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Antimicrobial treatment challenges in the era of carbapenem resistance

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ABSTRACT

Infections due to carbapenem-resistant Gram-negative bacteria are burdened by high mortality and represent an urgent threat to address. Clinicians are currently at a dawn of a new era in which antibiotic resistance in Gram-negative bacilli is being dealt with by the availability of the first new antibiotics in this field for many years. Although new antibiotics have shown promising results in clinical trials, there is still uncertainty over whether their use will improve clinical outcomes in real world practice. Some observational studies have reported a survival benefit in carbapenem-resistant *Enterobacteriaceae* bloodstream infections using combination therapy, often including "old" antibiotics such as colistin, aminoglycosides, tigecycline, and carbapenems. These regimens, however, are linked to increased risk of antimicrobial resistance, and their efficacy has yet to be compared to new antimicrobial options. While awaiting more definitive evidence, antibiotic stewards need clear direction on how to optimize the use of old and novel antibiotic options. Furthermore, carbapenem-sparing regimens should be carefully considered as a potential tool to reduce selective antimicrobial pressure.

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1. Introduction

Carbapenem-resistant Gram-negative bacteria (CR GNB) are regarded by the Centers for Disease Control and Prevention (CDC) as posing an urgent threat to global health (Centers for Disease Control

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and Prevention (CDC): Health Alert Network 2013; Centers for Disease Control and Prevention (CDC) 2013). The increase in infections caused by carbapenem-resistant *Enterobacteriaceae* (CRE) is particularly challenging due to the lack of consolidated first line treatment options. To treat severe infections caused by CRE, clinicians often rely on therapeutic regimens characterized by increased toxicity or suboptimal pharmacokinetics. In this scenario, the need for antimicrobial stewardship (AMS) programs is a critical matter. The cornerstone of AMS is optimization of appropriate antibiotic use in order to improve patient outcomes and to contain the emergence of further resistance (Pollack and Srinivasan 2014; Wong and Spellberg 2017). Recently, two novel β-lactam-β-lactamase inhibitor combinations, ceftazidime-avibactam and meropenem-vaborbactam, received Food and Drug Administration (FDA) approval and became available to fight CRE infections. While this represents a unique opportunity, it also poses several challenges in AMS. Current data on the use of "old" antibiotics against CRE suggest that combination regimens (often including a carbapenem, colistin, an aminoglycoside, or tigecycline) provide some clinical advantage in selected patient populations (Daikos et al. 2014; Machuca et al. 2017; Tumbarello et al. 2012; Tumbarello et al. 2015). This, however, remains particularly problematic for antibiotic stewards when clinicians intend to use these regimens as empiric therapy. Given the likelihood that carbapenem use promotes carbapenem resistance, clear direction should be provided about when alternatives to carbapenems can be used. Data on the potential use of "carbapenem-sparing" regimens, however, remain conflicting (Rodríguez-Baño et al. 2012; Tamma et al. 2015).

Here we outline these, and other, conundrums faced by clinicians in the current era of CR GNB and the arrival of new antibiotics. We have reviewed current and novel therapeutic options and provided proposals for the use of new antibiotics against CRE as well as multidrug-resistant (MDR) *Pseudomonas aeruginosa* and *Acinetobacter baumannii*.

2. Challenges and benefits of the use of new antibiotics in AMS programs

The pipeline of new antibiotics active against MDR GNB is being rejuvenated by several new entities. These antibiotics fall into three main categories - "old" β-lactam antibiotics combined with "new" β-lactamase inhibitors (BLBLIs), "new" cephalosporins, and non-β lactam antibiotics. The approval or development status of some of these new antibiotics is summarized in Table 1. New β-lactamase inhibitors such as avibactam, relebactam and vaborbactam can inhibit the activity of *Klebsiella pneumoniae* carbapenemase (KPC), which is the most commonly encountered carbapenemase in both North America and Europe, as well as extended-spectrum β-lactamases (ESBL) and AmpC β-lactamases (Toussaint and Gallagher 2015). Novel cephalosporins include ceftolozane, used in combination with tazobactam for the treatment of MDR *P. aeruginosa* infections, and cefiderocol (S-649266), a novel siderophore cephalosporin stable against relevant carbapenemases including metallo-β-lactamases (MBLs), KPC carbapenemases, and OXA-48-group carbapenemases (Falagas et al. 2017). Non-β lactam antibiotics, such as plazomicin and eravacycline, are not targeted by β-lactamases and also represent potential options for the treatment of CR GNB infections (Bassetti and Righi 2014; Rodríguez-Avial et al. 2015).

Table 1
Current developmental status and indications of new antibiotics active against multidrug resistant Gram-negative bacilli.

Category and Drug	Current Status	Indication
"Old" β-lactam antibiotics combined with new β-lactamase inhibitors		
Ceftazidime-avibactam	FDA-approved	cUTI, including pyelonephritis; cIAI (in combination with metronidazole); HAP / VAP due to susceptible aerobic Gram negative bacilli
Imipenem-relebactam	FDA - IDIQ "fast-track"	
Meropenem-vaborbactam	FDA-approved	cUTI, including pyelonephritis
Aztreonam-avibactam	Phase 3 trial	
New β-lactam antibiotics		
Ceftolozane-tazobactam	FDA-approved	cUTI, including pyelonephritis; cIAI (in combination with metronidazole)
Cefiderocol (S-649266)	Phase 3 trial	
Non-β-lactam antibiotics		
Plazomicin	FDA-approved	cUTI, including pyelonephritis
Eravacycline	FDA-approved	cIAI

FDA = Food and Drug Administration; IDIQ = indefinite delivery/indefinite quantity; cUTI = complicated urinary tract infections; cIAI = complicated intra-abdominal Infections; HAP / VAP = hospital-acquired pneumonia / ventilator-associated pneumonia.

