillin-tazobactam as empirical or definitive therapy of ESBL-producing *Enterobacterales* BSIs.[17] Indeed, it should be mentioned that a number of issues affected trial conclusions.[17,32] The low mortality rate in the meropenem group was an unexpected finding; the primary source of BSI was imbalanced between arms (higher UTIs rate in the meropenem group); the number of neutropenic and immunocompromised patients was higher in the piperacillin-tazobactam group; sample size calculation was suboptimal; there was a high prevalence of $bla_{\text{OXA-1}}$ genes (67%) strictly associated with high MICs for piperacillin-tazobactam (8–16 mg/L);[33] pharmacokinetic/pharmacodynamic (PK/PD) properties of piperacillin-tazobactam were not maximized (administration by intermittent rather than by prolonged infusion). Conversely, a large body of evidence coming from well-design observational studies and systematic review[34–46] showed no significant difference in efficacy and mortality rate between piperacillin-tazobactam and carbapenems among patients with ESBL-producing primary or secondary BSI in settings with ICU admission rate up to 40%. An RCT of piperacillin-tazobactam vs ertapenem found no significant difference in clinical cure and mortality rate among patients with bacteraemic cUTIs.[47] Two studies showed a lower occurrence of MDR bacterial or fungal infections at 30-day from treatment with piperacillin-tazobactam compared to carbapenems (7.4% vs 24.6%; p=0.01),[39] and a trend toward lower CRE isolation rate (2% vs 8%; p=0.09).[46] Conversely, two other observational studies showed significantly lower mortality rate in patients treated with carbapenems compared to piperacillin-tazobactam.[48,49] However, in one of this[48] some limits must be recognized, as 61% of patients received lower-than-desirable dosage of piperacillin-tazobactam (3.375g q6h) by intermittent infusion, and 60% of *Enterobacterales* isolates had piperacillin-tazobactam MIC ≥8 mg/L. Overall, the available literature may provide support for considering piperacillin-tazobactam a valuable carbapenem-sparing agent in the

Table 2 Summary of the Studies Investigating the Treatment of Extended Spectrum Beta-Lactamase (ESBL)-Producing *Enterobacterales* Bloodstream Infections (BSIs), Complicated Intraabdominal (cIAIs) and Urinary Tract Infections (cUTIs) with Carbapenems Compared to Piperacillin-Tazobactam or Novel Beta-Lactam/Beta-Lactamase Inhibitors (BL/BLIs)

Author, Year and Reference	Study Design	No. of Patients	Antibiotic and Dosing	Source of Infection	ESBL-Producing Pathogens and Molecular Profile	Severity	Clinical Outcomes	Relapse Rate – Resistance Development	Comments
Piperacillin-tazobactam vs carbapenems									
Harris et al, 2018[31]	Randomized controlled, open-label, parallel-group, multicentric	379 (188 PIP-TZB vs 191 MER)	PIP-TZB 4.5 g q6h II vs MER 1 g q8h II	All BSI 231 cUTI 62 cIAI 12 pneumonia 6 CR-BSI 5 SSTI 63 others	Ceftriaxone-resistant *Enterobacterales* 327 *E. coli* 52 *K. pneumoniae*	ICU admission 7.1% Immunocompromised 24% Neutropenia 6.6% Mean APACHE II score 17.9 vs 21	30-day mortality rate: 12.3% vs 3.7% (p=0.90 for non-inferiority)	NA	Definitive treatment with PIP-TZB compared to MER did not result in non-inferior 30-day mortality rate
Seo et al, 2017[47]	Randomized controlled, multicenter	66 (33 PIP-TZB vs 33 ERT)	PIP-TZB 4.5 g q6h vs ERT 1 g/day	All cUTI 16 secondary BSI	100% *E. coli* MIC PIP-TZB 16 mg/L (72.7% of isolates)	Septic shock 30.3% Mean APACHE II score 12.9 vs 16.6	28-day mortality rate: 6.1% vs 6.1%	0% vs 0%	No difference between PIP-TZB and ERT in mortality and clinical cure rate
Rodriguez-Bano et al, 2012[35]	Post-hoc analysis of six prospective cohort	204 Empiric: 35 PIP-TZB vs 31 carbapenems Definitive: 18 PIP-TZB vs 120 carbapenems	PIP-TZB vs MER/IMI/ERT	100% BSI 70% cUTI or biliary source	100% *E. coli*	ICU admission 13% Severe sepsis or septic shock 23% Neutropenia 5.8% Immunocompromised 13.5%	30-day mortality rate Empiric treatment: 9.7% vs 19.4% Definitive treatment: 9.3% vs 16.7%	NA	PIP-TZB is a suitable alternative to carbapenems for treating patients with BSIs caused by ESBL-producing *Enterobacterales*

(*Continued*)

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Table 2 (Continued).

Author, Year and Reference	Study Design	No. of Patients	Antibiotic and Dosing	Source of Infection	ESBL-Producing Pathogens and Molecular Profile	Severity	Clinical Outcomes	Relapse Rate – Resistance Development	Comments
Gutierrez-Gutierrez et al, 2016[38]	Retrospective international cohort	887 (Empiric: 123 PIP-TZB vs 195 carbapenems Definitive: 60 PIP-TZB vs 509 carbapenems)	PIP-TZB 4.5 g q6-8h vs MER 1 g q8-12h or ERT 1 g/day or IMP 0.5 g q6-8h	All BSIs 440 cUTI 120 biliary	73% *E. coli* 19% *K. pneumoniae* 8% Other	ICU admission 11.8% Severe sepsis or septic shock 37.7% Median Pitt score 1	30-day mortality rate Empiric treatment: 17.6% vs 20% Definitive treatment: 13.9% vs 9.8%	NA	PIP-TZB, if active in vitro, appears to be as effective as carbapenems for empiric and target therapy of BSI due to ESLB-producing *Enterobacterales* regardless of the source and specific species
Gudiol et al, 2017[40]	Retrospective propensity matched cohort	416 (Empiric: 44 PIP-TZB vs 126 carbapenems Definitive: 12 PIP-TZB vs 234 carbapenems)	PIP-TZB vs MER (223) or IMI (110) or ERT (27)	All BSIs 52.8% primary 18.1% CR-BSI 8.1% neutropenic colitis 6.9% cUTI	74% *E. coli* 23% *K. pneumoniae* 1.5% *K. oxytoca* 1.5% *E. cloacae*	ICU admission 20% Septic shock 24.3% Haematological neutropenic patients 100%	30-day mortality rate Empiric treatment: 20.8% vs 13.4% (p=0.33) Definitive treatment: 5.8% vs 15.8% (p=0.99)	Persistent BSI: 17.6% vs 4.7% (p=0.059) No difference in superinfection and colonization-infection by MDR isolates	PIP-TZB could be carbapenem-sparing alternatives for the treatment of BSI due to ESBLs in haematological patients.
Nasir et al, 2019[45]	Retrospective cohort, monocentric	263 (89 PIP-TZB vs 174 carbapenems)	PIP-TZB vs carbapenems	All BSIs 195 cUTI 68 cIAI 8 CR-BSI	100% *E. coli* (ceftriaxone-resistant)	ICU admission 38% Septic shock 17%	Overall mortality rate for definitive therapy: 13% vs 21% (p=NS)	NA	PIP-TZB showed similar efficacy compared to carbapenems

Ko et al, 2018[42]	Retrospective cohort, multicentric	224 (41 PIP-TZB vs 183 carbapenems)	PIP-TZB vs carbapenems	All BSIs 86 cUTI 65 cIAI 56 primary BSI 8 CR-BSI 17 other	159 *E. coli* 73 *K. pneumoniae*	ICU admission 34.4%	30-day mortality rate: 6.3% vs 11.4% Empirical use of PTZ was not associated with 30-day all-cause mortality (HR 1.21, CI 0.37–4.00)	NA	Appropriate non-carbapenems were not inferior to carbapenems as initial empirical therapy for ESBL-BSIs
Tamma et al, 2015[48]	Retrospective propensity score matched	213 (103 PIP-TZB vs 110 carbapenems)	PIP-TZB 3.375/4.5 g q6h II vs MER/IMI/ERT (MER 1–2 q8h II)	100% BSI 97 CR-BSI 44 cUTI 36 cIAI 20 pneumonia 19 biliary	68% *K. pneumoniae* 31% *E. coli* 1% *P. mirabilis* MIC PIP-TZB ≥8 mg/L 60%	ICU admission 33.8% Neutropenia 15% Immunocompromised 58.7%	14-day mortality rate: 17% vs 8% (p< 0.05) 30-day mortality rate: 26% vs 11% (p< 0.05)	NA	The adjusted risk of death was 1.92 times higher for patients receiving empiric PIP-TZB compared with empiric carbapenem therapy (95% CI: 1.07–3.45)
Sharara et al, 2020[46]	Retrospective cohort, multicenter	186 (45 PIP-TZB vs 141 carbapenems)	PIP-TZB vs carbapenems	100% cUTI All non-bacteraemic	56% *E. coli* 30% *K. Pneumoniae* 10% *P. mirabilis* 4% *K. oxytoca*	ICU admission 27% Septic shock 5.9% Immunocompromised 48%	30-day mortality rate: 4% vs 7%	30-day recurrent cUTI: 20% vs 25% (OR 0.75; CI 0.31–1.81) 30-day CRE isolation: 2% vs 8% (p=0.09)	PIP-TZB may be a reasonable alternative to carbapenems for the management of ESBL-producing cUTI and may mitigate the risk of emergence of carbapenem-resistant organisms

(*Continued*)

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Table 2 (Continued).

