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How to manage KPC infections

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***Abstract*:** Carbapenemase-producing Enterobacteriaceae represent an increasing global threat worldwide and *Klebsiella pneumoniae* carbapenemase (KPC)-producing *K. pneumoniae* (KPC-KP) has become one of the most important contemporary pathogens, especially in endemic areas. Risk stratification and rapid diagnostics laboratory workflows are of paramount importance and indication for therapy of KPC-KP infection must be individualized according to the baseline characteristics of the patient and severity of infection. The optimal treatment of infection because of KPC-KP organisms is uncertain and antibiotic options are limited. The knowledge of the patient's pathophysiology, infection site, and application of the pharmacokinetic/pharmacodynamic principles on the basis of minimum inhibitory concentration (MIC) has progressively gained major relevance. Combination therapies including high-dose meropenem, colistin, fosfomycin, tigecycline, and aminoglycosides are widely used, with suboptimal results. In the past few years, new antimicrobials targeting KPC-KP have been developed and are now at various stages of clinical research. However, their optimal use should be guaranteed in the long term for delaying, as much as possible, the emergence of resistance. Strict infection control measures remain necessary. The aim of this review is to discuss the challenges in the management and treatment of patients with infections because KPC-KP and provide an expert opinion.

Keywords: carbapenem-resistant Enterobacteriaceae, Klebsiella pneumoniae carbapenemase producing K. pneumoniae, KPC, KPC-KP, MDR-GNB, multidrug-resistant Gram-negative, new antibiotics

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Introduction

The continuing increase of multidrug-resistant Gram-negative (MDR-GNB) pathogens represents an alarming problem worldwide.[1] One of the most common mechanism of resistance among MDR-GNB is represented by the production of β-lactamases, with an increasing role of acquired carbapenemase-producing strains. The vast majority of carbapenemases belong to three of the four known classes of β-lactamases, namely Ambler class A, B, and D, and are carried either on chromosome or acquired *via* plasmids. *Klebsiella pneumoniae* has been the main producer of the KPC type class A carbapenemases so far and has become one of the major threats in clinical practice (Table 1).[2] Of note, despite the majority of data coming from infections due to KPC, several studies include other types of carbapenem-resistant Enterobacteriaceae. The aim of this review is to discuss the challenges in the management and treatment of patients with infections because of *K. pneumoniae* carbapenemase (KPC)-producing *K. pneumoniae* (KPC-KP) and provide an expert opinion.

Risk stratification

Inadequate empirical antimicrobial therapy of severe infections caused by KPC-KP has been associated with an increased morbidity and mortality. To avoid the overuse of broad-spectrum antibiotics, a careful selection of patients who may receive empirical treatment covering KPC-KP infections is important.[3] A bedridden status, presence of indwelling devices, recent hospitalization (<12 months), or contact with healthcare facilities, prior colonization, and recent (<3 months) antibiotic therapy (cephalosporins,

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Table 1. Species distribution of Class A KPC. Modified by Miriagou and colleagues.[2]

Organism	Class A KPC
Pseudomonas aeruginosa	+
Acinetobacter spp.	–
Enterobacteriaceae	
Klebsiella pneumoniae	++
Escherichia coli	+
Proteus mirabilis	–
Klebsiella oxytoca	+
Enterobacter spp.	+
Citrobacter freundii	+

++, Prevalent species-enzyme type combinations.
+, Occasionally reported species–enzyme type combinations.
KPC, *Klebsiella pneumoniae* carbapenemase.

Table 2. Risk factors for KPC-KP strain isolation and for KPC-KP infection. Modified by Tumbarello and colleagues.[9]

KPC-KP isolation or infection
previous acute-care hospitalization
Indwelling central venous catheter
Recent carbapenem therapy
Recent fluoroquinolone therapy
KPC-KP isolation
Previous intensive care unit admission
Indwelling urinary catheter
Hematological cancer
Surgical drain
KPC-KP infection
Charlson score ⩾3
Recent surgical procedure
Neutropenia

