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How I manage patients with New Delhi metallo-beta-lactamase and OXA-48-producing Enterobacterales infections: a practical approach

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Purpose of review
Infections caused by New Delhi metallo-β-lactamase (NDM) and OXA-48-producing Enterobacterales pose a critical threat due to increasing global prevalence and limited therapeutic options. This review provides an updated overview of evolving epidemiological trends, clinical implications, and both current and emerging treatment options.

Recent findings
In the past decade, the epidemiology of carbapenem-resistant Enterobacterales (CRE) has changed, with NDM and OXA-48 replacing KPC in several regions. Outcomes of infections caused by NDM-producing CRE remain poor, due to limited treatment options. Ceftazidime/avibactam and aztreonam is the first-line therapeutic option, whereas cefiderocol represents an alternative if susceptibility is confirmed. Resistance to both aztreonam/avibactam and cefiderocol has been reported among NDM-5–producing *Escherichia coli*, raising concerns in the scientific community. New agents, including cefepime–zidebactam and cefepime–taniborbactam, are currently in development and may expand the future treatment landscape. For OXA-48–producing CRE, ceftazidime/avibactam and cefiderocol are currently available therapeutic options, whereas cefepime/enmetazobactam may become available in the next future.

Summary
Optimal management of NDM- and OXA-48-producing Enterobacterales requires individualized approach guided by pathogen type, resistance profile, and patient characteristics. Improved diagnostics and surveillance are essential to guide early treatment, while novel agents may enhance therapeutic options in the near future.

Keywords
aztreonam-avibactam, carbapenemase-producing Enterobacterales, cefepime/enmetazobactam, cefiderocol, multidrug-resistant Gram-negative bacteria, New Delhi metallo-β-lactamase, OXA-48

INTRODUCTION

Over the past decades, the global spread of carbapenemase-producing Enterobacterales (CPE) has become one of the greatest challenges for human health [1▪▪,2▪]. Until the early 2010s, KPC was the most prevalent carbapenemase worldwide in the United States, Europe, and Israel [3–8]. This led to widespread use of the terms CRE and "carbapenemase-producing Enterobacterales" as near-synonyms [9]. At that time, metallo-β-lactamases (MBL) were primarily reported in Enterobacterales in the Indian subcontinent but were sporadic in Europe [10]. OXA-48 was historically more commonly detected in *Klebsiella pneumoniae* and *Escherichia coli* from North Africa and Turkey [11]. In recent years, the epidemiological landscape has greatly changed. Both NDM- and OXA-48-producing Enterobacterales have expanded beyond their original endemic regions, becoming increasingly prevalent in several settings.

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KEY POINTS

- The global epidemiology of carbapenem-resistant Enterobacterales is shifting, with New Delhi metallo-β-lactamase (NDM) and OXA-48 now replacing KPC in several regions.
- Infections caused by NDM-producing strains are challenging due to resistance to last-line agents like cefiderocol and aztreonam/avibactam, especially in NDM-5-producing *E. coli*.
- Aztreonam/avibactam represents the first-line therapy for NDM producers.
- Further studies should confirm the similar efficacy of ceftazidime/avibactam plus aztreonam and aztreonam/avibactam.
- Cefepime–enmetazobactam is a promising options for OXA-48 infections.
- Individualized treatment strategies based on colonization status, resistance genes, and infection site are critical for optimizing outcomes.

Thus, knowledge of local epidemiology, use of rapid diagnostic testing methods and implementation of therapeutic strategies to manage infections caused by NDM- or OXA-48-producing Enterobacterales are critical for an optimal patient management. Here, the practical management of a patient with NDM-producing *Klebsiella pneumoniae* infection is discussed.

CLINICAL VIGNETTE

A 75-year-old man with multiple comorbidities, including type 2 diabetes, chronic kidney disease, and benign prostatic hyperplasia, was admitted to the Emergency Department with fever. Over the past year, he had experienced recurrent urinary tract infections (UTIs) and he had also been recently hospitalized for a complicated UTI caused by extended-spectrum beta-lactamases (ESBL)-producing *Klebsiella pneumoniae* treated with meropenem. On admission, the patient had hypotension, fever and oliguria. Laboratory exams revealed elevated inflammatory markers (C-reactive protein 34 mg/dl, procalcitonin >100 ng/ml), lactates 4 mmol/l and acute kidney injury (creatinine values 2.3 mg/dl). A urinary source was suspected. A rectal swab for molecular screening, performed upon admission as part of the hospital's surveillance protocol, tested positive for New Delhi metallo-β-lactamases (NDM). Bedside ultrasonography revealed right-sided hydronephrosis and a large obstructive calculus lodged at the ureteropelvic junction. A percutaneous nephrostomy tube was urgently placed to relieve the obstruction and allow for urine drainage. Urine and blood cultures were collected, and empiric antimicrobial therapy was initiated pending microbiological confirmation and susceptibility testing.