Author, Year and Reference	Study Design	No. of Patients	Antibiotic and Dosing	Source of Infection	ESBL-Producing Pathogens and Molecular Profile	Severity	Clinical Outcomes	Relapse Rate – Resistance Development	Comments
Ng et al, 2016[39]	Retrospective cohort multicenter	151 (94 PIP-TZB vs 57 carbapenems)	PIP-TZB 4.5 g q6h II or q8h EI vs MER 1 g q8h or ERT 1 g/day or IMP 0.5 g q6h	All BSIs 89 cUTI 14 biliary 13 pneumonia 8 cIAI 6 CR-BSI 18 other	67% *E. coli* 33% *K. pneumoniae*	ICU admission 8.6% Median Pitt score 1	30-day mortality rate: 30.9% vs 29.8% (p= NS)	30-day relapsed BSI: 3.2% vs 15.8% (p=0.05)	PIP-TZB was significantly associated with lower acquisition of MDR bacterial or fungal infections at 30-day (7.4% vs 24.6%; p=0.01)
Yoon et al, 2017[41]	Retrospective cohort, monocentric	150 (68 PIP-TZB vs 82 ERT)	PIP-TZB 4.5 g q8h vs ERT 1 g/day	All cUTI 23 secondary BSI	100% *E. coli*	ICU admission 24.7% Septic shock 16% Immunocompromised 14%	In-hospital mortality rate: 4.4% vs 13.4% (p=0.059)	NA	MIC> 4–8 mg/L for PIP-TZB was not significant associated with treatment failure. PIP-TZB could be an effective alternative to ERT for the treatment of cUTI caused by ESBL isolates
John et al, 2019[44]	Retrospective cohort, multicenter	117 (66 PIP-TZB vs 51 carbapenems)	PIP-TZB vs MER/ERT	All BSIs 85 cUTI 22 cIAI 1 Pneumonia 9 unknown	101 *E. coli* 16 *K. pneumoniae*	ICU admission 38.5% Septic shock 17.1% Mechanical ventilation 2.6% Immunocompromised 12%	In-hospital mortality: 3% vs 7.8%	Relapse ESBL-BSI: 7.6% vs 7.8%	Empiric PIP-TZB use and avoidance of empiric carbapenem therapy in the first 24 hours of infection can be considered until a microbiological diagnosis is confirmed.
Kang et al, 2012[36]	Retrospective case-control	114 (36 PIP-TZB vs 78 carbapenems)	PIP-TZB vs Carbapenems	100% BSI	68% *E. coli* 32% *K. pneumoniae*	Haematological malignancies 22.8%	30-day mortality rate 22.2% vs 26.9%	NA	At propensity score analysis, empirical therapy with PIP-TZB was not associated with mortality (OR 0.63; CI 0.17–2.27)

Ofer-Friedman et al, 2015[49]	Retrospective cohort	79 (10 PIP-TZB vs 69 carbapenems)	PIP-TZB vs MER/IMI/ DOR/ERT	Non urinary BSIs 27 pneumonia 22 SSTI 13 biliary 7 cIAI 6 CR-BSI 4 unknown	53% *E. coli* 28% *K. pneumoniae* 19% *P. mirabilis*	Mean Pitt bacteraemia score 3.1 Immunocompromised 28%	30-day mortality rate: 60% vs 34% (p=NS) 90-day mortality rate: 80% vs 48% (p=0.05)	NA	In multivariate analysis, therapy with PIP-TZB was associated with increased 90-day mortality (adjusted odds ratio, 7.9, P=0.03). For ESBL BSIs of a non-urinary origin, carbapenems should be considered a superior treatment to BL/BLIs
Benanti et al, 2019[43]	Retrospective cohort, monocentric	63 (21 PIP-TZB vs 42 carbapenems – 41 MER/1 ERT)	PIP-TZB 4.5 g q6h vs MER 1 g q8h	All BSIs 25 cIAI 7 CR-BSI 7 pneumonia 6 cUTI 6 SSTI 12 unknown	100% *E. coli*	ICU admission 30.2% Haematological malignancies 100% Neutropenia 88.9% Median Pitt score 2	14-day mortality rate: 0% vs 19% (p=0.04)	Persistent bacteraemia: 36% vs 5% (p=0.03)	Empiric treatment PIP-TZB did not result in increased mortality compared to carbapenems. In multivariate logistic regression, empiric treatment with PIP-TZB was a significant predictor of persistent BSI (aOR, 27.1; CI 1.8–410.1)
Harris et al, 2015[37]	Retrospective observational cohort	47 (24 PIP-TZB vs 23 carbapenem)	PIP-TZB 4.5 g q6h vs MER 1 g q8h or IMI 0.5g q6h or ERT 1 g/ day	All BSIs 22 cUTI 4 biliary	Cefotaxime non-susceptible BSIs 39 *E. coli* 8 *K. pneumoniae*	ICU admission 14.9% Median Pitt score 1 Median APACHE II score 24 Immunocompromised 12.8% Neutropenia 2.1%	30-day mortality rate: 8.3% vs 17.4% (p=NS)	0% vs 2%	BL/BLIs appear to have a similar efficacy to carbapenems in the treatment of cefotaxime-resistant *Enterobacterales* BSIs. Directed therapy with a BL/BLI, when susceptibility is proven, may represent an appropriate carbapenem-sparing option.

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Table 2 (Continued).

Author, Year and Reference	Study Design	No. of Patients	Antibiotic and Dosing	Source of Infection	ESBL-Producing Pathogens and Molecular Profile	Severity	Clinical Outcomes	Relapse Rate – Resistance Development	Comments
Novel BL/BLIs (Carba-sparing)									
Solomkin et al, 2015[53]	Prospective, randomized, double-blind, multicentric	993 (487 LOZ-TAZ vs 506 MER)	LOZ-TAZ 1.5 g q8h + Metronidazole 0.5 g q8h vs MER 1 g q8h	993 cIAI 20 secondary BSI	Overall proportion of ESBL isolates: 7.2% 50 ESBL-producing 24 CTX-M-14/15	APACHE II score >15: 3.1%	Clinical cure in ESBL-isolates: 95.8% vs 88.5% Clinical cure in CTX-M-14/15 ESBLs: 100% vs 72.7%	NA	Treatment with LOZ-TAZ plus metronidazole was noninferior to MER in adult patients with cIAI, including infections caused by MDR pathogens
Wagenlehner et al, 2015[52]	Randomized, double-blind, double-dummy, non-inferiority, multicenter	800 (398 LOZ-TAZ vs 402 LEV)	LOZ-TAZ 1.5 g q8h vs LEV 750 mg/day	800 cUTI 62 secondary BSI	72 *E. coli* 17 *K. pneumoniae*	NA	Clinical cure: 76.9% vs 68.4% (percentage difference 8.5 CI 2.3–14.6) Microbiological eradication: 80.4% vs 72.1% (8.3 CI 2.4–14.1)	NA	LOZ-TAZ superior to LEV in composite cure

Mazuski et al, 2016[55]	Prospective, randomized, multicenter, double-dummy, double-blind, comparative	1066 (413 CAZ-AVI vs 410 MER in mMITT)	CAZ-AVI 2.5 g q8h + Metronidazole 0.5 g q8h vs MER 1 g q8h	1066 cIAI	Overall proportion of ceftazidime non-susceptible isolates: 13.5% (of which about 80% ESBL-producers)	APACHE II score >10: 15.3%	Clinical cure at TOC: 81.6% vs 85.1% (−3.5% CI −8.64–1.58%) Ceftazidime non-susceptible isolates (clinical response at TOC): 83% vs 85.9% (−3% CI −17.89–10.6%)	NA	CAZ-AVI was highly effective for the empiric and definitive treatment of cIAI (including ceftazidime non-susceptible and ESBL-producers isolates), and may offer an alternative to carbapenems in this setting
Wagenlehner et al, 2016[54]	Randomized, multicenter, double-blind, double-dummy, parallel-group	1033 (490 CAZ-AVI vs 492 DOR at TOC analysis)	CAZ-AVI 2.5 g q8h vs DOR 0.5 g q8h	1033 cUTI 71 secondary BSI	Overall proportion of ESBL isolates: 147 (19.6%)	NA	Clinical resolution at day 5: 70.2% vs 66.2% (4% CI −2.39–10.42%) Microbiological eradication at TOC: 71.2% vs 64.5% (6.7% CI 0.3–13.12%) Ceftazidime non-susceptible isolates (microbiological response rate): 63.2% vs 58.2% (5% CI −10.87–20.5)	NA	CAZ-AVI was highly effective for the empiric treatment of cUTI (including acute pyelonephritis), and may offer an alternative to carbapenems in this setting

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Table 2 (Continued).

Author, Year and Reference	Study Design	No. of Patients	Antibiotic and Dosing	Source of Infection	ESBL-Producing Pathogens and Molecular Profile	Severity	Clinical Outcomes	Relapse Rate – Resistance Development	Comments
Qin et al, 2017[56]	Prospective, randomized, multicenter, double-dummy, double-blind, comparative	432 (215 CAZ-AVI vs 217 MER)	CAZ-AVI 2.5 g q8h + Metronidazole 0.5 g q8h vs MER 1 g q8h	432 cIAI 15 secondary BSI	Overall proportion of ceftazidime non-susceptible isolates: 23.4%	APACHE II score >10: 6.7%	Clinical cure at TOC: 93.8% vs 94.2% (−0.2% CI −5.53–4.97%) Ceftazidime non-susceptible isolates (clinical response at TOC): 95.2% vs 96.0% (−0.8% CI −19.51–15.78%)	NA	CAZ-AVI was highly effective for the empiric and definitive treatment of cIAI (including ceftazidime non-susceptible and ESBL-producers isolates) in Asian patients, and may offer an alternative to carbapenems in this setting
Carmeli et al, 2016[57]	Prospective, randomized, multicenter, double-dummy, double-blind, comparative	333 (165 CAZ-AVI vs 168 BAT)	CAZ-AVI 2.5 g q8h	281 cUTI 21 cIAI	Ceftazidime-resistant *Enterobacterales* and *Pseudomonas aeruginosa*	APACHE II score >10: 19% (only for cIAI)	Clinical cure at TOC: 91% vs 91%	NA	CAZ-AVI was effective as a potential alternative to carbapenems in patients with ceftazidime-resistant *Enterobacterales* and *P. aeruginosa*.