CI, confidence interval; KPC-KP, *Klebsiella pneumoniae* carbapenemase producing-*Klebsiella pneumoniae*; OR, odds ratio.
The presence of ⩾3 risk factors was associated with an OR for KPC-KP isolation of 11.33 (95% CI, 8.95–14.34; p 0.001).
The presence of ⩾3 risk factors was associated with ORs for KPC-KP infection of 10.25 (95% CI, 7.57–13.91; p 0.001).

fluoroquinolones, carbapenems) may represent the most important risk factors for development of emerging KPC-KP infections. In addition, KPC-KP infections have been associated with travel, immigration, and recent medical care in endemic areas such as the USA, Italy, Greece, Turkey, and Israel.[4,5]

However, the identification of patients with a KPC-KP infection is a clinical challenge because risk factors are generic and frequently do not allow a reliable risk stratification. Specific scores have been drawn up to establish objective criteria to help physicians in daily practice

Tumbarello and colleagues found a predictive model for identification of KPC-KP isolation and infection in hospitalized patients[6] (Table 2). KPC-KP infection is usually preceded by colonization but the risk of developing an active KPC-KP infection in colonized patients is controversial. Giannella and colleagues developed a bacteremia risk score (range 0–28) for colonized patients (GRS)[7] based on four independent variables and found that colonization at multiple sites with KPC-KP carbapenem-resistant *K. pneumoniae*, including KPC-KP, was the strongest predictor of blood stream infection (Table 3). An external validation of the GRS was performed by Cano and colleagues[8] and showed a very good predictive ability for the development of not only bacteremia (for which the GRS was developed), but also any type of KPC-KP infection.

In addition to the clinical assessment of risk factors for infection, local epidemiology of antibiotic resistance and fast microbiology providing in a few hours the molecular mechanism or carbapenem resistance, are important tools to guide antibiotic therapy. Providing high-level comparable evidence on the clinical impact of rapid identification and antimicrobial susceptibility testing is becoming of paramount importance for MDR-GNB infections, since in the near future rapid identification of specific resistance mechanisms could be crucial for guiding rapid, effective, and targeted therapy against specific resistance mechanisms.[10]

Table 3. Giannella risk score. Risk factors for CR-KP BSI development in rectal carriers.[7]

Risk factors	Risk score point
Admission to ICU	2
Invasive abdominal procedures	3
Chemotherapy/radiation therapy	4
Colonization at site besides stool (risk per each additional site)	5 per site

CR-KP BSI, blood stream infection; carbapenem-resistant *Klebsiella pneumoniae* blood stream infection; ICU, intensive care unit. Cut-off of ⩾2: sensitivity 93%, specificity 42%, positive predictive value 29% and negative predictive value 93%.

Optimization of treatment for KPC-KP infections

The optimal treatment of infection because of KPC-KP organisms is uncertain given the observational nature of most of the studies on this topic and limited antibiotic options so a multifaceted approach is needed[11] (Table 5).

Source control is a cornerstone in the treatment of infectious diseases and represents the multidisciplinary team required in order to optimize critical care for patients with severe infections and MDR-GNB.[9] Source control measures include all those actions taken in the process of care to control the foci of infection and to restore optimal function of the site of infection.

Knowledge of a patient's pathophysiology, infection site, and application of the pharmacokinetic/pharmacodynamics (PK/PD) principles on the basis of MIC has progressively gained major relevance.[12] The use of β-lactams should be maximized by a PK/PD point of view with the administration of high dosages and prolonged infusion strategies maximizing the time above the MIC ($t>$MIC). A loading dose followed by maintenance doses with extended or continuous infusion is recommended.

Inadequate empirical therapy for KPC-KP infection may have a negative impact on mortality. Empiric treatment is frequently inadequate, and appropriate treatment is initiated after the susceptibility test is available. The majority of available studies highlighted the effectiveness of adequate combination antibiotic treatment.[12,13]

Gutierrez-Gutierrez and colleagues developed a mortality risk score (INCREMENT-CPE)[14] in patients with bacteremia to determine the best treatment option (monotherapy *versus* combination therapy). In the INCREMENT-CPE cohort, overall mortality was not different between patients receiving combination therapy or monotherapy (35% *versus* 41%), However, combination therapy was associated with lower mortality than monotherapy in the high-mortality-score stratum (score 8–15; Table 4). In addition, an external validation of both the GRS and the INCREMENT-CPE score (ICS)[8] was developed for indicating empiric therapy in CPE colonized patients, including KPC-KP.