Given the widespread nature of carbapenem resistance, these antibiotics have the potential to be widely used in the future. Some unanswered questions, however, remain on how to position them in hospital formularies and AMS programs. Firstly, although new antibiotics have a high degree of in vitro activity against CR GNB, some of them still need to demonstrate clinical efficacy in the setting of serious CR GNB infections. Trials aimed at determining the comparative efficacy of new compounds versus best available therapy (BAT) for the treatment of CR GNB are ongoing (Table 2). The development of large-scale randomized controlled trials (RCTs), however, is often not feasible in a reasonable time frame due to the limited number of patients with highly resistant serious infections who are suitable for enrollment in such trials. In 2017, the FDA evaluated the challenges in developing clinical programs for antibacterial drugs targeting single bacterial species (FDA Briefing Document 2017), approving the Limited Population Antibacterial Drug (LPAD) pathway. The newly granted LPAD pathway aims to provide a feasible mechanism to gain regulatory approval from smaller clinical studies for specific populations and areas of urgent unmet medical needs (US Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research 2013). Secondly, until conclusive data on the superiority of new compounds versus traditional therapies become available, AMS programs need to weigh the trade-off between advantages and disadvantages pertaining to the different therapeutic options. Combinations of "old antibiotics" including meropenem, colistin and/or aminoglycosides have been associated to renal toxicity and may increase the selection pressure for CRE (Li et al. 2006; Nation et al. 2016; Shields et al. 2017a). Conversely, ceftazidime-avibactam has shown good tolerability in clinical trials and represents a potential carbapenem-sparing option in the treatment of CRE. The cost of ceftazidime-avibactam, however, is significantly higher compared to colistin or aminoglycosides and exceeds more than 6 times the cost of meropenem. Finally, emergence of antimicrobial resistance and activity against different carbapenemases should also be considered to optimize AMS programs. Most new BLBLIs, including ceftazidime-avibactam and meropenem-vaborbactam, lack activity against MBLs, including New Delhi (NDM) and Verona integron-encoded (VIM) that circulate in certain geographical areas (e.g. India, West Europe) (Notes from the Field 2014; Struelens et al. 2010). For these reasons, antimicrobial susceptibility testing should always be available so that clinicians can make informed decisions regarding continuation of empiric therapy and antibiotic de-escalation (European Centre for Disease Prevention and Control 2018). The detection of specific resistance genes (KPC, NDM, VIM, and OXA-48 type) can also be performed using rapid and highly sensitive molecular tests that have been successfully employed in regional surveillance networks (Richter and Marchaim 2017; van Duin et al. 2014). Diagnostic tests designed to screen CRE for specific carbapenemase enzymes from clinical specimens represent promising tools when used in conjunction with AMS interventions. Previous studies showed that molecular tests could rapidly detect GNB infections, direct appropriate choice for early antibiotic therapy, and improve patient outcomes (Rivard et al. 2017; Walker et al. 2016).

Table 2
Randomized clinical trials in patients with carbapenem-resistant organisms.

Trial number	Drug	Comparator	Type of infection	Study design; patient n; expected completion date
NCT02168946	Meropenem-vaborbactam	Best available therapy	BSI or HAP or cUTI/acute pyelonephritis due to CRE	Open-label; n = 77; completed in July 2017
NCT02452047	Imipenem- relebactam	Imipenem plus colistin	HAP; cIAI; cUTI due to CR-GNB	Double-blind; n = 50; completed in September 2017
NCT02714595	Cefiderocol (S-649266)	Best available therapy	HAP; cUTI; BSI; sepsis due to CRE, CR-GNB	Open-label; n = 150; April 2019
NCT01597973	Colistin plus meropenem	Colistin monotherapy	BSI or pneumonia due to CRE, XDR-*Pseudomonas* or XDR-*Acinetobacter*	Double-blind; n = 444; September 2021
NCT01732250	Colistin plus meropenem	Colistin monotherapy	BSI, pneumonia or UTI due to CR, colistin susceptible organisms	Open-label; n = 360; completed in February 2017
NCT03159078	Polymyxin B	Polymyxin B plus carbapenem	BSI, HAP, VAP, cUTI due to CR polymyxin susceptible only organisms	Double-blind; n = 40; December 2019

BSI = bloodstream infections, HAP = hospital-acquired pneumonia, VAP = ventilator-associated pneumonia, CRE = carbapenem-resistant *Enterobacteriaceae*, cUTI = complicated urinary tract infections, cIAI = complicated intra-abdominal infections, GNB = Gram-negative bacteria; XDR = extensively drug-resistant.

2.1. Novel antibiotics for the treatment of CRE

Ceftazidime-avibactam was the first new antibiotic to come to the market for the treatment of CRE infections (Livermore et al. 2018). Ceftazidime-avibactam has in vitro activity against MDR *P. aeruginosa*, KPC-producing *K. pneumoniae* (KPC-*Kp*), and some class D β-lactamases, including OXA-48 that are becoming endemic in certain areas of Europe (e.g. Belgium, France, and Spain) (Aktaş et al. 2012; Albiger et al. 2015; Castanheira et al. 2015).

An association between KPC subtypes and ceftazidime-avibactam MICs has been reported. Specifically, higher median ceftazidime-avibactam MICs were detected against KPC-3 than KPC-2 variants due to the increased hydrolytic activity of KPC-3 against ceftazidime (Manning et al. 2018; Shields et al. 2015). Development of ceftazidime-avibactam resistance among KPC-3-producing strains has also been documented (Both et al. 2017; Giddins et al. 2018; Shields et al. 2016; Shields et al. 2017b; Wolter et al. 2009). Promising results were reported from observational studies comparing ceftazidime-avibactam with other therapies in the treatment of CRE infections. Shields et al. showed higher rates of clinical success among patients receiving ceftazidime-avibactam than among those who received a carbapenem plus aminoglycoside ($P = 0.04$), or colistin ($P = 0.009$), or other regimens ($P = 0.004$) (Shields et al. 2017a). The efficacy of ceftazidime-avibactam versus colistin was also assessed in a study including 137 patients from the CRACKLE (Consortium on Resistance Against Carbapenems in *Klebsiella* and other Enterobacteriaceae) cohort (van Duin et al. 2018). Compared to colistin, treatment with ceftazidime-avibactam showed higher probability of better outcomes (64%, 95% CI, 57–71%) and lower 30-day adjusted all-cause hospital mortality (9% vs. 32% respectively, p = 0.001). Unfortunately, the emergence of resistance to ceftazidime-avibactam shown in pre-clinical studies has been confirmed by real-world evidence (Livermore et al. 2015). Shields et al. reported emergence of ceftazidime-avibactam resistance in 3 patients with ST258 KPC-*Kp* infection after 10, 15 and 19 days of therapy, showing MIC ranges increasing from 2/4–4/4 to 32/4–256/4 mg/L before and after treatment, respectively (Shields et al. 2016). Whole genome sequencing (WGS) identified mutations in plasmid-borne bla_{KPC-3} in all three patients (Both et al. 2017; Shields et al. 2017b). Since ST258 KPC-3 strains predominate in US hospitals and have spread worldwide, the emergence of these resistant variants is concerning (Satlin et al. 2017; Wolter et al. 2009). Interestingly, the mutation was able to restore meropenem susceptibility in some isolates. A potential restoration of meropenem susceptibility with KPC-3 variants conferring ceftazidime-avibactam resistance, however, remains an unpredictable event and has unclear implications in clinical practice (Giddins et al. 2018). Both et al. analyzed the emergence of resistance during treatment with ceftazidime-avibactam in an OXA-48-producing *K. pneumoniae* strain, which was associated with a mutation in CTX-M-14. Furthermore, WGS identified that additional CTX-M-independent mechanisms can contribute to resistance, suggesting that isolates with complex resistance mechanisms could impair the efficacy of ceftazidime-avibactam, especially when used as monotherapy (Both et al. 2017). For these reasons, the use of ceftazidime-avibactam in combination with other antibiotics (e.g. aminoglycosides, polymyxin B/colistin, tigecycline, or carbapenems) has been proposed (Krapp et al. 2017; Shields et al. 2016). There is currently not enough data, however, to universally support ceftazidime-avibactam use in combination versus monotherapy (King et al. 2017; Shields et al. 2018).