Abbreviations: BAT, best available therapy; BL/BLIs, beta-lactam/beta-lactamase inhibitors; BSIs, bloodstream infections; CAZ-AVI, ceftazidime-avibactam; CI, confidence interval; cIAI, complicated intra abdominal infections; CR-BSI, catheter-related bloodstream infections; CRE, carbapenem-resistant *Enterobacterales*; cUTI, complicated urinary tract infection; DOR, doripenem; EI, extended infusion; ERT, ertapenem; ESBL, extended-spectrum beta-lactamase; HR, hazard ratio; ICU, intensive care unit; IMI, imipenem; LEV, levofloxacin; LOZ-TAZ, ceftolozane-tazobactam; MDR, multidrug-resistant; MER, meropenem; MIC, minimum inhibitory concentration; mMITT, modified microbiological intention-to-treat; NA, not available; NS, not significant; OR, odds ratio; PIP-TZB, piperacillin-tazobactam; SSTI, skin and soft tissue infections; TOC, test of cure.

management of ESBL-related infections when dealing with fully susceptible pathogens (MIC ≤8 mg/L). Notably, CI of high-dose piperacillin-tazobactam (18g) should be strongly recommended to achieve optimal PK/PD target in critically ill patients affected by ESBL-producing *Enterobacterales* infections, especially when dealing with isolates exhibiting high MIC values.[50,51] Evidence supporting ceftolozane-tazobactam and/or ceftazidime-avibactam as carbapenem-sparing options for the treatment of for BSIs, cUTIs, and cIAIs caused by ESBL-producing *Enterobacterales* came from the non-inferiority showed vs carbapenems in pivotal Phase III trials.[52–57] Indeed, it should be recognized that the overall proportion of ESBL-producing isolates was 100% only in one study that enrolled exclusively patients with documented ceftazidime-resistant infections,[57] whereas it was <20% in all of the others.

AmpC Beta-Lactamase-Producing Enterobacterales

Recommendations are depicted in Figure 2, panel A.3. Meropenem (0.5–1g q6h over 6h CI after 2g LD) is recommended as first-line treatment for BSIs, cUTIs, and cIAIs caused by AmpC-producing *Enterobacterales*. Cefepime (6g CI after 2g LD) may be a "carbapenem-sparing" alternative option if the MIC is ≤1 mg/L. AmpC beta-lactamases belong to the class C of the Ambler's classification, and genes encoding for them are usually located in the chromosome of bacteria belonging to the so-called ESCPM group (namely *Enterobacter cloacae complex, Enterobacter aerogenes, Serratia marcescens, Citrobacter freundii, Providencia stuartii*, and *Morganella morganii*),[58] but can also be carried on transferable plasmids and found in isolates of other species (eg, *E. coli, K. pneumoniae, P. mirabilis*). AmpC may hydrolyse all the penicillins, the 1st, 2nd and 3rd cephalosporins, and the monobactam aztreonam, but not the 4th generation cephalosporins and the carbapenems. Furthermore, beta-lactamase inhibitors (tazobactam, sulbactam, clavulanate) exhibit no activity against AmpC-producing isolates. Evidences coming from comparative studies between carbapenems and cefepime in the treatment of BSIs, cUTIs, and cIAIs caused by AmpC-producing *Enterobacterales* is provided in Table 3. Overall, a large body of evidence obtained from well-design prospective and retrospective observational studies and from systematic reviews showed no significant difference in terms of clinical cure and mortality rate between cefepime and carbapenems in settings characterized by ICU admission up to 60%.[59–66] However, it should not be overlooked that cefepime was less effective against strains with an MIC ≥2 mg/L. One study showed significantly higher mortality rate in patients affected by cefepime-susceptible dose dependent (SDD) isolates (MIC 4–8 mg/L) who were treated with cefepime compared to those treated with carbapenems (71.4% vs 18.2%; p=0.045), even if a full-dose cefepime (6g/day) was administered only in 38.6% of cases.[65] Likewise, higher rate of persistent bacteraemia was shown among patients affected with cefepime-SDD isolates who were treated with cefepime.[62] However, only 16% of patients received full-dose cefepime.

Klebsiella Pneumoniae Carbapenemase (KPC)-Producing Enterobacterales

Recommendations are depicted in Figure 2, panel A.4. Ceftazidime-avibactam (2.5g LD followed by 2.5g q8h over 8h CI) is recommended as first-line therapy for the management of BSIs, cIAIs, and cUTIs caused by KPC-producing *Enterobacterales*. Meropenem-vaborbactam (2g/2g q8h over 8h CI after 2g/2g LD), imipenem-relebactam (0.5g/0.25g q6h over 3h), and cefiderocol (2g LD followed by 2g q8h over 8h CI) could be alternative options, and are listed in a hierarchical scale. A summary of scientific evidences is provided in Table 4. One prospective and eight retrospective observational studies support the role of ceftazidime-avibactam in the management of KPC-producing BSIs, cIAIs, and cUTIs in settings with an ICU admission up to 60%.[67–75] Van Duin et al assessed prospectively 137 carbapenemase-producing *Enterobacterales* (CPE) infections (38 treated with ceftazidime-avibactam vs 99 with colistin-based regimens).[67] Ceftazidime-avibactam showed a better adjusted probability of favourable outcome (64%; p=0.0012), and a 3.5-fold lower all-cause mortality rate than colistin-based regimens (8% vs 33%; p=0.001). Caston et al analysed retrospectively 31 CPE infections among hematologic patients (8 treated with CAZ-AVI vs 23 treated with other antibiotic combinations, mainly carbapenems and aminoglycosides).[68] Patients treated with ceftazidime-avibactam showed significantly higher clinical cure rate (85.7% vs 34.8%; p=0.03). Tumbarello et al analysed 208 patients with KPC-producing *Klebsiella pneumoniae* BSIs (104 treated with ceftazidime-avibactam as second line therapy vs 104 treated with different rescue mono- or

Table 3 Summary of the Studies Investigating the Treatment of AmpC-Producing *Enterobacterales* Bloodstream Infections (BSIs), Complicated Intraabdominal (cIAIs) and Urinary Tract Infections (cUTIs) with Carbapenems and Cefepime

Author, Year and Reference	Study Design	No. of Patients	Antibiotic and Dosing	Source of Infection	AmpC-Producing Pathogens and Molecular Profile	Severity	Clinical Outcomes	Relapse Rate – Resistance Development	Comments
Carbapenems vs Cefepime									
Harris et al, 2015[59]	Systematic review with meta-analysis	11 studies (6 retrospective 5 prospective)	Carbapenems vs BL/BLIs – cefepime - FQ	BSI	*Enterobacter spp* *Citrobacter spp* *Serratia spp* *Morganella spp*	8 studies including cefepime vs carbapenems. No significant difference in mortality rate was found for both empiric (OR 0.60; CI 0.17–2.20) or definitive therapy (OR 0.61; CI 0.27–1.38).			
Tamma et al, 2013[61]	Prospective propensity score matched cohort	78 (46 CEF vs 32 MER)	Cefepime (1–2 g q8h) vs Meropenem (1–2 g q8h) Dose adjustment for renal impairment	40 HAP 38 BSI 38 cIAI	51 *E. cloacae* 31 *E. aerogenes* 13 *S. marcescens* 1 *C. freundii*	ICU admission 42.7% vs 62.5% Mechanical ventilation 29.2% vs 37.5% Septic shock 22.9% vs 34.4% Immunocompromised 29.2% vs 50%	No difference in 30-day mortality rate (OR 0.63 95% CI 0.23–2.11) No difference in hospital length of stay (OR 0.96 95% CI 0.79–1.26)	Relapse 25% Resistance 1.6% (in cefepime group)	Cefepime may be a reasonable option for the treatment of invasive infections due to AmpC β-lactamase–producing organisms
Tan et al, 2020[64]	Retrospective cohort study	241 of which 189 with definitive therapy with CEF (N=57) or carbapenems (N=132)	CEF (N=57) vs IMI (N=16) or MER (N=55) or ERT (N=61)	55 cUTI 53 CR-BSI 46 cIAI 30 Pneumonia 13 SSTI 44 others All BSI	140 *Enterobacter spp* 54 *Serratia spp* 40 *M. morganii* 5 *C. freundii* 2 *Providencia spp*	ICU admission 21.6%	30-day mortality rate: 5.3% CEF vs 18.9% carbapenems (p=0.02) At multivariate analysis carbapenems not associated with significant higher mortality compared to CEF (OR 2.25; CI 0.86–5.91)	NA	Empirical PIP/TZB and definitive CEF were not associated with 30-day mortality compared to carbapenems

Cheng et al, 2017[66]	Retrospective matched case-control	165 (88 PIP/TZB vs 77 CEF or MER)	PIP-TZB vs CEF or MER	33 cIAI 31 cUTI 28 HAP/VAP 22 CR-BSI 15 SSTI 36 others All BSI	85 *E. cloacae* 43 *S. marcescens* 17 *Citrobacter spp* 15 *E. aerogenes* 2 *S. liquefaciens* 2 *E. absuriae* 1 *E. cancerogenus*	ICU admission 40% RRT 17% Septic shock 24.2% Neutropenia 6.1% Immunocompromised 26.1%	30-day mortality rate: 10% PIP/TZB vs 12% CEF or MER	Persistent BSI 16% PIP/TZB vs 13% MER	Piperacillin-tazobactam may be a suitable alternative for the treatment of BSIs with AmpC-producing *Enterobacter, Serratia*, and *Citrobacter spp*
Lee et al, 2015[65]	Retrospective cohort study	144 (72 CEF vs 72 carbapenems)	CEF (2–6 g/day) vs IMI (0.5 g q6h) or MER (1 g q8h) or ERT (1 g/day)	53 CR-BSI 45 primary BSI 13 HAP 11 cUTI 11 cIAI 8 SSTI All BSI	144 *E. cloacae*	Pitt score ≥ 4 38.9% Neutropenia 9%	30-day mortality rate: 26.4% CEF vs 22.6% carbapenems Higher mortality rate with CEF vs carbapenems in CEF-SDD isolates (71.4% vs 18.2%; p=0.045)	NA	CEF-SDD isolates (MIC 4–8 mg/L) independently associated with 30-day mortality at multivariate analysis
Siedner et al, 2014[62]	Retrospective cohort study	271 of which 52 (36 CEF monotherapy vs 16 carbapenem monotherapy)	Cefepime (<2 – 6 g/day)	All BSI 76% primary BSI 7% cUTI 6% pneumonia 4% cIAI 4% CR-BSI	271 *Enterobacter spp*	ICU admission 22% Neutropenia 19% Pitt score ≥5 7% Solid organ transplant 6% Haematopoietic stem cell transplant 6%	No difference in-hospital mortality rate 17% CEF vs 26% carbapenem	Persistent bacteraemia: 25% carbapenem vs 0% CEF (p=0.002) in monotherapy	In patients who received cefepime with evaluable MIC results, only 2 of 74 (3%) patients with an isolate with a cefepime MIC of ≤2 μg/mL had persistent bacteraemia within 24 hours vs 6 of 23 (26%) patients with an MIC ≥ 4 μg/mL (P < 0.001)

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Table 3 (Continued).