Table 4. INCREMENT-CPE score for mortality. Low mortality score (0–7); High mortality score (8–15).[8]

Risk factor	Score
Severe sepsis or septic shock	5
Pitt score ⩾ 6	4
Charlson comorbidity index ⩾ 2	3
Source of BSI other than urinary or biliary tract	3
Inappropriate early targeted therapy	2

BSI, blood stream infection; CPE, Carbapenemase-Producing Enterobacteriaceae; CRE, carbapenem-resistant Enterobacteriaceae.

In our opinion, combination treatment should be preferred to treat KPC-KP infections compared with monotherapy in the case of severe infections and for critically ill patients. For noncritically ill patients without severe infections, results from randomized clinical trials are needed for ultimately weighing the related benefits and costs, also in terms of induction of resistance.[11]

Role of old antibiotics

Carbapenems

The role of carbapenems in infections caused by KPC-KP is still debated. Among old antibiotics,

Table 5. Expert opinion treatment options for KPC-KP infections.*

KPC-KP TREATMENT OPTIONS‡
KPC-KP meropenem MIC ⩽ 8–64 mg/l and new treatment options available
Ceftazidime-avibactam 2.5 g every 8 h iv$ Colistin 4.5 MU every 12 h iv‖ OR Gentamicin 3–5 mg/kg/d every 24 h iv¶ OR Fosfomycin 4 g every 4 h iv (24 daily) OR Tigecycline 100 mg every 12 h iv (preferred for intraabdominal infections)# Meropenem/vaborbactam 2 g/2 g q8h, iv Imipenem/relebactam 500 mg/250–125 mg q6h, iv
KPC-KP meropenem MIC ⩽ 8–64 mg/l§ and new treatment options not available
Meropenem 2 g every 8 h iv or 1.5 g every 6 h CIF**+ Tigecycline 100 mg every 12 h iv# + Colistin 4.5 MU every 12 h iv‖ OR Gentamicin 3–5 mg/kg/d every 24 h iv¶ OR Fosfomycin 4 g every 4 h iv (24 daily)
KPC-KP meropenem MIC > 8–64 mg/l and new treatment options not available
Ertapenem 500 mg every 6 h iv‡‡ + Meropenem 2 g every 8 h iv or 1.5 g every 6 h** +/– third drug‡ OR Ertapenem 500 mg every 6 h iv‡‡ + Doripenem 500 mg every 8 h$$ +/– third drug‡

CIF, continuous infusion; KPC-KP, *Klebsiella pneumoniae* carbapenemase producing-*Klebsiella pneumoniae*; MIC, Minimal inhibition concentration; MU, million Units; MUI, million International Units; q6h, every 6 hours; q8h, every 8 hours; VAP, Ventilator-associated pneumonia.
$Ceftazidime avibactam loading dose (2.5 g in 1 h) followed by maintenance doses with CIF every 8 h or extended infusion (4 h).
‡Dose adjustment is recommended depending on renal function. Antibiotic choice is recommended on the basis antimicrobial susceptibility tests.
Antimicrobial susceptibility test: colistin: MIC ⩽ 2 mg/l continue colistin; MIC > 2 mg/l consider alternative *in vitro* active antimicrobial. Tigecycline: MIC ⩽ 1 mg/l consider tigecycline; MIC > 1 mg/l consider alternative *in vitro* active antimicrobial. Fosfomycin: MIC ⩽ 32 mg/l consider fosfomycin; MIC > 32 mg/l consider alternative *in vitro* active antimicrobial. Aminoglycoside: MIC ⩽ 2 mg/l for Gentamicin/Tobramycin or ⩽ 4 mg/l for Amikacin consider aminoglycoside; MIC > 2 for Gentamicin/ Tobramycin or > 4 mg/l for Amikacin consider alternative *in vitro* active antimicrobial. Inhaled antibiotic should be evaluated for VAP: colistin 2 MUI every 8 h or tobramycin 300 mg every 12 h or amikacin 150 mg every 12 h.
§For MIC up to 32–64 mg/l, meropenem administration should be considered only if therapeutic drug monitoring is available to monitor optimal drug exposure.
‖Colistin: loading dose (9 MU) followed by maintenance doses with 4.5 MU every 12 h.
¶Gentamicin once a day or Amikacin 15–20 mg/kg/day every 24 h iv.
#Tigecycline: loading dose (200 mg) followed by maintenance doses with 100 mg every 12 h.
**Meropenem loading dose (2 g in 1 h) followed by maintenance doses with CIF or extended infusion.
‡‡Ertapenem: maintenance dose with continuous infusion (500 mg every 6 h in 4 h).
$$Doripenem: maintenance doses with Doripenem 500 mg every 8 h (infusion in 1 h).
*Doses recommended for: Trimethoprim-sulfamethoxazole 20 mg/kg/day divided every 6 h and rifampin 600–900 mg every 24 h iv.