What empirical antibiotic therapy would you start in this patient?

EPIDEMIOLOGICAL CONSIDERATIONS

Current epidemiology of New Delhi metallo-β-lactamase-producing carbapenemase-producing Enterobacterales

Figure 1 shows the current global spread of NDM-producing Enterobacterales and details about the reported circulating clones. As shown, NDM-producing CRE are characterized by broad species and clonal diversity, which varies by country and region. This heterogeneity is clinically relevant, as resistance profiles can differ according to the specific NDM variant. Underreporting and lack of data about circulating clones from several countries further complicate the landscape.

In the United States, the proportion of KPC-producing Enterobacterales decreased from 73.8% in 2019 to 57.1% in 2021, whereas MBL-producing CRE, particularly NDM-producers, increased from 3.8% to 20.4% in the same period [12] Among them, NDM-5-producing *Escherichia coli* has emerged as a significant threat, with isolates identified in both human and animal sources [13,14▪,15].

Similar trends have been observed in Europe. In Italy, a large regional outbreak of NDM-producing Enterobacterales was reported in Northwestern area of the Tuscany region in 2018, resulting in a shift from KPC to NDM as the predominant carbapenemase in the region [16,17▪▪,18,19]. This outbreak is mainly due to the clonal spread of ST-147 NDM-1-producing *Klebsiella pneumoniae* [17▪▪,19,20]. More recently, a novel clone, ST6668 (within clonal complex 147), has been reported to spread rapidly in Northern Italy [21]. It differs from ST147 by a point mutation (C414T) in the *phoE* locus [21]. Recently, co-production of NDM and OXA-48 in Enterobacterales has been increasingly reported in various Italian regions [22,23].

In the United Kingdom, the epidemiology is heterogeneous. Between July 2023 and June 2024, the most common carbapenemase families reported across all regions were NDM (35.7%) and OXA-48-like (35.1%), whereas KPC represented the 20.5% of carbapenemases. The distribution of carbapenemase families varied regionally: NDM predominates in London and the Southeast, whereas OXA-48-like enzymes are more common in Eastern England [24]