Author, Year and Reference	Study Design	No. of Patients	Antibiotic and Dosing	Source of Infection	AmpC-Producing Pathogens and Molecular Profile	Severity	Clinical Outcomes	Relapse Rate – Resistance Development	Comments
Blanchette et al, 2014[60]	Retrospective matched case-control	48 (32 CEF vs 16 ERT)	Cefepime vs Ertapenem	15 cUTI 10 BSI 9 SSTI 9 HAP 6 cIAI	32 *Enterobacter spp* 9 *Citrobacter spp* 7 *Serratia spp*	ICU admission 18.8% Immunocompromised 20.8% Median APACHE II score 11 vs 13.5	Clinical success: 88% CEF vs 69% ERT (p=0.138)	Resistance: 25% ERT vs 17% CEF	Cefepime may be a reasonable option for the treatment of invasive infections due to AmpC β-lactamase–producing organisms
Hilty et al, 2013[63]	Retrospective cohort study	43	Cefepime (2 g/day – 2 g q8h) Meropenem (1 g/day – 2 g q8h) Piperacillin-TZB Ceftriaxone	51 primary BSI 6 cUTI 3 CR-BSI 67.4% Hospital-acquired	57 *E. cloacae*	ICU admission 11.6% Septic shock 2.3% Mechanical ventilation 25.6% Immunocompromised 41.9% Neutropenia 30.2%	Clinical cure rate: 88.9% CEF vs 92.3% carbapenems	NA	Cefepime represents a safe therapeutic option and an alternative to carbapenems to treat BSIs due to EcI when the prevalence of ESBL-producers is low.

Abbreviations: BSIs, bloodstream infections; CEF, cefepime; cIAI, complicated intra abdominal infections; CR-BSI, catheter-related bloodstream infections; cUTI, complicated urinary tract infection; ERT, ertapenem; FQ, fluoroquinolones; HAP, hospital-acquired pneumonia; ICU, intensive care unit; IMI, imipenem; MER, meropenem; MIC, minimum inhibitory concentration; NA, not available; PIP-TZB, piperacillin-tazobactam; RRT, renal replacement therapy; SDD, susceptible dose dependent; SSTI, skin and soft tissue infections.

Table 4 Summary of the Studies Investigating the Treatment of *Klebsiella pneumoniae* Carbapenemase (KPC)-Producing *Enterobacterales* Bloodstream Infections (BSIs), Complicated Intraabdominal (cIAIs) and Urinary Tract Infections (cUTIs) with Ceftazidime-Avibactam, Meropenem-Vaborbactam, Imipenem-Relebactam and Cefiderocol

Author, Year and Reference	Study Design	No. of Patients	Antibiotic and Dosing	Source of Infection	CPE-producing Pathogens and Molecular Profile	Severity	Clinical Outcomes	Relapse Rate – Resistance Development	Comments
Ceftazidime-avibactam									
van Duin et al, 2018[67]	Prospective observational multicentric, comparative	137 (38 CAZ-AVI vs 99 colisitn-based treatment)	CAZ-AVI 100% target therapy	16 primary BSIs 9 HAP 6 cUTIs 6 SSTIs 2 others	37 *K. pneumoniae* 1 *Enterobacter spp* All KPC-2 or −3	ICU admission 53% Pitt score > 4 18% Immunosuppressed 29%	Mortality rate at 30-day: 8% vs 33% (p=0.001)	NA	64% of probability of better outcome with CAZ-AVI compared to colistin at DOOR analysis
Tumbarello et al, 2021[75]	Retrospective observational, non-comparative	577	CAZ-AVI 2 g/0.5 g q8h 100% target therapy Prolonged infusion 42.6% Monotherapy 28.6%	391 BSI 71 cUTI 59 HAP 35 cIAI 21 others	All KPC-producing *K. pneumoniae*	ICU admission 23.7% Mechanical ventilation 28.1% Neutropenia 3.8% Transplant recipient 14.9% Immunocompromised 7.8%	Overall mortality rate at 30-day: 25.3%	Relapse 10.9% Resistance development 3.5%	Prolonged infusion of CAZ-AVI was negatively associated with mortality at multivariate analysis. No difference in mortality rate between monotherapy and combination therapy (26.1% vs 25.0%; p=0.79)
Tumbarello et al, 2019[69]	Retrospective observational multicentric, comparative	138 treated with CAZ-AVI Case-control matching between 104 BSIs treated with CAZ-AVI and 104 BSI patients treated with other treatments*	CAZ-AVI 2 g /0.5 g q8h 100% target therapy Dose adjustment for renal impairment according to manufacturer's instruction	104 BSI 13 HAP 12 cIAI 6 cUTI 3 others	138 *K. pneumoniae* 138 KPC (93.5% meropenem MIC ≥16 mg/L)	ICU admission 33.3% Mechanical ventilation 31.2% Septic shock 31.2% Median Pitt index 4 Neutropenia 10.9%	Overall mortality rate at 30-day: 34.1% Mortality rate at 30-day (only BSIs) 36.5% vs 55.8% (p=0.005)	Relapse 8.7% Resistance development 2.2%	At multivariate analysis CAZ-AVI was the only variable independently associated with survival.

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Table 4 (Continued).

Author, Year and Reference	Study Design	No. of Patients	Antibiotic and Dosing	Source of Infection	CPE-producing Pathogens and Molecular Profile	Severity	Clinical Outcomes	Relapse Rate – Resistance Development	Comments
Shields et al, 2017[70]	Retrospective observational, comparative	109 (13 CAZ-AVI vs 96 other treatments*)	CAZ-AVI 100% target therapy	3 primary BSIs 10 secondary BSIs (5 cUTI; 3 HAP; 2 cIAI)	13 *K. pneumoniae* 9 KPC-2 4 KPC-3 (CAZ-AVI MIC 0.25–2 mg/L)	ICU admission 46% RRT 15% Median Pitt score 4 Median APACHE II score 20 Immunocompromised 38% Solid organ transplant recipient 23%	Mortality rate at 30-day: 8% vs 31.3% (p=0.01) Mortality rate at 90-day: 8% vs 44.8% Clinical cure rate at 14-day: 85% vs 40.6% (p=0.006)	Relapse 15%	At multivariate analysis CAZ-AVI was an independent predictor of clinical success.
Shields et al, 2018[74]	Retrospective observational, non-comparative	77	CAZ-AVI 2 g /0.5 g q8h 100% target therapy Dose adjustment for renal impairment according to manufacturer's instruction	34 HAP 20 primary BSI 8 cUTI 7 cIAI 6 SSTI 1 mediastinitis 1 meningitis	60 *K. pneumoniae* 9 *E. coli* 5 *E. cloacae* 1 *E. aerogenes* 1 *K. oxytoca* 1 *Serratia marcescens* 58 KPC	Median SOFA 5 Median SAPS II 41 CRRT 21% Transplant recipient 26%	Overall mortality rate at 30-day: 19% Overall mortality rate at 90-day: 31% Overall clinical cure rate: 55%	Relapse 32% Resistance development 10%	Pneumonia was an independent predictor of clinical and microbiological failure at multivariate analysis. RRT was an independent predictor of clinical failure and resistance development at multivariate analysis.
King et al, 2017[72]	Retrospective observational multicentric, non-comparative	60	CAZ-AVI 100% target therapy Dosage according to manufacturer's instruction	23 primary BSI 17 cUTI 16 HAP 8 SSTI 4 cIAI 2 osteomyelitis	50 *K. pneumoniae* 5 *E. coli* 4 *Enterobacter spp* 1 *Providencia stuartii* 1 *Serratia marcescens* 1 *K. oxytoca*	ICU admission 59% Mechanical ventilation 38% Septic shock 21% RRT 23% Median Pitt score 2 Solid organ transplant recipient 25%	Overall in-hospital mortality rate: 32% Overall clinical cure rate: 65%	NA	Patients who required a renal adjustment of CAZ-AVI trended toward high in-hospital mortality (42% versus 19% without renal adjustment, p= 0.0567).