high-dose carbapenem regimens have been associated with a better outcome, especially relevant when included in combination regimens with other active agents (Table 5).

Previous studies supported the use of carbapenems for the treatment of KPC-KP but with some fundamental conditions, such as low carbapenem MIC for the infecting organism

(⩽16 mg/l), optimal PK/PD exposure and combination with another active compound.[13,15,16] There is uncertainty about the usefulness of including meropenem in combination regimens when the meropenem MIC of KPC-KP strains is >16 mg/l.[17] However Pea and colleagues found that high-dose continuous-infusion meropenem, optimized by means of a rapid regimen adjustment based on real-time therapeutic drug monitoring (TDM), may be helpful in improving clinical outcome when dealing with the treatment of infections caused by KPC-KP with a meropenem MIC up to ⩽64 mg/l.[18]

Previous reports showed clinical and *in-vitro* effectiveness of double-carbapenem regimen (ertapenem and meropenem/doripenem) in patients with KPC-KP infections. This regimen is a possible therapeutic strategy in KPC-KP with colistin resistance and/or high carbapenem MIC (meropenem MIC > 8–64 mg/ml). However due to potential negative ecological effects and limited data, since most studies are characterized by multiple bias (retrospective nature, small sample sizes), this combination should be considered only when there are no other reasonable options.[12]

Colistin

The polymyxin antibiotics colistin (polymyxin E) and polymyxin B have recently resurged, assuming an important role as salvage therapy for otherwise untreatable MDR-GNB[19] Colistin is considered a highly active *in-vitro* agent against KPC-KP.[20] However, there is an overall lack of understanding how to optimally administer this agent due to the existence of several different conventions used to describe doses of the polymyxins, differences in their formulations, outdated product information, and uncertainties about susceptibility testing. International consensus guidelines for the optimal use of the polymyxins have been recently published. The treatment guidelines provide the first ever consensus recommendations for colistin and polymyxin B therapy that are intended to guide optimal clinical use.[19]

A recent global survey revealed that polymyxins are available in most countries worldwide, but majority use colistin and a few use polymyxin B.[21]

There are several clinical pharmacologic differences between colistin and polymyxin B administered IV. Polymyxin B is the preferred agent for routine systemic use in invasive infections since polymyxin B has superior PK characteristics in humans as well as a decreased potential to cause nephrotoxicity. In contrast colistin is the preferred polymyxin for the treatment of lower urinary tract infections given renal clearance of the prodrug colistimethate sodium that then converts to the active colistin in the urinary tract.

A recent meta-analysis found no differences between intravenous colistin monotherapy and colistin-based combination therapy against carbapenem-resistant Gram-negative bacteria (CR-GNB) infections, including KPC.[22] However, the emergence of resistance to polymyxins represents a major concern in various areas and has been associated with the KPC-KP strain type and the increased use of this drug, especially as monotherapy and with reduced dose exposures.[23] Colistin utility is still limited by its neurotoxicity and nephrotoxicity, which remains a concerning adverse effect of colistin, especially when used at high doses with need for a careful management.[24,25] TDM[20] and adaptive feedback control should be used wherever possible for both colistin and polymyxin B.