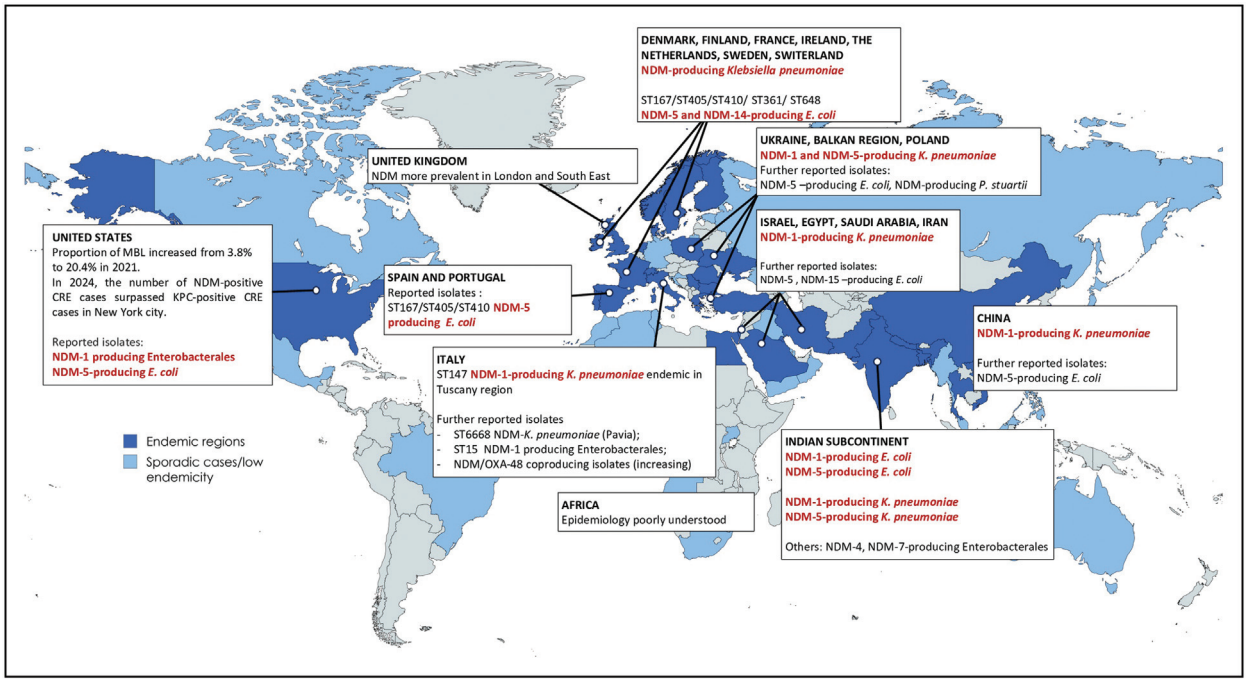

FIGURE 1. Global epidemiology of NDM-producing CRE.

In Israel, long dominated by KPC-producing strains, NDM-producing Enterobacterales is increasingly detected. In a retrospective study including 1694 individuals colonized with KPC- or NDM-producing Enterobacterales who underwent the process of isolation discontinuation, the majority were KPC carriers (78.9%), followed by NDM (18%) and KPC/NDM (3.1%) carriers [7]. Recent data showed that NDM now account for 34.9% of incident CPE cases in Israel [25]. NDM-1-producing *Klebsiella pneumoniae* represents the most prevalent MBL-CPE [25].

NDM-producing Klebsiella pneumoniae versus NDM-producing *Escherichia coli*

An important global threat is represented by NDM-producing *Escherichia coli*. In fact, resistance to newly available treatment options, including both aztreonam/avibactam (ATM/AVI) and cefiderocol, has been reported in NDM-producing *Escherichia coli,* particularly among isolates that produce NDM-5 that carry penicillin-binding protein 3 (PBP-3) mutations and harbor variants of CMY-42, a transferable AmpC enzyme [26].

A variety of NDM-5-producing *Escherichia coli* isolates with diverse clonal backgrounds exhibiting decreased susceptibility or resistance to aztreonam/avibactam have already disseminated worldwide (Switzerland, Denmark, Finland, France, Ireland, the Netherlands, Sweden, Pakistan, India, Kuwait, Thailand, Israel and the USA) (Fig. 1) [13,14▪,26–28].

A recent rapid risk assessment published by the European Centre for Disease Prevention and Control (ECDC) reported a concerning increase in *Escherichia coli* isolates carrying the carbapenemase gene $bla_{\text{NDM-5}}$ across the European Union [29]. The isolates were predominantly associated with globally disseminated lineages, including ST167, ST405, ST410, ST361, and ST648, all of which are well recognized for their role in the spread of antimicrobial resistance genes and their adaptability to both healthcare and community settings. Notably, around 84% of isolates were linked to travel or hospitalization outside the EU/EEA, particularly in South Asia and North Africa [29].

Current epidemiology of OXA-48 producing carbapenemase-producing Enterobacterales

Following its initial identification in Turkey in 2001, OXA-48–like carbapenemases have rapidly disseminated, becoming endemic in several regions, particularly across the Mediterranean basin, the Middle East, and North Africa (Fig. 2) [30–32]. In Europe, Spain and France have experienced sustained endemicity of OXA-48 producers, driven by the clonal expansion of *Klebsiella pneumoniae* ST11, ST405, and ST15, often harboring IncL/M plasmids encoding $bla_{\text{OXA-48}}$[33,34▪▪]. Surprisingly, OXA-48 producing Enterobacterales are sporadic in Italy, that remains characterized by a high prevalence of KPC and increasing occurrence of MBL carbapenemases. In