Temkin et al, 2017[71]	Retrospective observational multicentric, non-comparative	38	CAZ-AVI 100% target therapy	15 cIAI 7 HAP 4 SSTI 3 cUTI 7 primary BSI or CR-BSI 2 endocarditis 3 osteomyelitis 2 surgical site infection 3 Others	34 *K. pneumoniae* 1 *K. oxytoca* 1 *E. coli* 2 *P. aeruginosa* 23 KPC 13 OXA-48	Septic shock 44.7% Mechanical ventilation 36.8% Immunosuppression 23%	Overall mortality rate: 39.5% Overall clinical/ microbiological cure rate: 73.7%	5.3% relapse	
Shields et al, 2016[73]	Retrospective observational, non-comparative	37	CAZ-AVI 2 g /0.5 g q8h 100% target therapy Dose adjustment for renal impairment according to manufacturer's instruction	13 HAP 10 primary BSI 4 cIAI 4 SSTI 4 cUTI 1 mediastinitis 1 meningitis	31 *K. pneumoniae* 3 *E. coli* 2 *E. cloacae* 1 *E. aerogenes* 16 KPC-3 13 KPC-2 7 CTX-M 4 OXA-1-like 1 ESBL 1 AmpC	Mean SOFA 5 Mean SAPS-II 34 CRRT 16.2% Transplant recipient 30%	Overall mortality rate at 30-day: 24% Overall clinical cure rate: 59%	Relapse 27% Resistance development 8%	Success rates were lower for patients who required CRRT: 17% vs 68%; p= 0.03.
Caston et al, 2017[68]	Retrospective observational multicentric, comparative	31 (8 CAZ-AVI vs 23 other treatments*)	CAZ-AVI 2 g /0.5 g q8h 100% target therapy Dose adjustment for renal impairment according to manufacturer's instruction	2 HAP 2 BSI 1 CR-BSI 1 cIAI 1 SSTI 1 other	6 *K. pneumoniae* 1 *E. coli* 1 *K. oxytoca* 5 OXA-48 3 KPC	ICU admission 16.7% Septic shock 37.5% Renal failure 25.0% Median Pitt index 3 Neutropenia 62.5%	Clinical cure at-14 day: 85.7% vs 34.8% (p=0.03) Mortality rate at 30-day: 25.0% vs 52.2% (p=0.24)	NA	CAZ-AVI associated with higher clinical cure rate compared to combination of other treatments. Trend to lower mortality rate with CAZ-AVI.

(*Continued*)

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Table 4 (Continued).

Author, Year and Reference	Study Design	No. of Patients	Antibiotic and Dosing	Source of Infection	CPE-producing Pathogens and Molecular Profile	Severity	Clinical Outcomes	Relapse Rate – Resistance Development	Comments
Meropenem-vaborbactam									
Wunderink et al, 2018[77]	Phase 3, randomized, prospective, multicenter, open-label	47 (32 MER-VAB vs 15 BAT)	MER-VAB 2 g/2 g q8h (3h-infusion) 100% target therapy Dose adjustment for renal impairment according to manufacturer's instruction	14 primary BSI 12 cUTI/AP 4 HAP/VAP 2 cIAI	29 *K. pneumoniae* 3 *E. coli* 1 *E. cloacae* 1 *S. marcescens*	ICU admission 15.6% Immunocompromised 34.4%	Clinical cure rate at the end of treatment: 65.6% vs 33.3% (p=0.03) Clinical cure rate at test of cure: 59.4% vs 26.7% (p=0.02) Mortality rate at 28-day: 15.6% vs 33.3%	NA	Monotherapy with MER-VAB for CRE infection was associated with increased clinical cure, decreased mortality, and reduced nephrotoxicity compared with BAT
Ackley et al, 2020[78]	Retrospective observational cohort, multicenter, comparative	131 (26 MER-VAB vs 105 CAZ-AVI)	MER-VAB 2 g/2 g q8h 100% target therapy	12 HAP/VAP (2) 8 cIAI (3) 3 SSTI (1) 1 primary BSI 1 cUTI (1) 1 other (1) () number of secondary BSIs	15 *Klebsiella spp* 8 *Enterobacter spp* 3 *E. coli* 2 *Citrobacter spp* 1 *Serratia spp*	ICU admission 65.4% Median APACHE II score 27 RRT 4.8% Immunocompromised 15.4%	Overall clinical success: 69.2% vs 61.9% Mortality rate at 30-day: 11.5% vs 19.1%	Relapse 11.5% No resistance development	Similar rates of clinical success between MER-VAB and CAZ-AVI in KPC-producing CRE infections

Alosaimy et al, 2020[79]	Retrospective observational, multicenter, non-comparative	40	MER-VAB 2 g/2 g q8h 100% target therapy	13 HAP/VAP 11 BSI 8 cUTI 5 cIAI 5 SSTI	21 *K. pneumoniae* 9 *E. cloacae* 6 *E. coli* 3 *B. cepacian* 2 *P. aeruginosa* 1 *A. baumannii* 1 *M. morganii* 1 *P. mirabilis* 1 *S. marcescens*	ICU admission 70% Median APACHE II score 17	Overall clinical success: 70% Mortality rate at 90-day: 22.5%	Relapse 12.5%	
Shields et al, 2020[80]	Prospective observational, non-comapartive	20	MER-VAB 2 g/2 g q8h 100% target therapy Dose adjustment for renal impairment according to manufacturer's instruction	8 BSI 6 HAP/VAP 2 SSTI 2 UTRI 1 cUTI 1 cIAI	14 *K. pneumoniae* 2 *K. oxytoca* 2 *E. coli* 1 *E. cloacae* 1 *C. freundii* 10 KPC-3 7 KPC-2 1 KPC-31	ICU admission 70% RRT 35% Median SOFA 5 Median APACHE II score 20	Clinical success at 30-day: 65% Mortality rate at 30-day: 10%	Relapse 15% Resistance development 5%	
Imipenem-relebactam									
Motsch et al, 2019[81]	Phase 3, randomized, prospective, multicenter, open-label	31 (21 IMI-REL vs 10 IMI + COL)	IMP-REL 0.5 g/0.25 g q6h 100% target therapy Dose adjustment according to renal function	11 cUTI 8 HAP/VAP 2 cIAI	16 *P. aeruginosa* 3 *K. pneumoniae* 1 *E. cloacae* 1 *C. freundii* 4 KPC	APACHE II score > 15: 33.3%	Overall response rate: 71.4% vs 70% Clinical response at 28-day: 71.4% vs 40% ($p< 0.05$) Mortality rate at 28-day: 9.5% vs 30.0%	Relapse 9.5%	IMI-REL as a suitable treatment option for serious gram-negative infections, including CRE in high-risk patients. IMI/REL had comparable efficacy but significantly less nephrotoxicity and other AEs compared to COL.

(*Continued*)

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Table 4 (Continued).

Author, Year and Reference	Study Design	No. of Patients	Antibiotic and Dosing	Source of Infection	CPE-producing Pathogens and Molecular Profile	Severity	Clinical Outcomes	Relapse Rate – Resistance Development	Comments
Cefiderocol									
Bassetti et al, 2020[82]	Phase 3, randomized, prospective, multicenter, open-label	150 (101 cefiderocol vs 49 BAT)	Cefiderocol 2 g q8h (3h-infusion) 100% target therapy Dose adjustment according to renal function	45 HAP/VAP 30 BSI 26 cUTI	37 *A. baumannii* 27 *K. pneumoniae* 12 *P. aeruginosa* 5 *S. maltophilia* 2 *E. coli* 2 *E. cloacae* 2 *A. nosocomialis*	ICU admission 56% Septic shock 19% Mechanical ventilation 50% Immunocompromised 27% Mean SOFA score 5.1	Mortality rate at 14-day: 19% vs 12% Mortality rate at 28-day: 25% vs 18% Overall clinical cure at the end of treatment: 66% vs 58% Overall microbiological cure at the end of treatment: 48% vs 26%		A numerically higher proportion of patients with CRE infections achieved a clinical cure in the cefiderocol group than in the BAT group (66% vs 45%)

Abbreviations: AP, acute pyelonephritis; BAT, best available therapy; BSIs, bloodstream infections; CAZ-AVI, ceftazidime-avibactam; cIAI, complicated intra abdominal infections; COL, colistin; CR-BSI, catheter-related bloodstream infections; CRE, carbapenem-resistant *Enterobacterales*; CRRT, continuous renal replacement therapy; cUTI, complicated urinary tract infection; DOOR, desirability of outcome ranking; ICU, intensive care unit; IMI, imipenem; IMI-REL, imipenem-relebactam; KPC, Klebsiella pneumoniae-producing carbapenemase; MER-VAB, meropenem-vaborbactam; MIC, minimum inhibitory concentration; NA, not available; RRT, renal replacement therapy; SOFA, sequential organ failure assessment; SSTI, skin and soft tissue infections; URTI, upper respiratory tract infections; VAP, ventilator-associated pneumonia.