Tigecycline

Tigecycline has promising *in vitro* and *in vivo* efficacy against many CR-GNB, including KPC-KP. Tigecycline has poor serum concentrations.[26]

In 2010 and 2013, the US Food and Drug Administration (FDA) reported an increased risk of mortality associated with tigecycline use in comparison with other drugs in the treatment of serious infections. Data from real-life prospective studies showed that monotherapy might not be sufficient to control severe infections and probably could be a treatment option only in selected patients with mild complicated intraabdominal infections and complicated skin and soft tissue infections with other few adequate alternative options.[27]

A recent systematic review found that CR-GNB tigecycline combination therapy and high-dose regimens may be more effective than monotherapy and standard-dose regimens, respectively in treating Carbapenem resistant Enterobacteriaceae (CRE).[28] The increased medical need represented by the growing impact of MDR infections and the current lack of alternative or new antibiotics suggests that tigecycline benefit–risk continues to be positive. Increased tigecycline doses

(up to 100 mg BID or TID) have been proposed and should be considered for septic shock, ventilator associated pneumonia, extracorporeal membrane oxygenation or Enterobacteriaceae with MIC ⩾1 mg/l.[29] Previous studies have shown that the most common adverse effects of tigecycline are gastrointestinal and should be carefully monitored.[30]

Fosfomycin

Recent studies revealed that many KPC-KP strains retain susceptibility to fosfomycin and intravenous fosfomycin is now considered a valuable anti-KPC-KP.[31] The accuracy of susceptibility testing of fosfomycin with CRE strains has become a crucial issue in clinical microbiology laboratories. MIC values are very difficult to determine and discrepancies in fosfomycin susceptibility testing of KPC-KP with various commercial methods have been found.[32] In a Greek study involving critically ill patients with various nosocomial infections caused by KPC-KP other MDR Gram-negative bacteria, intravenous fosfomycin was used at a median dose of 24 g/day for a median of 14 days, mainly in combination with colistin or tigecycline. Favorable clinical and microbiological outcomes occurred in a majority (55%) of patients, whilst failure, indeterminate outcome and superinfection were documented in 33.3%, 6.3% and 6.3%, respectively.[33]

No clinical trials have investigated fosfomycin use alone or in combination, but there is great concern about the use of fosfomycin as a monotherapy, although the emergence of resistance has been described even in combination therapy.[33,34] High dose intravenous fosfomycin is associated with electrolytes abnormalities (hypokalemia and a high sodium concentration).[33]

However several issues regarding effectiveness, safety, and resistance need to be addressed, namely, the susceptibility breakpoints, the appropriate dose and duration of administration for both oral and intravenous formulations, the effectiveness of monotherapy and combination, and the concerns over increased probability of development of resistance during treatment.[35]

Oral fosfomycin has emerged as a novel therapeutic option with high bactericidal activity against the MDR uropathogens, including KPC-KP and as a promising alternative for outpatient therapy of urinary tract infections.[36]

Aminoglycosides

A significant proportion of KPC-KP shows *in-vitro* susceptibility to aminoglycosides, usually only to gentamicin. Antibiotic choice is recommended on the basis of antimicrobial susceptibility tests (Table 5). Treatment with gentamicin may be most appropriate as a component of a combination regimen for KPC-KP and has been associated with increased survival, including in colistin- and carbapenem-resistant KPC-KP infections.[15] Monotherapy probably could be a treatment option in infections secondary to the urinary source.[37] Use of aminoglycosides is associated with a risk of nephrotoxicity and combination therapy with colistin should be avoided because of the high risk of renal toxicity.

Trimethoprim-sulfamethoxazole

Trimethoprim-sulfamethoxazole (TMP-SMX) could be a low-cost alternative treatment but TMP-SMX but showed a limited role in the treatment of less severe CRE infections.[38] *In vitro* susceptibility rates of KPC-KP to TMP-SMX reported in the literature are highly variable (29–82%) and dependent on the geographical area.[38] A recent case series described 14 patients with KPC-KP infections treated with TMP-SMX, of whom 10 received monotherapy.[39]