Meropenem-vaborbactam has demonstrated excellent in vitro activity against KPC-producing Enterobacteriaceae, showing 99% of isolates to be susceptible with MIC_{50} and MIC_{90} values of 0.06/8 and 1/8 mg/L, respectively (Hackel et al. 2017). Against KPC producers, MICs were lower for meropenem-vaborbactam compared to ceftazidime-avibactam (MIC50 and MIC90 of 1/4 and 4/4 mg/L, respectively) (Lomovskaya et al. 2017a). Furthermore, no differences in meropenem-vaborbactam MICs were shown between two engineered KPC-3 and KPC-2-producing *K. pneumoniae* derivative strains characterized by augmented efflux or multiple permeability defects (e.g. expression of major efflux pump AcrAB-TolC and defective porins OmpK35 and OmpK36) (Lomovskaya et al. 2017a). Meropenem-vaborbactam has no improvement in activity over meropenem alone against strains producing OXA-48-group carbapenemases, MBLs, and lactose-non-fermenting CR GNB (Lomovskaya et al. 2017a).

A Phase 3 open-label study encompassing 72 patients with various CRE infections, including bloodstream infections (BSI), complicated urinary tract infections (cUTI), hospital-acquired or ventilator-associated pneumonia (HAP/VAP), and complicated intra-abdominal infections (cIAI), compared the efficacy of meropenem-vaborbactam (2 g/2 g q8h in a 3 h infusion) versus BAT (ceftazidime-avibactam monotherapy or treatment with a carbapenem, an aminoglycoside, polymyxin B/colistin, or tigecycline monotherapy or combination treatment). While this was a non-inferential, descriptive trial, meropenem-vaborbactam was associated with significantly increased clinical cure rate and lower all-cause mortality rate at day 28 compared with BAT (68% vs. 27%, $P = 0.008$ and 5% vs. 33%, $P = 0.03$ respectively) (Kaye et al. 2017). Fortunately, current data show low propensity of meropenem-vaborbactam for resistance selection and infrequent cross-resistance between meropenem-vaborbactam and ceftazidime-avibactam (Hackel et al. 2017; Lomovskaya et al. 2017b; Sun et al. 2017). Of 991 KPC isolates tested, 0.4% and 1.8% were resistant to meropenem-vaborbactam and ceftazidime-avibactam, respectively (Hackel et al. 2017).

Plazomicin is a new generation aminoglycoside with increased in vitro activity against KPC-producing bacteria compared to older aminoglycosides due to increased stability against various aminoglycoside-modifying enzymes (Endimiani et al. 2009; Galani et al. 2012). Similarly to gentamicin and amikacin, however, the activity of plazomicin is limited against strains producing NDM-group MBLs due to production of

16S ribosomal RNA methyltransferases (Livermore et al. 2012). In the CARE study, which included patients with BSI or HAP/VAP due to CRE, 17 patients were treated with plazomicin (15 mg/kg once daily) while 20 received colistin in combination with meropenem or tigecycline. All-cause mortality was nominally lower for plazomicin compared to colistin (24% vs. 50%, difference 26.5%, range − 0.7 to 51.2), while serum creatinine increase was higher in the colistin arm (38% vs. 8%, respectively) (McKinnell et al. 2017). Based on these efficacy and safety data, a recent FDA briefing document confirmed plazomicin indication for the treatment of cUTI but did not recognize substantial evidence for recommending its use in BSI (Cloutier et al. 2017; Connolly et al. 2018).

Eravacycline is a novel fluorocycline antibiotic that is structurally similar to tigecycline (Clark et al. 2012). Eravacycline is not affected by most mechanisms causing tetracycline resistance and is active against ESBL-, KPC- and OXA-producing Enterobacteriaceae, MDR *A. baumannii* and *Stenotrophomonas maltophilia* (Zhanel et al. 2018). As a tetracycline, eravacycline is not active against *P. aeruginosa*. The FDA recently approved the intravenous formulation of eravacycline for the treatment of cIAI, based on the IGNITE 1 and 4 trials showing non-inferiority of eravacycline compared with ertapenem and meropenem, respectively (Ditch et al. 2018; Solomkin et al. 2017). For cUTI, however, eravacycline was inferior to levofloxacin (IGNITE 2 and 3 trials), probably due to the drug's suboptimal urinary pharmacokinetics (ClinicalTrials.gov, 2013, 2017). The oral formulation of eravacycline has also shown limited bioavailability and reduced efficacy in cUTI compared to oral levofloxacin (ClinicalTrials.gov, 2013, 2017). As such, no novel oral options are currently available to allow sequential step-down therapy against CRE-related infections.

3. Old antibiotics used for the treatment of CRE

Various “old” antibiotics, such as aminoglycosides, tigecycline, fosfomycin, and polymyxins often retain activity against CRE and are employed in clinical practice, usually as part of combination regimens.

CRE are frequently susceptible to aminoglycosides such as gentamicin and amikacin, with the exception of 16S rRNA methyltransferase-producing isolates that circulate among NDM and, occasionally, KPC-producing strains (Doi et al. 2016). Aminoglycosides are commonly used as part of combination treatment in the management of infections caused by CRE. Clancy et al. demonstrated in vitro bactericidal activity of gentamicin against KPC-2-producing *K. pneumoniae* carrying a mutant *ompK35* porin gene and higher efficacy of doripenem-gentamicin compared with doripenem-colistin combination (79% vs. 29% respectively, $p = 0.02$) (Clancy et al. 2014). A retrospective study examining 50 cases of sepsis caused by an outbreak of CR *K. pneumoniae* producing KPC-3, SHV-11 and TEM-1 showed that targeted use of gentamicin was independently associated with reduced mortality (21% versus 62%, $p = 0.02$) (Gonzalez-Padilla et al. 2015). Decreased susceptibility to aminoglycosides, however, is emerging. MICs close to gentamicin and amikacin breakpoints have been associated to inadequate pharmacokinetic-pharmacodynamic (PK/PD) targets, especially among critically ill patients (Zavascki et al. 2017). Furthermore, aminoglycosides breakpoints have been recently reassessed by USCAST (National Antimicrobial Susceptibility Testing Committee for the United States) using applications of PK/PD models and MIC distribution statistics, resulting in lower susceptibility breakpoints compared to those by the CLSI (Clinical and Laboratory Standards Institute) and EUCAST (European Committee on Antimicrobial Susceptibility Testing) (Bhavnani et al. 2018). The impact of the newly updated breakpoints on aminoglycoside resistance rates has been recently analyzed at a tertiary hospital, showing a marked decrease in susceptibility of CRE to amikacin and gentamicin (55% vs. 86% and 21% vs. 31% using USCAST or CLSI guidelines, respectively) (Kulengowski et al. 2018).