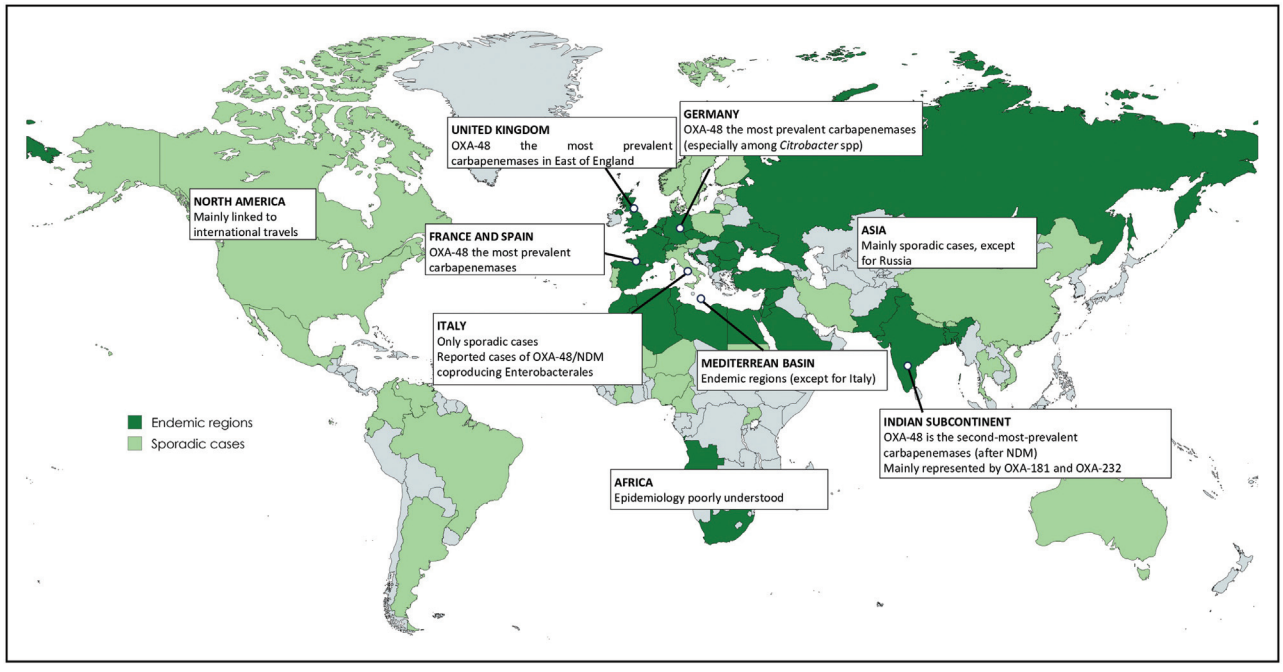

FIGURE 2. Global epidemiology of OXA-48 producing CRE.

the Arabian Peninsula NDM-1 were detected in the 46.5% and OXA-48 in 32.5% of CPE [35]. Interestingly, a recent population-based study reported an increasing spread of OXA-48-producing *Escherichia coli* in Israel during 2016–2023, both in nosocomial and community settings [36].

In contrast, in North America, Northern Europe, and Latin America only sporadic or travel-related cases of OXA-48 producers have been reported [7,34▪▪]. However, the risk of a silent spread is concerning, especially due to the low-level hydrolytic activity of OXA-48 against extended-spectrum cephalosporins, which can lead to misclassification as susceptible and delays in detection [7,34▪▪,37]. This can lead to under-diagnosis and under-reporting of this carbapenemase [37].

CLINICAL CONSIDERATIONS

Risk factors

Infections caused by NDM or OXA-48-producing CRE are associated with several risk factors, including rectal colonization, previous hospitalization, and exposure to broad-spectrum antibiotics.

A multicenter study showed that previous antimicrobial therapy, invasive procedure, and geographical proximity (defined as a room located adjacent to or in front of the index patient's room), were factors independently associated with the acquisition of OXA-48-producing Enterobacterales [38]. Endoscopic retrograde cholangiopancreatography has been implicated in nosocomial transmission of carbapenemase-producing organisms, including NDM and OXA-48, due to persistent contamination of duodenoscopes despite high-level disinfection [39].

In the CHIMERA study, which evaluated bloodstream infections (BSIs) in patients with rectal colonization by *Klebsiella pneumoniae* carrying different carbapenemases, multisite extraintestinal colonization, solid organ transplantation, invasive procedures, intravascular device, admission to intensive care unit, cephalosporin, fluoroquinolones and NDM rectal colonization were independently associated with an increased risk of BSI [40].