combo-treatments).[69] Patients treated with ceftazidime-avibactam showed significantly lower 30-day mortality rate (36.5% vs 55.8%; p=0.005), and ceftazidime-avibactam was the only independent predictor of survival at multivariate analysis. Shields et al analysed 109 CPE infections, 13 of whom treated with ceftazidime-avibactam and the other 96 with other antimicrobials (mainly colistin, aminoglycosides and carbapenems).[70] Patients receiving ceftazidime-avibactam showed significantly lower 30-day mortality rate (8% vs 31.3%; p=0.01) and higher clinical success rate (85% vs 40.6%; p=0.006). Very recently, Tumbarello et al analysed 577 patients with KPC-producing *Klebsiella pneumoniae* infections (67.8% with BSIs) treated with ceftazidime-avibactam.[75] No difference in mortality rate was found between ceftazidime-avibactam monotherapy vs combination therapy (26.1% vs 25.0%; p=0.79). Notably, ceftazidime-avibactam prolonged infusion resulted protective against mortality at multivariate analysis (p=0.006). In regard to meropenem-vaborbactam, it should be mentioned that vaborbactam was specifically developed to restore the activity of meropenem against KPCs.[76] A phase III RCT (TANGO II) assessed 47 patients affected by KPC-producing *Enterobacterales* infections, 32 of whom were treated with meropenem-vaborbactam and the other 15 with best-available therapy (including mono/combination therapy with colistin, carbapenems, aminoglycosides, tigecycline, or ceftazidime-avibactam alone). Meropenem-vaborbactam showed better clinical cure rate (65.6% vs 33.3%; p=0.03) and a trend toward lower mortality rate (15.6% vs 33.3%; p=0.20) compared to best available therapy.[77] However, it should be recognized that patients enrolled in this RCT required ICU admission only in 15.6% of cases. More attractive evidence for meropenem-vaborbactam as targeted therapy for KPC-producing *Enterobacterales* infections in critically ill patients came from observational studies, in which ICU admission ranged from 65.4% to 70%.[78–80] Clinical cure rate ranged 65–70%, and mortality rate 10–22.5%. Relapse rate of CPE infections ranged 11.5–15%, and in up to 5% of patients was reported resistance development to meropenem-vaborbactam. One retrospective study[78] reported no significant difference between 26 patients receiving meropenem-vaborbactam and 105 receiving ceftazidime-avibactam in terms of clinical cure rate (69.2 vs 61.9%) and mortality rate (11.5 vs 19.1%). In regard to imipenem-relebactam, it's worth mentioning that relebactam was combined to imipenem-cilastatin in order to restore activity against carbapenemase producing *Enterobacterales* and *Pseudomonas aeruginosa*.[76] In a phase III RCT of patients with severe Gram-negative infections, imipenem-relebactam demonstrated significantly better clinical cure rate compared to imipenem plus colistin (71.4% vs 40%; p<0.05).[81] However, infection by KPC-producing *Enterobacterales* was documented in only 4 out of the 21 patients enrolled in the imipenem-relebactam group. In regard to cefiderocol, in a phase III RCT 150 patients affected by carbapenem-resistant Gram-negative infections were randomized to cefiderocol (n=101) or best available therapy (including combination of aminoglycoside, carbapenems, colistin, fosfomycin or tigecycline) (n=49).[82] Clinical and microbiological cure rates between groups did not significantly differ. However, the number of documented KPC-producing *Enterobacterales* infections was quite limited.

OXA-48-Producing Enterobacterales

Recommendations are depicted in Figure 2, panel A.5. Ceftazidime-avibactam (2.5g LD followed by 2.5g q8h over 8h CI) is recommended as first-line therapy for the management of BSIs, cIAIs, and cUTIs caused by OXA-48 and OXA-48-like-producing *Enterobacterales*. (avibactam inhibits OXA-48, and ceftazidime is stable to this enzyme).[83] Cefiderocol (2g LD followed by 2g q8h over 8h CI) could be an alternative option. A summary of the studies evaluating the efficacy of ceftazidime-avibactam and cefiderocol in this setting is provided in Table 5. Alraddadi et al[84] compared retrospectively 10 patients treated with ceftazidime-avibactam with 28 treated with other mono- or combo-therapy (colistin, carbapenems, aminoglycosides, tigecycline, quinolone, cotrimoxazole, and aztreonam) for the management of CPE. After restricting analysis to OXA-48 infections, no difference in clinical cure (75% vs 40%; p=0.21) and in mortality rate (37.5% vs 50%; p=0.69) were reported. In two observational studies concerning the treatment with ceftazidime-avibactam of infections caused by OXA-48-producing *Enterobacterales*,[85,86] the clinical cure rate and mortality rate were similar to those found in other studies where it was used for the treatment of KPC infections [59–62]. Conversely, in one retrospective study assessing ceftazidime-avibactam as salvage therapy for infections caused by carbapenem-resistant organisms,[71] among the 13 patients who were affected by OXA-48 infections a trend toward lower microbiological cure (25% vs 75%; p=0.07) and survival to hospital discharge (22.7% vs 77.3%; p=0.07) compared to the 23 who had KPC infections was

Table 5 Summary of the Studies Investigating the Treatment of OXA-48 Producing *Enterobacterales* Bloodstream Infections (BSIs), Complicated Intraabdominal (cIAIs) and Urinary Tract Infections (cUTIs) with Ceftazidime-Avibactam and Cefiderocol

Author, Year and Reference	Study Design	No. of Patients	Antibiotic and Dosing	Source of Infection	CPE-Producing Pathogens and Molecular Profile	Severity	Clinical Outcomes	Relapse Rate – Resistance Development	Comments
Ceftazidime-avibactam									
Sousa et al, 2018[86]	Prospective observational, non-comparative	57	CAZ-AVI 2 g /0.5 g q8h 100% target therapy Dose adjustment for renal impairment according to manufacturer's instruction	16 cIAI 15 HAP/VAP 14 cUTI 6 CR-BSI 3 SSTI 1 meningitis 1 osteomyelitis 1 mediastinitis	54 *K. pneumoniae* 2 *E. coli* 1 *E. cloacae* All OXA-48	ICU admission 38% Septic shock 35% Mechanical ventilation 30% Median APACHE II score 24	Overall clinical cure rate: 77% Mortality rate at 30-day: 22%	10% relapse	CAZ-AVI showed similar clinical cure and survival rate in OXA-48 infection compared to KPC
Temkin et al, 2017[71]	Retrospective observational multicentric, non-comparative	38	CAZ-AVI 100% target therapy	15 cIAI 7 HAP 4 SSTI 3 cUTI 7 primary BSI or CR-BSI 2 endocarditis 3 osteomyelitis 2 surgical site infection 3 Others	34 *K. pneumoniae* 1 *K. oxytoca* 1 *E. coli* 2 *P. aeruginosa* 23 KPC 13 OXA-48	Septic shock 44.7% Mechanical ventilation 36.8% Immunosuppression 23%	Overall mortality rate: 39.5% Overall clinical/ microbiological cure rate: 73.7%	5.3% relapse	A trend to lower documented microbiological cure (25% vs 75%; p=0.07) and survival to hospital discharge (22.7% vs 77.3%; p=0.07) was found for the treatment of OXA-48 compared to KPC infections with CAZ-AVI
Alraddadi et al, 2019[84]	Retrospective observational cohort, comparative	38 (10 CAZ-AVI vs 28 other agents)	CAZ-AVI 2 g /0.5 g q8h 100% target therapy	5 HAP 3 cUTI 3 cIAI 2 SSTI 1 CR-BSI	7 *K. pneumoniae* 3 *E. coli* 8 OXA-48 1 NDM 1 NA	Transplant recipient 50%	Overall clinical cure rate: 80% vs 53.6% Overall mortality rate: 50% vs 57.1%	20% relapse	No difference in clinical cure (75% vs 40%; p=0.21) and mortality rate (37.5% vs 50%; p=0.69) after restricting analysis on patients with OXA-48 infections

De la Calle et al, 2019[85]	Retrospective observational, non-comparative	24	CAZ-AVI 2 g /0.5 g q8h 100% target therapy Dose adjustment for renal impairment according to manufacturer's instruction	7 cIAI 6 cUTI 5 HAP 4 SSTI 1 meningitis 1 CR-BSI	23 *K. pneumoniae* 1 *E. coli* All OXA-48 (range MIC CAZ-AVI 0.5–1 mg/L)	ICU admission 33.3% Septic shock 16.7% Mean SOFA score 3.3 Immunosuppression 21.7% Solid organ transplantation 21.7%	Overall clinical cure rate: 62.5% Mortality rate at 30-day: 8.3%	29.2% relapse	CAZ-AVI showed similar clinical cure and survival rate in OXA-48 infection compared to KPC
Cefiderocol									
Contreras et al, 2019[87]	Case report	1	Cefiderocol 1.5 g q12h	bacteraemic cIAI	*K. pneumoniae* NDM-1-OXA-48	ICU admission CRRT/ECMO Kidney transplant recipient	Clinical and microbiological cure, but death due to ischaemic colitis	No relapse	
Dobias et al, 2017[88]	In vitro study	154 OXA-48 isolates	88 *K. pneumoniae*, 42 *E. coli*, 24 *Enterobacter spp.* Cefiderocol MIC range: 0.03–64 (MIC_{50} 0.25 mg/L; MIC_{90}: 2 mg/L)						
Delgado-Valverde et al, 2020[91]	In vitro study	57 OXA-48 isolates	25 ST11/OXA-48 + CTX-M-15 *K. pneumoniae*. Cefiderocol MIC range ≤0.03–4 (MIC_{50} 0.25 mg/L; MIC_{90}: 2 mg/L) 25 ST15/OXA-48 + CTX-M-15 *K. pneumoniae*. Cefiderocol MIC range ≤0.03–4 (MIC_{50} 0.25 mg/L; MIC_{90}: 4 mg/L) 3 ST147/OXA-48 *K. pneumoniae*. Cefiderocol MIC range 0.06–0.5 (MIC_{50} 0.25 mg/L; MIC_{90}: 0.5 mg/L) 4 ST392/OXA-48 + CTX-M-15 *K. pneumoniae*. Cefiderocol MIC range 0.06–1 (MIC_{50} 0.25 mg/L; MIC_{90}: 1 mg/L)						
Kazmierczak et al, 2019[89]	In vitro study	32 OXA-48 isolates	21 *K. pneumoniae*, 4 *E. cloacae*, 3 *E. coli*, 3 *C. freundii*, 1 *K. Oxytoca*. Cefiderocol MIC range: 0.03–4 (MIC_{50} 0.5 mg/L; MIC_{90}: 4 mg/L)						
Jacobs et al, 2019[90]	In vitro study	7 OXA-48 isolates	7 *K. pneumoniae*. Cefiderocol MIC range ≤0.03–1 (MIC_{50} 0.25 mg/L; MIC_{90}: 1 mg/L)						

Abbreviations: BSIs, bloodstream infections; CAZ-AVI, ceftazidime-avibactam; cIAI, complicated intra abdominal infections; CR-BSI, catheter-related bloodstream infections; CRRT, continuous renal replacement therapy; cUTI, complicated urinary tract infection; ECMO, extracorporeal membrane oxygenation; ICU, intensive care unit; MIC, minimum inhibitory concentration; NA, not available; NDM, New-Delhi metallo-beta-lactamase; SSTI, skin and soft tissue infections; VAP, ventilator-associated pneumonia.