Tigecycline, the first glycylcycline to be approved for clinical use, usually retains in vitro activity against CRE (Kontopidou et al. 2014; Renteria et al. 2014; Sader et al. 2015;Tumbarello et al. 2012, 2015). Susceptibility rates of 95% and 89% to tigecycline were reported in CRE isolates from Africa, Middle East, and Europe, respectively, showing MIC_{90} of 2 mg/dl (Renteria et al. 2014; Sader et al. 2015). Tigecycline is usually used in association with colistin, aminoglycosides, or meropenem against severe KPC-*Kp* infections (Kontopidou et al. 2014; Sader et al. 2015). Tigecycline does not exhibit efficient bactericidal activity against most of KPC-producing strains in time-kill studies when used as single agent (Pournaras et al. 2011). In a multicenter, observational study including 125 KPC-*Kp* BSI showing overall tigecycline susceptibility of 91%, significant reduction in 30-day mortality was reported when combination therapy with tigecycline, colistin and meropenem was used instead of monotherapy with colistin or tigecycline ($p = 0.02$) (Tumbarello et al. 2012). In severe infections, some studies suggested that high-dose tigecycline (200 mg initially, then 100 mg twice daily) might improve clinical outcomes (Geng et al. 2018). In a phase II randomized trial of HAP, a trend towards increased cure rates was shown for patients treated with high-dose compared with standard dose tigecycline or with imipenem–cilastatin (85% vs. 70% and 75%, respectively) (Ramirez et al. 2013). High-dose tigecycline was also associated with higher clinical cure rates and microbiological eradication compared with the standard dose in an observational study including 100 critically ill patients ($p = 0.08$ and $p = 0.10$, respectively) (De Pascale et al. 2014). Experimental models of pneumonia due to NDM-1-producing *K. pneumoniae* and *E. coli* strains demonstrated that high-dose tigecycline was more effective than colistin, which did not reach sufficient drug levels in the lung tissue (Docobo-Perez et al. 2012). Well-controlled studies, however, are still needed to evaluate the efficacy and safety profiles of high-dose tigecycline, especially in HAP/VAP.

The polymyxins (including polymixin E/colistin and polymixin B) are an old class of antibiotics displaying in vitro activity against most MDR GNB. Both polymyxins have been extensively used in infections due to CRE, although more data and clinical experience exist for colistin (Tumbarello et al. 2012, 2015). Main limitations associated with colistin use include potential nephrotoxicity, unpredictable PK due to use of prodrug, and dosing regimens that are not well established (Garonzik et al. 2011; Mohamed et al. 2012; Plachouras et al. 2009; Poulakou et al. 2014). Monotherapy with polymyxins is associated with emergence of resistance in vitro, suggesting that this class should be administered in combination with other agents (Bergen et al. 2015). Some clinical studies also demonstrated increased efficacy of colistin when used in combination with other drugs (Hirsch and Tam 2010; Zusman et al. 2017). In the INCREMENT cohort, colistin monotherapy was associated with increased mortality compared to combinations of tigecycline, colistin, or carbapenems (Gutiérrez-Gutiérrez et al. 2017). Conversely, among 406 patients with severe infections caused by CR GNB enrolled in an international randomized trial, colistin combined with meropenem showed similar clinical failure rates compared with colistin monotherapy (73% vs. 79% respectively, risk difference −5.7%, 95% CI, −13.9 to 2.4). This trial, however, included mainly *A. baumannii* isolates and was underpowered to compare treatment outcomes for other GNB, including CRE (Paul et al. 2018). A similar RCT is currently ongoing and should provide data on the efficacy of colistin monotherapy for infections caused by CRE (Table 2).

Colistin use has been limited by emergence of resistance among KPC-*Kp*, with reported rates up to 40% especially in areas burdened by high CR prevalence (Aydın et al. 2018; Monaco et al. 2014). The recent discovery of plasmid-mediated colistin resistance has also important implications for the spread of these highly resistant strains (Liu et al. 2016).

Despite decades of use in the treatment of UTI, fosfomycin still displays in vitro activity against the majority of MDR *Enterobacteriaceae*, including MBL producers (Falagas et al. 2008; Falagas et al. 2010a). A small, prospective, single-arm study assessed intravenous fosfomycin safety and effectiveness as part of combination regimens with colistin or gentamicin in 11 critically ill patients with severe CR-*Kp* infections. Fosfomycin was well tolerated and all-cause in-hospital mortality was 18% (Michalopoulos et al. 2010). In a multicenter prospective case

series, intravenous fosfomycin was administered in combination with colistin or tigecycline to 68 ICU patients with BSI or VAP caused by CR *K. pneumoniae* (60%) or *P. aeruginosa* (40%). Favorable clinical outcome and bacterial eradication were observed in 54% and 56% of patients, respectively, while fosfomycin resistance developed in three cases (Pontikis et al. 2014).

Oral antimicrobial options for the treatment of resistant infections caused by GNB are lacking. Oral fosfomycin is currently not indicated for systemic MDR GNB infections and in most countries is only approved as a 3 g single dose for treatment of uncomplicated cystitis. Due to the poor bioavailability shown by the oral formulation, currently recommended fosfomycin dosing regimen appears insufficient to achieve efficacious serum and tissue concentration and to suppress emergence of resistance (Ortiz et al. 2018). Although population PK models estimated that 6 to 12 g per day may be required to obtain optimal oral fosfomycin exposure, more data on surrogate PD indices are needed to investigate potential safety issues associated with high-dose fosfomycin (Ortiz et al. 2018).

Minocycline could also represent an option for sequential therapy in the treatment of MDR GNB. To date, however, minocycline activity on CRE has only been documented by in vitro studies (Khatri et al. 2017).

3.1. Combination versus monotherapy for CRE treatment

There are currently no RCTs comparing combination therapy with monotherapy for CRE infections. Data reporting the superiority of combination treatment (most often including meropenem, colistin, gentamicin, or tigecycline) versus monotherapy have been limited due to the observational nature of the studies and included mainly KPC-*Kp* isolates (Daikos et al. 2014; Qureshi et al. 2012; Tumbarello et al. 2012, 2015).

Qureshi et al. showed higher 28-day survival for combination therapies including a carbapenem, tigecycline, or a fluoroquinolone versus monotherapy (57.8% vs. 13.3% respectively, $p = 0.01$) in 41 patients with KPC-*Kp* BSI (Qureshi et al. 2012). A study encompassing 661 patients with KPC-*Kp* infections documented lower 14-day mortality for combination therapy with at least two in vitro active drugs (e.g. meropenem plus colistin, gentamicin, or tigecycline) compared with monotherapy (30% vs. 38% respectively, $p = 0.03$) (Tumbarello et al. 2015). Higher survival was associated with meropenem MICs ≤8 mg/L compared with MICs >8 mg/L (24% vs. 35% respectively, $p = 0.005$). Daikos et al. compared the outcomes of 205 patients with BSI caused by KPC-, VIM-, and KPC/VIM-producing *K. pneumoniae* treated with combination therapy (including tigecycline, an aminoglycoside, or colistin in 67% of cases) with those receiving monotherapy with meropenem, colistin, tigecycline, or an aminoglycoside. Higher 28-day mortality was reported for monotherapy compared with combination treatment (44% vs. 27% respectively, $p = 0.018$), while the lowest mortality rate (19%) was associated with carbapenem-based triple combinations (e.g. meropenem plus tigecycline plus colistin or an aminoglycoside) (Daikos et al. 2014). A correlation between carbapenem MICs and mortality has also been confirmed by other studies. High-dose meropenem (2 g q8h by extended infusion) was more likely to be effective against CRE if MICs were < 8 mg/L (Tumbarello et al. 2015). Positive clinical outcomes, however, were reported also for higher MICs (Giannella et al. 2018). A recent study in critically ill patients highlighted that meropenem doses of 8 and 12 grams/day by continuous infusion may be necessary to reach PK/PD targets for MICs of 32 and 64 mg/L, respectively (Cojutti et al. 2017).