Rifampin

Rifampin has been reported to have synergistic activity with meropenem against KPC-KP.[40] In addition, the combination of colistin and rifampicin showed synergistic antimicrobial activity and postantibiotic effect against the KPC-KP colistin-resistant strains isolated.[41] Perturbation of the outer bacterial cellular membrane by colistin may favor the uptake of rifampin, allowing the drug to reach sufficient intracellular concentrations to inhibit protein synthesis.[42] However most studies on rifampin use for KPC-KP are characterized by multiple bias (retrospective nature, small sample sizes) and this combination should be considered only when there are no other reasonable options

Role of new antibiotics

Ceftazidime/avibactam

Ceftazidime-avibactam is a recently approved combination of a well-known antipseudomonal third-generation cephalosporin with a new β-lactamase inhibitor (avibactam) combination that

is active against class A (e.g. KPC-KP), C and some and class D carbapenemase-producing CRE.[43] Ceftazidime/avibactam is licensed to be used alone for hospital acquired pneumonia/ventilator associated pneumonia (HAP) and urinary tract infection (UTI) and in association with metronidazole for Intra-abdominal infection (IAI). In addition, it is approved by European Medicines Agency (EMA) for infections due to multidrug-resistant Gram-negative bacteria (MDRGNB) in adults with limited treatment option.

Activity against CRE is supported by the favorable results of observational studies. Among patients with KPC-KP bacteremia, rates of clinical success at 30-day were significantly higher among patients receiving ceftazidime-avibactam compared with those who received a carbapenem plus aminoglycoside ($p = 0.04$) or colistin ($p = 0.009$) and other regimens ($p = 0.004$).[44] Ceftazidime-avibactam has shown to be a reasonable alternative to colistin in the treatment of KPC-KP and with lower risk for nephrotoxicity.[45] In addition, in a retrospective study on 138 cases of infections caused by KPC-KP ceftazidime/avibactam demonstrated its efficacy as savage therapy after a first-line treatment.[46]

Whether ceftazidime-avibactam should be used alone or in combination for KPC-KP infections is a matter of debate. The use of ceftazidime-avibactam has been associated with the emergence of resistant strains conferred by blaKPC mutations and occurred more commonly among patients infected with KPC-3, pneumonia, and renal replacement therapy.[47] PK/PD optimization with the use of extended infusion and combination therapy may be considered as a potential option to avoid emergence of resistance.[48]

Meropenem/vaborbactam

Meropenem-vaborbactam is a combination of a carbapenem and a class A (e.g. KPC-KP), and class C-β-lactamase inhibitor. Meropenem/vaborbactam was recently licensed by EMA for complicated UTI, complicated intra-abdominal infections (cIAI), HAP, Ventilator-associated pneumonia (VAP), and infections due to aerobic Gram-negative organisms in adult.

In the TANGO II randomized clinical trial, the use of meropenem-vaborbactam monotherapy for CRE infection was associated with increased clinical cure, decreased mortality, and reduced nephrotoxicity compared with the best available therapy (mono/combination therapy with polymyxins, carbapenems, aminoglycosides, tigecycline; or ceftazidime/avibactam alone).[49,50] Selection of mutants with reduced sensitivity to meropenem-vaborbactam from KPC-KP strains has been described and is associated with mechanisms involving porin mutations and the increase in the blaKPC gene copy number (not changes in the KPC enzyme) and can be prevented by the drug concentrations achieved with optimal dosing of the combination. Therefore, the use of optimal exposures for meropenem-vaborbactam to minimize resistance emergence at infection sites is an essential strategy for the long-term clinical utility of this drug.[51]

Other new antibiotics

β-lactam and β-lactamase inhibitor. Imipenem-relebactam inhibits the activity of class A, and C β-lactamase. *In vitro* studies have demonstrated the role of relebactam to restore imipenem's activity against KPC-producing CRE, including KPC-KP and to reduce imipenem MICs in *Pseudomonas aeruginosa*.[52] The RESTORE-IMI1 study of imipenem/relebactam compared with colistin plus imipenem for infections due to imipenem nonsusceptible bacteria (but colistin and imipenem/relebactam susceptible) showed a favorable overall response with lower risk for drug-related adverse events.[53]

Aztreonam-avibactam showed a potent *in vitro* activity against class C blactamase, Metallo-β-Lactamase (MBL), and KPC-producing strains with an activity 10 times that of aztreonam alone.[54] Two-phase III clinical trials are currently enrolling patients.[55,56]

Ceftaroline/avibactam antimicrobial spectrum to include KPC-producing Enterobacteriaceae, and anaerobes.[57] However, no studies investigating the role of ceftaroline/avibactam for the treatment of KPC-KP infections are currently available.