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found. In regard to cefiderocol, there is only one case[87] that reported its use for the management of a secondary BSI caused by carbapenem-resistant *K. pneumoniae* co-producing OXA-48-like and New Delhi metallo-beta-lactamase-1 (NDM-1). Microbiological cure was proven, and the patient died because of an ischaemic colitis secondary to *Clostridium difficile* infection. Besides, several in vitro studies[88–91] support the good activity of cefiderocol against OXA-48 producing *Enterobacterales*, with MIC_{50} and MIC_{90} ranging 0.25–0.5 mg/L, and 0.5–4 mg/L, respectively.

Metallo-Beta-Lactamase (MBL)-Positive Enterobacterales

Recommendations are depicted in Figure 2, panel A.6. Ceftazidime-avibactam (2.5g LD followed by 2.5g q8h over 8h CI) plus aztreonam (2g q8h over 8h CI after 2g LD) is the recommended first-line therapy for the management of BSIs, cIAIs, and cUTIs caused by New-Delhi metallo beta-lactamases (NDM)-producing *Enterobacterales*. Cefiderocol (2g LD followed by 2g q8h over 8h CI) is recommended for the treatment of infections caused by Verona Integron-encoded metallo-beta-lactamase (VIM)-producing and/or imipenemase (IMP)-producing *Enterobacterales*. Fosfomycin (6g LD followed by 16g CI) plus high-dose meropenem (1.5–2g q6h over 6h CI after 2g LD) could be an alternative option for both NDM-producing and VIM-IMP-producing *Enterobacterales*. MBLs are associated with extremely-drug-resistant (XDR) phenotypes, as they may hydrolyse the vast majority of currently available beta-lactams.[92] A summary of the studies evaluating the efficacy of these antibiotics in the setting is provided in Table 6. One prospective observational study, two case series and five case reports suggest the efficacy of the combination therapy ceftazidime-avibactam plus aztreonam in the treatment of critically ill patients affected by NDM infections (mainly expressed by *Klebsiella pneumoniae*).[93–100] Falcone et al[93] compared in a prospective observational study 52 patients receiving the combination ceftazidime-avibactam plus aztreonam with 50 subjects receiving other active antibiotics in the management of BSIs due to NDM-producing and/or VIM-producing *Enterobacterales*. Patients treated with ceftazidime-avibactam plus aztreonam showed significantly lower mortality rate (19.2% vs 44%; p=0.007) and clinical failure rate (25% vs 52%; p=0.005). Shaw et al[94] reported a case series of ceftazidime-avibactam plus aztreonam for the treatment of an outbreak caused by NDM-1/OXA-48-producing *Klebsiella pneumoniae* strain. Among 10 treated patients, 4 were solid organ transplant recipients, and half had bacteraemic infections (including cUTIs and cIAIs). Overall clinical cure rate at 30-day was 60%, and three patients died. Cairns et al[101] reported a case series of four immunocompromised patients affected by IMP-4-producing *Enterobacter cloacae* infections successfully treated with ceftazidime-avibactam plus aztreonam, and relapse occurred only in one case. In regard to cefiderocol, only one case reported its role in the management of a secondary BSI caused by carbapenem-resistant *K. pneumoniae* co-producing NDM-1 and OXA-48-like beta-lactamases.[87] However, several in vitro studies support the good activity of cefiderocol against NDM-producing *Enterobacterales* (MIC_{50}: 1–4 mg/L and MIC_{90}: 4–8 mg/L, susceptibility rate of 41–72.1%), and IMP-VIM-positive isolates (MIC_{50} 1 mg/L, MIC_{90} 4 mg/L, susceptibility rate of 80.9–95.7%).[88,89,102] In regard to the combination of fosfomycin with high-dose meropenem, only one case documented the efficacy of this combo in a kidney transplant recipient affected by bacteraemic cUTI due to NDM-1-producing *Morganella morganii*.[103] An i*n vitro* study showed the synergistic effect of this combination against 10 NDM-producing *Klebsiella pneumoniae* strains (including five isolates co-producing OXA-48 carbapenemases).[104]

Overview of Recommendations

The widespread diffusion of CRE isolates and the different genotypes of resistance of *Enterobacterales* requires careful attention for the right place in therapy of novel beta-lactams and the prompt adoption of strategies for sparing the broadest-spectrum antibiotics whenever possible. Ampicillin-sulbactam and ceftriaxone still represent the first-choice treatment of BSIs, cIAIs, or cUTIs caused by multi-susceptible *Enterobacterales*. Piperacillin-tazobactam should be recommended for the treatment of BSIs, cIAIs, or cUTIs caused by ESBL-producing *Enterobacterales* with an MIC ≤8 mg/L, especially in low-risk patients.[105] In this scenario, altered dosing strategies based on high-doses administered by CI may maximize clinical efficacy of piperacillin-tazobactam against ESBL isolates, and this approach has been recently suggested by the EUCAST as well.[105] Ertapenem was not recommended for the treatment of ESBL-producing infections in critically ill patients, as some studies[106,107] showed that among patients affected by septic shock treatment with ertapenem was associated with higher mortality rate compared to other carbapenems. Cefepime may represent an effective "carbapenem-sparing" strategy for the treatment of infections caused by AmpC-producing

Table 6 Summary of the Studies Investigating the Treatment of Metallo-Beta-Lactamase (MBL) Producing *Enterobacterales* Bloodstream Infections (BSIs), Complicated Intraabdominal (cIAIs) and Urinary Tract Infections (cUTIs) with Aztreonam-Avibactam, Cefiderocol and Combination Therapy with Meropenem and Fosfomycin

Author, Year and Reference	Study Design	No. of Patients	Antibiotic and Dosing	Source of Infection	CPE-Producing Pathogens and Molecular Profile	Severity	Clinical Outcomes	Relapse Rate – Resistance Development	Comments
NDM+ pathogens									
Ceftazidime-avibactam + Aztreonam									
Falcone et al, 2020[93]	Prospective observational, multicenter with propensity score analysis	102 (52 CAZ-AVI + Aztreonam vs 50 other active antibiotics)	CAZ-AVI (2.5 g q8h – 50% of cases CI) + Aztreonam (2 g q8h) vs Colistin (LD 9 MU – MD 4.5 MU q12h); Tigecycline (LD 100 mg – MD 50 mg q12h); Fosfomycin (4–6 g q6h); Meropenem (2 g q8h); Gentamicin (3–5 mg/kg/day)	All BSIs 33 cUTI 32 CR-BSI 12 SSTI 9 HAP/VAP 7 cIAI 14 unknown	93 *K. pneumoniae* 5 *Enterobacter spp* 3 *E. coli* 1 *M. morganii* 82 NDM-producing 20 VIM-producing	ICU admission 34.3% Solid organ transplantation 7.8% Septic shock 27.5% Mechanical ventilation 30.4% Median SOFA 4	30-day mortality rate: 19.2% vs 44% (p=0.007)	NA	CAZ-AVI + ATM was associated with lower 30-day mortality (HR 0.37; P=0.01), lower clinical failure at day 14 (HR 0.30; P=0.002), and shorter length of stay (HR 0.49; P=0.007)

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Table 6 (Continued).

Author, Year and Reference	Study Design	No. of Patients	Antibiotic and Dosing	Source of Infection	CPE-Producing Pathogens and Molecular Profile	Severity	Clinical Outcomes	Relapse Rate – Resistance Development	Comments
Shaw et al, 2017[94]	Case series	10	CAZ-AVI (0.94 g/day – 2.5 g q8h EI) + Aztreonam (1 g q8h – 2g q8h CI)	4 cUTI 2 cIAI 2 HAP 1 CR-BSI 1 mediastinitis 50% bacteraemic	10 *K. pneumoniae* 10 NDM-1/ OXA-48/CTX-M-15 (outbreak)	Mean SOFA: 3.7 Solid organ transplant recipient: 40% Immunocompromised: 50%	Clinical cure rate at 30-day: 60% Mortality rate at 30-day: 30%	Relapse 30%	
Benchetrit et al, 2019[95]	Case series	2	CAZ-AVI (0.94 g/day – 2.5 g/day EI) + Aztreonam 2 g q12-24 EI	1 BSI 1 VAP	2 *K. pneumoniae* 2 NDM-1 (MIC 0.032–0.064 mg/L)	ICU admission: 100% Solid transplant recipient: 100% Immunocompromised: 100%	Overall clinical cure rate: 100% Overall survival rate: 0%	Relapse 100%	
Shah et al, 2019[96]	Case report	1	CAZ-AVI 0.94 g q12h + Aztreonam 1 g q8h	bacteraemic cUTI	*K. pneumoniae* No genotypification	-	Clinical failure	-	
Hobson et al, 2019[97]	Case report	1	CAZ-AVI 150 mg/kg/day + Aztreonam (100 mg/kg/day)	BSI	*Morganella morganii* NDM-1 (MIC 0.016 mg/L)	Haematological malignancy	Clinical and microbiological cure	No relapse at 6-month	