Some studies do not support the superiority of combination therapy over monotherapy for the treatment of CRE infections. Gomez-Simmonds et al. analyzed 141 patients with BSI due to CR-*Kp* (MIC_{90} of >16 mg/L) showing comparable 30-day mortality in those receiving monotherapy versus combination therapy (26% vs. 38%, respectively, $p = 0.1$). Forty-eight % received monotherapy (75% with either polymyxin B or tigecycline) while 52% were treated with combination therapy including β-lactams, tigecycline, aminoglycosides, and polymyxin B. (Gomez-Simmonds et al. 2016). In a recent multicenter prospective study encompassing 437 patients with CRE BSI, mainly caused by KPC-*Kp*, the overall mortality rates were comparable between patients receiving combination of colistin plus tigecycline, an aminoglycoside plus tigecycline, or colistin plus a carbapenem versus monotherapy with colistin, a carbapenem or an aminoglycoside, or tigecycline (35% vs. 41% respectively, $p = 0.28$). A lower mortality rate, however, was recorded among patients receiving combination therapy in the high-mortality-score stratum compared with the low-mortality-score stratum (48% vs. 62% respectively, $p = 0.02$) (Gutiérrez-Gutiérrez et al. 2017).

Systematic reviews aimed at comparing the efficacy of combination therapy vs. monotherapy found major limitations in the studies included for analysis (e.g. heterogeneity of infection sites, pathogen types, and different susceptibility breakpoints) and could not provide definitive data favoring one strategy over the other (Falagas et al. 2014; Shiber et al. 2015; Zusman et al. 2017).

4. Carbapenem-sparing regimens

Carbapenems have long been regarded as the treatment of choice for infections due to ESBL-producing bacteria. Some data, however, suggest that BLBLIs such as piperacillin-tazobactam may be as effective as carbapenems against ESBL producers (Gutiérrez-Gutiérrez et al. 2016; Harris et al. 2015; Kaniga et al. 2010; Rodríguez-Baño et al. 2012; Vardakas et al. 2012). In the absence of other concomitant mechanisms of resistance, such as AmpC enzymes, amoxicillin-clavulanic acid and piperacillin-tazobactam may be active against ESBL producers (Pérez and Bonomo 2012). Although the use of carbapenem-sparing regimens appears to be a sensible option in the treatment of ESBL-producing strains in order to reduce further selection of carbapenem resistance, controversial data on the efficacy of BLBLIs, in particular piperacillin-tazobactam, recently emerged. Current evidence suggests that piperacillin-tazobactam activity is impaired when lower doses are used instead of higher doses (e.g. 4.5 g every 6 h, administered by extended infusion) or for infections with high inoculum, such as undrained abscesses or pneumonia (Ambrose et al. 2003; Docobo-Pérez et al. 2013; Rodríguez-Baño et al. 2012; Yang et al. 2015). A retrospective study of BSI due to ESBL producers, mostly *K. pneumoniae*, found higher mortality among patients treated with empiric piperacillin-tazobactam compared with carbapenems (Tamma et al. 2015). Furthermore, the results of a non-inferiority RCT (MERINO trial) comparing piperacillin-tazobactam with meropenem in 378 patients with BSI due to ceftriaxone non-susceptible *Escherichia coli* and *K. pneumoniae* do not support the use of piperacillin-tazobactam as a carbapenem-sparing therapy in these infections (Harris et al., 2018). Specifically, 12% of patients in the piperacillin-tazobactam arm and 4% in the meropenem arm met the primary outcome of mortality (risk difference 8.6%, $p = 0.90$ for non-inferiority) (Harris et al. 2018). Based on these data, carbapenem use should be preferred among patients with high-inoculum infections or septic shock due to ESBL producers, including those with BSI (Table 3).

Among other molecules, aminoglycosides are also active against ESBL (Gudiol et al. 2010; Palacios-Baena et al. 2017) and may be useful in cUTI and sepsis, although concerns regarding toxicity and limitation in PK/PD target attainment have been reported (Galani et al. 2012). In areas with high ESBL prevalence, addition of an aminoglycoside to piperacillin-tazobactam could be useful for empiric therapy (Table 3). Fosfomycin is also being studied as an alternative to carbapenems for UTI due to ESBL-producing bacteria and for step-down therapy, however definitive data are still not available (Clinicaltrials.gov, 2014; Veve et al. 2016). Another potential carbapenem-sparing option is tigecycline, but limited data are available for infections caused by ESBL-producing organisms.

Table 3
Currently available carbapenem-sparing regimens for empiric and confirmed infections due to multidrug resistant *Enterobacteriaceae*.

Type of infection	Carbapenem-based regimen	Carbapenem-sparing regimen
Empiric treatment for suspected ESBL	Meropenem/[1]Doripenem (Gutiérrez-Gutiérrez et al. 2016; Harris et al. 2015, 2018; Kaniga et al. 2010; Tamma et al. 2015; Vardakas et al. 2012)	[2]Piperacillin-tazobactam ± aminoglycosides (Gutiérrez-Gutiérrez et al. 2016; Harris et al. 2015; Kaniga et al. 2010; Palacios-Baena et al. 2017; Rodríguez-Baño et al. 2012; Vardakas et al. 2012; Yang et al. 2015)
Confirmed ESBL (piperacillin-tazobactam susceptible)	Meropenem/[1]Doripenem (Gutiérrez-Gutiérrez et al. 2016; Harris et al. 2015, 2018; Kaniga et al. 2010; Tamma et al. 2015; Vardakas et al. 2012)	[2]Piperacillin-tazobactam (Gutiérrez-Gutiérrez et al. 2016; Harris et al. 2015; Kaniga et al. 2010; Rodríguez-Baño et al. 2012; Vardakas et al. 2012); [3]consider tigecycline
Confirmed ESBL (piperacillin-tazobactam resistant)	Meropenem/[1]Doripenem (Gutiérrez-Gutiérrez et al. 2016; Harris et al. 2015; Kaniga et al. 2010; Tamma et al. 2015; Vardakas et al. 2012)	Ceftazidime-avibactam or Ceftolozane-tazobactam (Ambrose et al. 2003; Gutiérrez-Gutiérrez et al. 2016; King et al. 2017; Pérez and Bonomo 2012; Shields et al. 2016, 2017a; van Duin et al. 2018); [3] consider tigecycline
Suspected or confirmed CRE	Meropenem-vaborbactam (Kaye et al. 2017); Meropenem/[1]Doripenem (combined with an aminoglycosides, colistin or tigecycline) (Daikos et al. 2014; Giannella et al. 2018; Paul et al. 2018; Qureshi et al. 2012; Tumbarello et al. 2012, 2015)	Ceftazidime-avibactam ± adjunctive drug (Shields et al. 2016; 2017a; Shields et al. 2018; Tumbarello et al. 2018)

ESBL = extended spectrum β-lactamases; CRE = carbapenem-resistant *Enterobacteriaceae*.
[1] Doripenem is not indicated for the treatment of VAP due to lower clinical cure rates and increased mortality compared to imipenem-cilastatin (drug label revisions including FDA warning performed in 2014) (Doribax drug label n.d.; Kollef et al. 2012).
[2] Carbapenem preferred in high inoculum infections and patients with septic shock (Ambrose et al. 2003; Docobo-Pérez et al. 2013); a recent RCT did not support noninferiority of piperacillin-tazobactam versus meropenem (Harris et al. 2018).
[3] According to susceptibility data and type of infection; limited data available.