Rectal colonization has been recognized as a key predictor of BSI etiology. In a recent study, 15.6% of patients colonized with CRE developed a BSI caused by the same colonizing strain, with high concordance rate observed for KPC- and NDM-producing Enterobacterales [41]. Knowledge of colonization status may facilitate timely initiation of early active antimicrobial therapy, especially in cases of septic shock, where timing of administration of active treatment is critical [5]. Thus, in high-risk patients and in endemic settings, the rectal screening for CPE using molecular assays able to discriminate different carbapenemases is of critical importance. Further prospective studies are warranted to validate the clinical

benefit of a colonization-driven empirical therapy strategy and its impact on patient outcome.

THERAPEUTIC OPTIONS FOR MBL-PRODUCING CARBAPENEMASE-PRODUCING ENTEROBACTERALES

Limited therapeutic landscape and clinical impact

The management of infections caused by MBL-producing Enterobacterales represents a challenge in the clinical practice due to limited treatment options. This therapeutic gap might contribute to the poor outcomes in patients infected with MBL-producing strains. In the prospective ALARICO study including more than 1200 patients with BSIs caused by carbapenem-resistant Gram-negative bacilli, the attributable mortality for MBL-producing Enterobacterales was 35%, substantially higher than that reported for KPC-producing strains (5%). This difference likely reflects the lack of effective antimicrobial options for MBL, in contrast to the last decade's wave of development targeting KPC [6,42,43]. Currently available and new treatment options for MBL-producing CRE are summarized in Table 1.

Ceftazidime/avibactam *plus* aztreonam

Current guidelines recommend the use of ceftazidime/avibactam (CZA) in combination with aztreonam (ATM) as preferred option for the treatment of severe infections due to MBL-producing Enterobacterales [44–47]. Avibactam inhibits serine β-lactamases (e.g., ESBLs, AmpC), thereby protecting ATM from degradation by serine enzymes, that are coproduced in these isolates. This combination was found to be active against MBL in more than 97% of

Table 1. Therapeutic options for MBL-producing CRE

Antibiotic	Available studies	Limitations in the clinical practice	Future perspectives
Combo CZA *plus* ATM	Observational cohort studies, Lack of RCTs	Lack of standardized testing methods Need of multiple lines for infusion	Harmonized testing methodologies ATM/AVI might replace CZA *plus* ATM, but it's not clear whether CZA *plus* ATM may remain useful in specific situations (e.g. NDM-producing *E. coli* with PBP3 mutations)
Cefiderocol	Post-hoc analysis of phase 3 RCTs (CREDIBLE-CR, APEKS-NP)	Absence of standard susceptibility testing (DD versus BMD). Different breakpoints provided by CLSI and EUCAST. Challenges in interpreting susceptibility results (e.g. ATU). Reduced activity against NDM-producing CRE and reported outbreaks of NDM-producing CRE resistant to cefiderocol. Need of susceptibility testing before clinical use.	Optimization of susceptibility testing Evaluation of a partner drug for NDM-producing CRE
ATM/AVI	Phase 3 RCT (REVISIT) including MBL-infections	Limited data in patients with MBL infections. Reported resistant NDM-5 producing *E. coli* isolates.	RCT and observational cohort studies specifically conducted among MBL-producing CRE infections
Eravacycline	In vitro studies	Limited PK/PD data for bloodstream and urinary tract infections. No observational clinical studies or RCT in patients with MBL infections.	It may be useful in polymicrobial intra-abdominal or deep-seated infections.
Cefepime–taniborbactam	RCT (CERTAIN-1) including MBL-infections	No specific data against MBL-infections. Emerging resistance in variants such as bla_{NDM-9}	New potential weapon
Cefepime–zidebactam	In vitro studies, Case reports	No specific data against MBL-infections.	New potential weapon
Other investigational agents	Preclinical or early-phase clinical studies (e.g., QPX7728, ANT2681, SPR206)	Under investigation	New potential weapons with novel mechanisms.

ATM, aztreonam; ATU, area of technical uncertainty; AVI, avibactam; CZA, ceftazidime/avibactam; MBL, metallo-β-lactamases; RCT, randomized controlled trial.

isolates [17▪▪]. Clinical studies support the efficacy of this combination [48,49]. A large recent cohort study including 343 patients with infections caused by MBL-producing CRE showed that the combination CZA *plus* ATM was associated with reduced mortality compared to colistin-containing regimens, also after propensity score matching [17▪▪].