Sieswerda et al, 2019[98]	Case report	1	CAZ-AVI 2.5 g q8h CI + Aztreonam 1 g q8h EI	cUTI	*K. pneumoniae* NDM-1 (MIC 0.5 mg/L)	Kidney transplant recipient	Clinical cure	Relapse at one month with the same strain. No difference in susceptibility	
Yasmin et al, 2020[99]	Case report	1	CAZ-AVI 50 mg/kg q8h (EI 3h) + Aztreonam 50 mg/kg q8h	BSI	*E. hormaechei* NDM-1/KPC-4 (MIC 2/4 + 2 mg/L)	Haematological malignancy	Clinical and microbiological cure	No relapse	
Bocanegra-Ibarias et al, 2020[100]	Case report	1	CAZ-AVI 2.5 g q8h + Aztreonam 2 g q8h	BSI	*K. pneumoniae* NDM-1 (MIC 4/4 mg/L)	Haematological malignancy	Clinical and microbiological cure	No relapse	
Cefiderocol									
Contreras et al, 2019[87]	Case report	1	Cefiderocol 1.5 g q12h	bacteraemic cIAI	*K. pneumoniae* NDM-1-OXA-48	ICU admission CRRT/ECMO Kidney transplant recipient	Clinical and microbiological cure, but death due to ischaemic colitis	No relapse	
Dobias et al, 2017[88]	In vitro study	134 NDM-VIM-IMP+ isolates	67 *E. coli*, 38 *K. pneumoniae*, 29 *Enterobacter spp*. Cefiderocol MIC range: 0.03–64 (MIC_{50} 1 mg/L; MIC_{90}: 4 mg/L)						
Mushtaq et al, 2020[102]	In vitro study	61 NDM isolates	21 *E.* coli, 20 *Klebsiella spp*, 10 *Enterobacter spp*, 3 *Citrobacter spp*, 3 *Providencia spp*, 2 *Morganella spp*, 1 *Serratia spp*, 1 *Proteus spp*. Cefiderocol MIC range: 0.25–32 (MIC 2 S 41%; MIC 4 S 72.1%)						
Kazmierczak et al, 2019[89]	In vitro study	12 NDM isolates	11 *K. pneumoniae*, 1 *E. cloacae*. Cefiderocol MIC range: 1–8 (MIC_{50} 4 mg/L; MIC_{90}: 8 mg/L)						

(*Continued*)

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Table 6 (Continued).

Author, Year and Reference	Study Design	No. of Patients	Antibiotic and Dosing	Source of Infection	CPE-Producing Pathogens and Molecular Profile	Severity	Clinical Outcomes	Relapse Rate – Resistance Development	Comments
Meropenem + fosfomycin									
Seija et al, 2015[103]	Case report	1	Meropenem 2 g q8h EI + Fosfomycin 4 g q8h	bacteraemic cUTI	*Morganella morganii* NDM-1	Kidney transplant recipient	Clinical and microbiological cure	No relapse	
Sengel et al, 2020[104]	In vitro study	10 NDM isolates (5 NDM + 5 OXA-48/NDM)	10 *K. pneumoniae*. Synergic activity in 100% of isolates						
IMP/VIM+ pathogens									
Ceftazidime-avibactam + Aztreonam									
Cairns et al, 2020[101]	Case series	4	CAZ-AVI 0.94 q12h - 2.5 g q8h + Aztreonam 1.5–2 g q8h	2 bacteraemic cUTI 1 sternal osteomyelitis 1 CR-BSI	4 *E. cloacae* IMP-4 (MIC 0.125–0.25 mg/L)	ICU admission 50% 3 Solid organ transplant recipients 1 Haematological malignancy	Clinical and microbiological cure: 100%	Relapse 25%	
Cefiderocol									
Mushtaq et al, 2020[102]	In vitro study	62 VIM/IMP + isolates	22 *Klebsiella spp*, 20 *E.* coli, 12 *Enterobacter spp*, 8 *Citrobacter spp*. Cefiderocol MIC range: 0.03–8 (MIC 2 S 80.9%; MIC 4 S 95.7%)						
Kazmierczak et al, 2019[89]	In vitro study	27 VIM+ isolates	8 *K. pneumoniae*, 7 *E. cloacae*, 7 *C. freundii*, 3 *S. marcescens*, 1 *K. Oxytoca, 1 C. amanolaticus*. Cefiderocol MIC range: 0.12–4 (MIC_{50} 1 mg/L; MIC_{90}: 4 mg/L)						

Abbreviations: BSIs, bloodstream infections; CAZ-AVI, ceftazidime-avibactam; CI, continuous infusion; cIAI, complicated intra abdominal infections; CR-BSI, catheter-related bloodstream infections; CRRT, continuous renal replacement therapy; cUTI, complicated urinary tract infection; ECMO, extracorporeal membrane oxygenation; EI, extended infusion; HR, hazard ratio; ICU, intensive care unit; LD, loading dose; MD, maintenance dose; MIC, minimum inhibitory concentration; NA, not available; NDM, New-Delhi metallo-beta-lactamase; SSTI, skin and soft tissue infections; VAP, ventilator-associated pneumonia; VIM, Verona-integrase metallo-beta-lactamase

Enterobacterales with an MIC ≤1 mg/L.[108] Hopefully, some ongoing studies (namely MERINO-2, MERINO-3, PETERPEN, and FOREST studies) could better clarify the role of old and novel BL/BLIs in the management of critically ill patients affected by ESBL-producing *Enterobacterales* infections. Ceftazidime-avibactam, meropenem-vaborbactam, imipenem-relebactam, and cefiderocol may represent first-line choices for the management of critically ill patients affected by CRE infections expressing class A (eg, KPC) or D (eg, OXA-48) beta-lactamases.[76] These agents should be administered in prolonged or continuous infusion as well to maximize efficacy and clinical outcome.[75,109] Monotherapy with novel BL and BL/BLIs should always be pursued in these settings considering that comparative studies showed no significant advantage in efficacy of combination therapy vs monotherapy.[110,111] Against MBL-producers, the use of ceftazidime-avibactam plus aztreonam may represent an effective strategy for the management of NDM-producing *Enterobacterales* infections, whereas cefiderocol should be reserved mainly to VIM- or IMP-producing *Enterobacterales* infections.[76] This latter recommendations is justified by the fact that the overall susceptibility rate of cefiderocol against NDM-producing *Enterobacterales* is <70%, and MIC_{50}/MIC_{90} are 2–4-fold higher compared to VIM- or IMP-producing strains.[89,102,112,113] Fosfomycin combined with high-dose meropenem could represent a valuable alternative against both types of MBL-producing *Enterobacterales* infections.

Overall, altered dosing strategies of beta-lactams based on CI administration are strongly recommended for attaining very aggressive PK/PD target of 100% $fT_{>4\text{-}8xMIC}$.[51,105] This approach may both maximize clinical efficacy and prevent the development of resistance.[105] CI is feasible with a unique daily solution infused over 24 hours for those drugs that are stable in aqueous solution at room temperature for ≥ 1 day (eg, piperacillin-tazobactam, ceftolozane-tazobactam). Otherwise, for those drugs that are stable in aqueous solution at room temperature for 6–12h, CI may be granted through reconstitution of the aqueous solution every 6–8h and infusion over 6–8h (eg, meropenem, ampicillin/sulbactam, ceftazidime/avibactam).

Clinicians must be aware that the antibiotic dosing regimens that we recommended throughout the manuscript are focused only on treatment of patients with normal renal function. It should not be overlooked that the pharmacokinetics of hydrophilic antimicrobial agents, namely beta-lactams and fosfomycin, may be affected among critically ill patients by several pathophysiological conditions that may alter volume of distribution and/or renal clearance. Consequently, dose adjustments are needed in critically ill renal patients, especially among those with transient acute kidney injury, augmented renal clearance, and/or undergoing renal replacement therapy.[114] Finally, it should be mentioned that for the treatment of patients with well-documented life-threatening beta-lactam allergies, alternative agents s should be considered. Fluoroquinolones, aminoglycosides and colistin could be helpful in these cases depending on the susceptibility pattern of the isolated *Enterobacterales*.

Conclusions

In an era characterized by the widespread diffusion of MDR Gram-negative pathogens and by the incremental spread of antibiotic resistance, implementation of a multidisciplinary approach focused at targeted therapy in critically ill patients has become a real necessity. This could simultaneously allow to promptly revise inappropriate/unnecessary antibiotic regimens, to implement "carbapenem-sparing" strategies based on monotherapy with traditional and/or novel beta-lactams and, whenever applicable, to optimize antibiotic exposure in each single patient by means of real-time TDM guided approach. It is expected that these strategies could be helpful either in improving clinical outcome or in containing the spread of antimicrobial resistance in the ICU setting. It should be noted that the availability of rapid diagnostic technologies, based on molecular methods, that can reveal the presence of clinically-relevant resistance determinants such as the main ESBL and carbapenemase genes can be very useful to shorten the time for revision of empiric therapy according to the proposed algorithms.

Disclosure

B. Viaggi participated in advisory boards and in speaker's bureau for, and received research contracts, contributions and study events from Abbott, Accelerate Diagnostics, Ada, Alifax, Angelini, Becton Dickinson, Bellco, Biomerieux, Biotest, Cepheid, Correvio, Gilead, Menarini, MSD Italia, Nordic Pharma, Pfizer, Shionogi, Thermo Fisher Scientific; G.M. Rossolini participated in advisory boards and speaker's bureau for, and received research contracts, contributions and travel grants from Accelerate, Angelini, Arrow, Beckman Biomedical Service, Coulter, Becton-Dickinson, bioMérieux, Cepheid, Hain Life Sciences, Menarini, Meridian, MSD, Nordic Pharma, Pfizer, Qiagen, Q-linea, Qpex, Quidel, Qvella, Roche, Seegene, Set-Lance,

Shionogi, Symcel, ThermoFisher, VenatorX, Zambon; F. Pea participated in speaker bureau for Angelini, Basilea Pharmaceutica, Gilead, Hikma, Merck Sharp & Dohme, Nordic Pharma, Pfizer, and Sanofi Aventis, and in advisory board for Angelini, Basilea Pharmaceutica, Correvio, Gilead, Merck Sharp & Dohme, Nordic Pharma, Novartis, Pfizer, and Thermo-Fisher. P. Viale has served as a consultant for Biomerieux, Gilead, Merck Sharp & Dohme, Nabriva, Nordic Pharma, Pfizer, Thermo-Fisher, and Venatorx, and received payment for serving on the speaker's bureau for Correvio, Gilead, Merck Sharp & Dohme, Nordic Pharma and Pfizer. The authors report no other conflicts of interest in this work.

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