The use of new BLBLIs as carbapenem-sparing regimens also remains controversial. Although ceftazidime-avibactam and ceftolozane-tazobactam display excellent activity against ESBL producers, they should generally be reserved for the treatment of CR GNB infections (Toussaint and Gallagher 2015), given the recent real-world data supporting the use of these agents as valid alternatives to carbapenem-based regimens for CR GNB infections (King et al. 2017; Munita et al. 2017; Sacha et al. 2016; Shields et al. 2016; Shields et al. 2017a; Tumbarello et al. 2018; van Duin et al. 2018) (Table 3). Another practical limitation in the use of these novel agents as carbapenem-sparing options for ESBL infections is their high cost compared to meropenem, which is the standard of care.

5. Treatment strategies for MDR *A. baumannii*

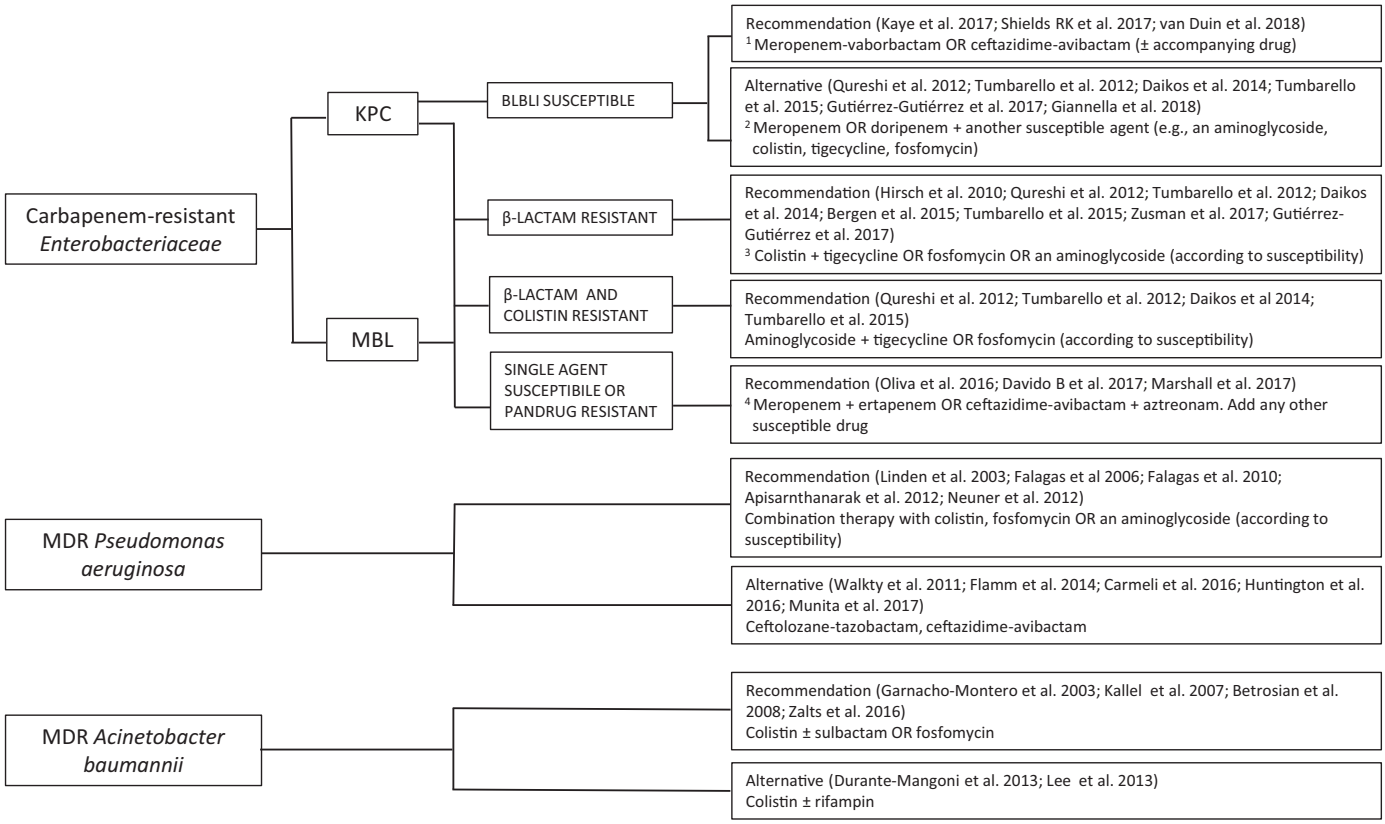
A. baumannii has acquired resistance genes to several antibiotics, including carbapenems. The efficacy of colistin in severe infections caused by CR *A. baumanni* has been demonstrated in retrospective studies (Garnacho-Montero et al. 2003; Kallel et al. 2007), and its use has been proposed for empiric therapy in high-risk patients and in endemic areas (Garnacho-Montero et al. 2015). Emergence of colistin resistance, however, currently represents a worrisome perspective not only for CRE but also for the management of MDR *A. baumanni* infections (Oikonomou et al. 2015). Several in vitro and experimental studies suggest a potential synergism between colistin and rifampin against XDR-*A. baumanii*, due to colistin's ability to enhance rifampin penetration into bacterial cells by altering the membrane permeability (Bassetti et al. 2008; Lee et al. 2013). However, a randomized trial comparing colistin monotherapy with colistin plus rifampin in 210 ICU patients showed similar 30-day mortality rates (43.3% vs. 42.9%) despite increased microbiologic eradication among those receiving combination therapy with rifampin compared with monotherapy (61% vs. 45%, p = 0.034) (Durante-Mangoni et al. 2013). The numerous drug–drug interactions caused by the inducing effect of rifampin on cytochrome P450 and the lack of evidence for clinical superiority represent significant limitations to rifampin use in clinical practice. In vitro synergism between fosfomycin and colistin has also been reported against *A. baumannii* (Santimaleeworagun et al. 2011). Similar to rifampin, in a RCT including 94 patients with CR *A. baumannii* infections the combination of colistin plus fosfomycin did not demonstrate clinical superiority but showed increased microbiological eradication versus monotherapy (100% vs. 81%, respectively; p = 0.01) (Sirijatuphat and Thamlikitkul 2014). Larger studies are needed to confirm these results.

In a recently reported randomized trial, colistin-meropenem combination therapy did not result in better survival, clinical cure, or microbiological cure compared to colistin monotherapy in patients with infections due to CR GNB, including 77% of patients with *A. baumannii* infections (Paul et al. 2018). A high patient mortality rate (44% at day 28) was reported even among patients with relatively low Charlson comorbidity index and SOFA score, highlighting the urgent need for new antibiotic options against CR *A. baumanni*.