However, some limitations to the use of CZA *plus* ATM should be underlined:

(1) a major challenge is the lack of a standardized approach to assess the *in vitro* activity. Several approaches, including the disc approximation method, the broth disc elution method, and the gradient test superposition method, are used but all these methods are not standardized and results are prone to subjective interpretations [14▪,17▪▪];
(2) the simultaneous administration of CZA *plus* ATM may be difficult in patients without multiple vascular lines. It is not known whether the nonsimultaneously administration of CZA *plus* ATM may affect the serum levels and pharmacokinetics of the drugs [50];
(3) some cases of NDM-producing *Escherichia coli* resistant to ATM/AVI have been reported, potentially limiting the use of CZA *plus* ATM [51].

Cefiderocol

In the CREDIBLE-CR trial, cefiderocol was associated with better outcome compared to the best available therapy in the MBL subgroup [52]. A post hoc analysis of the phase 3 clinical trials APEKS-NP and CREDIBLE-CR evaluating the efficacy of cefiderocol in treating infections caused by MBL-producing Gram-negative bacteria, showed a higher clinical cure rate in patients with infections caused by MBL-producing CRE treated with cefiderocol (73.3%) compared to those treated with comparators (20%) [53].

However, there are some concerns about the use of cefiderocol against MBL. NDM-producing CRE display high MIC values, usually close to the EUCAST breakpoint. At 2 μg/ml, cefiderocol inhibited only 41% of NDM-producing Enterobacterales [54]. Data from the SIDERO-CR 2014–2016 surveillance study in Europe showed susceptibility to cefiderocol in 79.0% of VIM producers and 51.4% of NDM producers based on EUCAST breakpoints [55]. Moreover, in the largest available cohort study, only 33.2% of MBL-producing CRE were fully susceptible to cefiderocol, whereas the majority had an alone of inhibition within the area of technical uncertainty (ATU), according to 2023 EUCAST breakpoints [17▪▪,56]. The new ATU definition (21–23 mm) further adds complexity, as a significant proportion of test results fall within this range, making definitive categorization challenging [57]. Moreover, determining the susceptibility of MBL to cefiderocol remains a challenge due to the lack of standardized and universally reliable testing methods [58]. Broth Microdilution (BMD) is considered the reference method. It requires the use of iron-depleted cation-adjusted Mueller–Hinton broth (ID-CAMHB) to mimic the drug's mechanism of utilizing bacterial iron transport systems. Despite its accuracy, BMD is labor-intensive and not routinely available in many clinical laboratories, limiting its widespread use. Disk Diffusion (DD) offers a more accessible alternative but presents several limitations. Studies have shown that DD results can be influenced by the composition of the agar medium and the presence of isolated colonies within inhibition zones, leading to variability in zone diameter measurements and potential misclassification of susceptibility [59]. Additionally, discrepancies between interpretive criteria set by different standards organizations further complicate susceptibility assessments. CLSI and EUCAST have established differing breakpoints, leading to variations in susceptibility categorization. Using EUCAST criteria there may be a higher proportion of isolates being categorized as resistant compared to CLSI criteria [60].

Taken together, these considerations suggest that cefiderocol may be used against MBL after confirming its susceptibility. There is a crucial need for having susceptibility testing using more reliable methods in the clinical practice.

Aztreonam/avibactam

Surveillance data from the ATLAS program showed that ATM/AVI inhibited 99.8% of Enterobacterales isolates at concentrations $\leq$8 mg/l [61]. Phase 2 (REJUVENATE) and phase 3 (REVISIT) trials showed a good efficacy and safety of ATM/AVI in patients with complicated intra-abdominal infections (cIAI) or hospital-acquired/ventilator-associated pneumonia (HAP/VAP) caused by Gram-negative bacteria [62,63▪▪]. However, data in the subset of infections by MBL-producing CRE are limited. Further studies focusing exclusively on patients infected with MBL-producing organisms are warranted.