Cefepime/zidebactam has shown promising activity against carbapenem-resistant Enterobacteriaceae, including KPC-KP, *P. aeruginosa* and *Acinetobacter*. Both cefepime/zidebactam and meropenem/nacubactam have demonstrated *in vitro* activity against MBL-producing CRE. *In vivo* studies are needed to confirm this data.[58,59]

Cephalosporins. Cefiderocol is a new generation siderophore cephalosporin based on the mechanism of bacterial cell entry binding to ferric iron. Cefiderocol demonstrated *in vitro* activity against CRE and meropenem-resistant *P. aeruginosa, Stenotrophomonas maltophilia*, and *Acinetobacter baumannii*, but no activity against Gram positives and anaerobes. Cefiderocol is currently in phase III of clinical development.[60–62]

Aminoglycosides. Plazomicin is a novel aminoglycoside that retains stability against several aminoglycoside-modifying enzymes showing better *in vitro* activity compared with old aminoglycosides and a synergistic effect in association with meropenem, colistin, and fosfomycin, but not with tigecycline. In addition, its efficacy was confirmed in KPC-KP strains expressing the mcr-1 gene of the colistin-resistance.[63] Its activity *in vitro* seems higher against CRE than against Carbapenem Resistant Pseudomonas aeruginosa (CRPA) and Carbapenem-resistant Acinetobacter baumannii (CRAB), although possible resistance has been described in some New Delhi metallo-beta-lactamase (NDM-1)-producing CRE. Once daily plazomicin is currently approved by the FDA for the treatment of complicated UTI.[64] In a small phase III trial, lower mortality was observed in patients with severe CRE infections receiving plazomicin than in those receiving colistin plus tigecycline or meropenem, The trial was stopped early and small sample sizes limit the interpretation of the findings, but a suggestion of activity of plazomicin was identified.[65]

Tetracyclines. Eravacycline is a novel synthetic fluorocycline, structurally similar to tigecycline (with a 2- to 4-fold greater activity) with broad-spectrum activity against anaerobes, Gram-positive and Gram-negative resistant pathogens, including KPC-KP, metallo-β-lactamase and *Acinetobacter* but is not effective against *P. aeruginosa*.[66] Eravacycline has been recently FDA and EMA approved for the treatment of cIAIs. Eravacycline can be administered intravenously and is also highly bioavailable after oral administration (more than 90%).[67]

Individual and hospital control measures. Infection control interventions to contain KPC outbreaks are usually implemented in the form of bundles including increased hand hygiene, contact precautions, and stewardship programs.[68]

Other infection prevention strategies include decolonization of patients by the use of selective oral, digestive, or intravenous decontamination strategies, decontamination of the environment, but success at decolonization may favor the emergence of resistant strains.[69,70]

Recent European Society of Clinical Microbiology and Infectious Diseases (ESCMID)-European Committee on Infection Control (EUCIC) clinical guidelines do not recommend routine decolonization of MDR-GNB carriers. The effectiveness and long-term side effects of decolonization of CRE in high-risk populations (e.g. intensive care units, neutropenic, and transplant populations) needs to be evaluated with randomized control trials.[71]

The potential benefit of fecal microbiota transplantation as an MDR-GNB decolonization strategy has been tested in uncontrolled studies with a high level of heterogeneity and new trials are currently ongoing.[71]

Conclusion

Management and treatment of patients with infections because of KPC-KP is a daily challenge in clinical practice. New agents for treatment of MDR-GNB infections are promising. However, more data are needed to incorporate into the armamentarium and daily clinical use as empiric *versus* targeted therapy or as monotherapy *versus* combination therapy. Additional focus on appropriate stewardship practices and fast microbiology for early diagnosis are vital in maximizing the efficacy and longevity of any new agents.

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Ethics

For review article ethical approval was not required.

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