The β-lactamase inhibitor sulbactam is not affected by common carbapenemases in *A. baumannii,* such as OXA-23, and retains activity against CR *A. baumanni*. A small RCT including 28 patients treated with ampicillin-sulbactam versus colistin showed comparable efficacy (62% vs. 60%, respectively) in the treatment of VAP caused by MDR *A. baumannii* (Betrosian et al. 2008). In a retrospective study including 98 patients with VAP due to CR *A. baumannii*, colistin was associated with a lower microbiological response rate compared to sulbactam (18% vs. 48%, respectively; p = 0.03) although the clinical cure rates were similar in both groups. (Zalts et al. 2016). These data suggest that sulbactam-based regimens may be a valid alternative for infections caused by MDR *A. baumannii* (Fig. 1).

Tigecycline often retains in vitro activity against *A. baumannii*. Tigecycline use, however, is not recommended in BSI and pneumonia, which represent the most frequent infections associated with *A. baumannii,* due to concerns over its unique pharmacokinetics. A recent meta-analysis assessing the efficacy of tigecycline showed that higher in-hospital mortality (OR = 1.57, 95% CI 1.04–2.35; p = 0.03) and lower microbial eradication (OR = 0.20, 95% CI 0.07–0.59; p = 0.003) were associated with tigecycline therapy versus comparators in the treatment of MDR *A. baumannii (Ni* et al. 2016*)*. Despite multiple limitations were identified in the studies included in the meta-analysis (e.g. small sample size, high heterogeneity, and lack of RCTs), current data do not support the use of tigecycline in this indication. Further studies are needed to investigate a potential role of tigecycline in association with other active antimicrobials in the treatment of CR *A. baumannii*.

Minocycline showed high susceptibility rates (79% compared with 99% of colistin) when tested against 5478 clinical isolates of *A. baumannii* (Castanheira et al. 2014). Furthermore, minocycline administered 100–200 mg twice daily intravenously has shown



[1] Ceftazidime-avibactam active also on OXA-48 (consider local epidemiology); combination therapy with new BLBLIs not established [2] Meropenem MIC ≤ 8 mg/L; one or two agents can be associated (Gutiérrez-Gutiérrez et al. 2017); [3] Resistant to all β-lactams, MIC meropenem > 8 mg/L; combination of colistin and an aminoglycoside associated with increased risk of nephrotoxicity; [4] Consider testing *in vitro* combinations for synergy

BLBLI= β-lactam/β-lactamase inhibitor; KPC-Kp=carpapenemase-producing *Klebsiella pneumoniae:* MBL=metallo β-lactamase; MDR=multidrug-resistant

Fig. 1. Recommendations for the use of old and new antibiotics against multidrug resistant Gram-negative bacilli.

bactericidal activity and enhanced effects if combined with colistin or other susceptible antimicrobials against resistant *A. baumannii* (Lomovskaya et al. 2016). Intravenous minocycline has recently received FDA approval (Qualified Infectious Disease Product designation under the Generating Antibiotic Incentives Now act) for the treatment of hospitalized patients with MDR *Acinetobacter* spp. infections. Although no RCTs have been performed, clinical data support the efficacy of minocycline in the treatment of MDR *Acinetobacter* spp. (Greig and Scott 2016). A review including 126 patients and 141 isolates from 7 studies reported an overall clinical success rate of 78% (range 50% to 89%) (Lashinsky et al. 2017). The two largest studies, including 35 and 55 patients with respiratory infections and BSI, showed clinical improvement in 81% and 73% of patients, respectively (Chan et al. 2010; Goff et al. 2014). Minocycline monotherapy was mainly used for respiratory tract infections showing clinical success rates between 82% and 100%.

6. Treatment strategies for MDR *P. aeruginosa*

Development of *P. aeruginosa* resistance to β-lactams and fluoroquinolones has been documented worldwide (Lister and Wolter 2009; Paterson 2006). The extensive use of carbapenems likely contributed to the increase of CR *P. aeruginosa* through different mechanisms, including production of MBL carbapenemases, AmpC β-lactamases, overproduction of efflux systems, and alterations in outer membrane porins (Lister and Wolter 2009; Paterson 2006). Among carbapenems, ertapenem has shown little activity against *Pseudomonas* spp. and could be considered, when possible, as an option to reduce the selective pressure on *Pseudomonas* and to avoid the use of other carbapenems. Although few clinical studies have shown no association between ertapenem use and decreased *P. aeruginosa* susceptibility, conflicting results on the selection for mutants with cross-resistance to other carbapenems have been reported (Nicolau et al. 2012).

Combination therapy for suspected infections caused by *Pseudomonas* spp. usually includes an antipseudomonal β-lactam (e.g. piperacillin-tazobactam, ceftazidime, cefepime) and a fluoroquinolone or an aminoglycoside. In areas with high prevalence of MDR *Pseudomonas,* however, alternatives to the classic antipseudomonal drugs may be necessary.

Ceftolozane-tazobactam has shown activity against the majority of CR *P. aeruginosa* and stability against overexpression of *Pseudomonas*-derived cephalosporinases or efflux pumps, preserving its activity against the majority of pan-β-lactam-resistant clinical strains (Takeda et al. 2007). Ceftolozane, however, is susceptible to hydrolysis by carbapenemase enzymes (e.g. MBL, KPC) and is not protected by tazobactam. Clinical efficacy of ceftozolane-tazobactam has been demonstrated in the treatment of cUTI and abdominal infections, although the number of patients infected with *P. aeruginosa* in the studies was limited (Huntington et al. 2016; Munita et al. 2017; Rivard et al. 2017). A phase 3 clinical trial comparing ceftolozane-tazobactam with meropenem in patients with HAP requiring mechanical ventilation or VAP has been recently completed and results are awaited (ClinicalTrials.gov, 2014).

In several in vitro studies against *P. aeruginosa*, avibactam has been shown to reverse ceftazidime resistance, reducing ceftazidime MICs to

values lower than the EUCAST and CLSI breakpoints (Flamm et al. 2014; Walkty et al. 2011). A Phase 3 trial confirmed efficacy of ceftazidime-avibactam comparable to BAT (represented by carbapenem monotherapy in >95% of cases) in 333 patients with cUTI or cIAI caused by ceftazidime-resistant Enterobacteriaceae or *P. aeruginosa.* Clinical cure rates with ceftazidime-avibactam or BAT were both 91%. Nevertheless, only a small proportion (7%) of ceftazidime-resistant *P. aeruginosa* infections were included in the study, and more evidence is needed to support the use of ceftazidime-avibactam as a potential alternative to carbapenems in these infections (Carmeli et al. 2016).

Colistin, usually in association with meropenem, has been employed to treat MDR *P. aeruginosa (Falagas* et al. 2006*; Falagas* et al. 2010b*; Linden* et al. 2003*)*. The use of aminoglycosides also represents a valid alternative in combination therapy, although the high risk of renal toxicity limits the association of an aminoglycoside with colistin in clinical practice (Neuner et al. 2012).

Fosfomycin use in the treatment of MDR *P. aeruginosa* has been reported by few retrospective studies as part of combination regimens including colistin, tigecycline, or a carbapenem (Apisarnthanarak and Mundy 2012; Neuner et al. 2012; Pontikis et al. 2014), but further data are necessary to confirm its efficacy.