NDM-5 producing *Escherichia coli* may have reduced susceptibility to ATM/AVI. Interestingly, Tamma *et al*. recently published a commentary on the REVISIT trial, advocating for continuing to consider CZA *plus* ATM combination against MBL. The authors emphasized the importance of accounting for specific mutations in PBP3 which may influence the choice between CZA *plus* ATM *versus* ATM/AVI [51,63▪▪,64]. In fact, while both ceftazidime and ATM target PBP3, they also display differential binding affinities to other PBPs, such as PBP1a, PBP1b, and PBP2. This broader

inhibition profile suggests that the CZA *plus* ATM combination may retain antimicrobial activity against certain MBL-producing Enterobacterales isolates harboring modified PBP3 targets, such as those with characteristic four-amino acid insertions observed in PBP3 of NDM-producing *Escherichia coli*. In contrast, ATM/AVI relies exclusively on aztreonam's activity, which is limited to PBP3, and may therefore be rendered ineffective in the presence of such mutations. This hypothesis should be confirmed in larger microbiological or clinical studies.

Eravacycline

Eravacycline has demonstrated *in vitro* activity against a broad range of multidrug-resistant Gram-negative pathogens, including NDM-producing CRE. *In vitro* studies have shown that eravacycline exhibits lower MICs than tigecycline against NDM-producing Enterobacterales [65]. However, while eravacycline is approved for cIAIs, its clinical utility against NDM producers in bloodstream or urinary tract infections remains less defined due to limited pharmacokinetic data in these compartments and a lack of clinical studies in such settings. Nevertheless, its excellent tissue penetration, favorable safety profile, and lack of cross-resistance with β-lactams make it a potentially valuable option in the treatment of infections caused by NDM-producing organisms, particularly in polymicrobial or deep-seated infections.

Future options

Several investigational agents may offer future therapeutic options for infections caused by MBL-producing Enterobacterales.

Cefepime–taniborbactam (VNRX-5133) is a β-lactam/β-lactamase inhibitor combination that includes a boronic acid–based inhibitor with activity against serine β-lactamases and some MBLs, including NDM [66]. In the phase 3 CERTAIN-1 trial cefepime–taniborbactam was associated with higher rate of composite clinical and microbiologic success at the test-of-cure visit compared to meropenem (70.6% vs. 58.0%), meeting criteria for both noninferiority and superiority [67]. NDM-variants (e.g., NDM-9) and VIM-variants (e.g., VIM-83) with single amino acid substitutions may have reduced susceptibility to inhibition by taniborbactam [68]. It has been hypothesized that MBL escape variants can arise from changes in electrostatic features due to single amino acid substitutions in MBL active site loops, leading to ineffective binding of taniborbactam [69].

Cefepime–zidebactam (WCK 5222) is another β-lactam/β-lactam enhancer combination currently in phase I/II trials. Although zidebactam is not directly active against MBL, it possesses an 'enhancer' effect on the PBP2 while its β-lactam partner (i.e. cefepime) acts on PBP3. Interestingly, a recent study evaluated the *in vitro* activity of both cefepime/taniborbactam and cefepime/zidebactam against aztreonam/avibactam resistant *E. coli*[70]. All the isolates produced NDM (mainly NDM-5), coproduced CMY-42 and harbored a four amino acid insertion into the PBP3 protein. The resistance rate to cefepime/taniborbactam was 100%, whereas all strains were susceptible to cefepime/zidebactam. Cefepime/taniborbactam was significantly impacted by the same resistance mechanisms that have been shown to counteract the efficacy of aztreonam/avibactam (that is the co-production of CMY-42 and NDM and the modification of the PBP3 target). Conversely, the PBP3 modifications did not impact the MICs for cefepime/zidebactam, confirming its enhancing effect on the *E. coli* PBP2 [70].

Other options, such as cefepime–ANT2681, cefepime–QPX7728 (that can be also deliver via oral route), and SPR206 (a novel polymyxin with better safety compared to colistin) are under investigations [71–73]. Although these agents are not yet widely available, their development underscores the dynamic innovation in this field.

THERAPEUTIC OPTIONS FOR OXA-48-PRODUCING ENTEROBACTERALES

Table 2 shows available antibiotic therapy against OXA-48 producing Enterobacterales. Ceftazidime–avibactam is recommended as the first line option for the treatment of infections caused by OXA-48-producing Enterobacterales [44–46]. A retrospective study compared ceftazidime–avibactam to best available therapy in patients with BSI due to OXA-48-producing K. *pneumoniae* and found that ceftazidime–avibactam was associated with higher clinical success rates and lower 14-day mortality compared to comparators [74]. Similarly, Alqahtani *et al.* demonstrated favorable clinical outcomes, with a 30-day mortality rate of 21% and a clinical cure rate of 78% in 171 patients with OXA-48 infections treated with ceftazidime/avibactam [75]. Similar findings were more recently confirmed among patients with OXA-48-producing *Klebsiella pneumoniae* infections in Turkey, where OXA-48 is endemic [76].

Cefiderocol also exhibits *in vitro* activity against OXA-48-producing strains [77]. However, the CREDIBLE-CR study included a very limited number of patients with OXA-48 infections [52]. Further clinical studies are needed in this setting.

More recently, cefepime–enmetazobactam, a next-generation β-lactam/β-lactamase inhibitor combination, has shown promising activity against ESBL- and OXA-48- producing Enterobacterales. OXA-48

Table 2. Therapeutic options for OXA-48-producing Enterobacterales

Antibiotic	Available studies	Limitations in the clinical practice	Future perspectives
Ceftazidime–avibactam	Observational cohort studies	Lack of activity if MBL are co-expressed	Need for more data to confirm real-world effectiveness
Cefiderocol	RCT (CREDIBLE-CR) including 7 patients with OXA-48 infections	ATU and lack of testing standardization	Need for more data to confirm real-world effectiveness.
Cefepime–enmetazobactam	RCT (ALLIUM) including 4 patients with OXA-48 infections	No clinical studies available in patients with infections by OXA-48 producing CRE	Need for more data to confirm real-world effectiveness.

ATU, area of technical uncertainty; MBL, metallo-β-lactamases; RCT, randomized controlled trial.

producers displayed high susceptibility to cefepime-enmetazobactam, which is similar to ceftazidime-avibactam, including for OXA-48 producers that coproduce a ceftazidime hydrolyzing enzyme (extended-spectrum β-lactamases or AmpC) [78▪]. In the ALLIUM phase 3 trial including patients with complicated UTI or acute pyelonephritis caused by Gram-negative pathogens, cefepime/enmetazobactam, compared with piperacillin/tazobactam, met criteria for noninferiority as well as superiority with respect to clinical cure and microbiological eradication [79▪].

However, studies about the optimal management of OXA-48 infections are limited. Further clinical studies are needed to better delineate the optimal therapeutic choice depending on infection site, resistance profile, and patient-specific factors.

CLINICAL VIGNETTE MANAGEMENT

The patient was treated empirically with a combination of CZA 2.5 g i.v. every 8 h plus ATM 2 g i.v. every 8 h. The standard dosage was maintained despite impaired renal clearance, given the patient's hemodynamic instability. Blood cultures and urine culture confirmed a BSI caused by NDM-producing *Klebsiella pneumoniae*. The *in vitro* synergy of CZA plus ATM was screened with a double disk synergy test and evaluated using a gradient-test superposition method. It was also confirmed using checkerboard analysis. Cefiderocol, tested using DD, showed an alone of inhibition of 21 mm (interpreted as ATU). After 7 days of antibiotic therapy, the patient underwent removal of the urinary stone with placement of a ureteral stent. Antibiotic treatment was continued for an additional 5 days following the procedure, with good clinical outcome.

CONCLUSION

Infections caused by NDM- and OXA-48-producing Enterobacterales represent an increasing global health threat. They are spreading worldwide and, in some epidemiological settings, have replaced KPC as the predominant mechanism of carbapenem resistance.

Currently, the combination of CZA plus ATM and cefiderocol are considered key therapeutic options for NDM-producing strains. However, emerging resistance mechanisms, particularly in NDM-5–producing *E. coli*, are of growing concern, especially due to resistance to last-resort agents such as ATM/AVI.

For OXA-48-producing Enterobacterales, CZA and cefiderocol remain the mainstay of therapy, with promising alternatives, such as cefepime/enmetazobactam, available in the near future.

The global rise of non-KPC carbapenemases underscores the urgent need to strengthen microbiological surveillance, implement robust infection control measures, and promote antimicrobial stewardship to contain further dissemination and preserve treatment efficacy.

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REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

- ▪ of special interest
- ▪▪ of outstanding interest

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This landmark study quantified the burden of antimicrobial resistance in Europe, providing essential public health data that underscores the need for urgent action against resistant pathogens.

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