As reported for *Enterobacteriaceae*, extended infusion of β-lactams appears as a promising option also for treatment of *Pseudomonas* severe infections (Apisarnthanarak and Mundy 2012; Bauer et al. 2013; Craig 1998; Lodise et al. 2007; Rodríguez-Baño et al. 2014). Treatment recommendations for severe infections due to MDR *Pseudomonas* spp. are listed in Fig. 1.

7. Treatment recommendations for CRE infections and relevance to AMS programs

7.1. General considerations for antibiotic selection

Relevant AMS elements include preservation of activity of new therapeutic options and the reduction of unnecessary use of antimicrobials (Wong and Spellberg 2017). In areas where CR infections are commonly reported, antibiotic stewards need to optimize the use of old antibiotic options and wisely select the novel compounds available in order to achieve better outcomes while reducing antibiotic resistance.

Key elements that guide treatment selection for CRE infections include the knowledge of local epidemiology, drug availability, data from well-designed clinical studies, and access to susceptibility testing. According to these variables, many patients will require individualized antibiotic therapy regimens (Perez et al. 2016; Rodríguez-Baño et al. 2014). Furthermore, new BLBLIs are characterized by susceptibility that changes as a function of the type of specific carbapenemase present (Toussaint and Gallagher 2015). Due to known significant differences in the worldwide distribution of carbapenemase-producing Enterobactericeae, local epidemiology will likely influence the therapeutic roles of the new agents and the choice of an empiric treatment (Aktaş et al. 2012; Albiger et al. 2015; Castanheira et al. 2015; Notes from the Field 2014; Struelens et al. 2010). Antibiotic selection and dosing are also influenced by PK/PD parameters. Attaining adequate PK/PD targets is an essential goal in the treatment of MDR infections, especially among critically ill patients (Neuner and Gallagher 2016). Standard dosing regimens, however, may not be sufficient to achieve exposures consistent with efficacy if the breakpoints are set too high, as shown by PK/PD target attainment analyses on old antibiotics such as carbapenems or aminoglycosides in pre-clinical infection models (Bhavnani et al. 2010; Livermore et al. 2012). The presence of optimal - or suboptimal - breakpoints for old antibiotics should also be taken into consideration when selecting the most effective antimicrobial regimen against MDR GNB.

Other aspects that need to be considered in the decision-making process for antimicrobial therapy of patients with CRE infections include the source of infection (e.g. VAP/HAP, cUTI, cIAI, etc.) and patient characteristics such as comorbidities, renal function, and infection severity. According to a validated mortality score (INCREMENT CPE score), combination therapy rather than monotherapy may be beneficial for high-risk patients characterized by certain clinical conditions (e.g. presentation with severe sepsis or shock, ≥6 points on the Pitt bacteremia score, ≥2 points on the Charlson comorbidity index, and source of BSI other than the urinary or biliary tract) (Gutiérrez-Gutiérrez et al. 2017). In patients with low mortality risk, monotherapy may be sufficient. Other studies found that combination therapy was protective in patients with septic shock and in BSI from non-urinary sources (Daikos et al. 2014; Tumbarello et al. 2015). Lower mortality has been associated with combination therapy compared to monotherapy among patients with septic shock caused by colistin-resistant, highly carbapenem-resistant KPC-*Kp* BSI (Machuca et al. 2017).

Finally, since prevention of the unnecessary use of antimicrobials is particularly relevant to AMS programs, careful evaluation of the clinical significance of a CRE isolate should be performed to confirm the presence of colonization versus infection (Ahn et al. 2014).

7.2. Therapy of CRE

7.2.1. New antimicrobials

Preliminary data demonstrated that patients experienced improved outcomes (e.g. decreased mortality, higher clinical success, and lower toxicity) with new BLBLI combinations over traditional CRE therapies for KPC-*Kp* infections (Kaye et al. 2017; Shields et al. 2017a; van Duin et al. 2018). For these reasons, the use of either ceftazidime-avibactam or meropenem-vaborbactam is currently considered as the preferred option for the treatment of infections caused by CRE (Fig. 1). There are not enough data to directly compare the efficacy of ceftazidime-avibactam versus meropenem-vaborbactam and indicate a preferred agent. It is likely, however, that both drugs will be needed for the management of these infections.

Due to avibactam's inhibitory capability against OXA-48 and ceftazidime's stability to hydrolysis by this enzyme, ceftazidime-avibactam represents the preferred agent for the treatment of OXA-48 producers over meropenem-vaborbactam. Furthermore, ceftazidime-avibactam represents a carbapenem-sparing option for AMS programs and has activity against CR *P. aeruginosa*. Against MBLs, ceftazidime-avibactam has the potential to be associated with aztreonam, which is not hydrolyzed by these enzymes, while avibactam maintains inhibitory activity against non-MBL β-lactamases (Marshall et al. 2017). Clinical data associated with the use of this combination, however, are scarce (Davido et al. 2017). The aztreonam-avibactam combination is currently under clinical development and represents a promising option for the management of CRE infections, including those caused by MBL producers.

In areas with low prevalence of OXA-48-group carbapenemases, such as the US, meropenem-vaborbactam could be preferred over ceftazidime-avibactam due to its higher potency against KPC producers and the potentially lower propensity for development of resistance (Hackel et al. 2017; Lomovskaya et al. 2017a). More data are needed to determine if meropenem-vaborbactam can act as a rescue therapy to ceftazidime-avibactam resistance, for example due to the potential restoration of carbapenem susceptibility shown by KPC-3 mutants (Giddins et al. 2018; Shields et al. 2016), and to assess whether its higher potency against KPC enzymes translates into better outcomes. Of note, it will be important to determine if ceftazidime-avibactam or meropenem-vaborbactam can select for resistance mechanisms that may compromise the use of both novel therapies. This is particularly relevant to AMS programs in order to select a preferred agent for clinical use.

Due to the presence of complex and concomitant mechanisms of resistance and the possibility of selecting resistance during treatment of CRE infections, it is highly recommended to routinely test ceftazidime-avibactam and meropenem-vaborbactam susceptibilities and to repeat testing in patients with persistently positive cultures (Albiger et al. 2015).

It remains unclear whether ceftazidime-avibactam should be used as monotherapy or combined with other agents. Various studies have

reported its use in combination with an "old" agent (most frequently aminoglycosides, but also polymyxins, tigecycline, and carbapenems) (Krapp et al. 2017; Satlin et al. 2017; Shields et al. 2015). This approach in our opinion appears reasonable, especially in severe infections and to potentially prevent resistance development (Shields et al. 2016). Although in vitro studies have investigated the synergy of ceftazidime-avibactam with other compounds, there are still not enough data to recommend the optimal accompanying drug and clinical scenarios under which such combinations should be implemented (Gaibani et al. 2017). In low risk patients (INCREMENT score < 8), ceftazidime-avibactam could potentially be used as monotherapy (Gutiérrez-Gutiérrez et al. 2017).

7.2.2. Old antibiotics

7.2.2.1. Carbapenems. When ceftazidime-avibactam or meropenem-vaborbactam cannot be used for the treatment of CRE infections, or meropenem displays MICs ≤8 mg/L, the use of a carbapenem in combination with another active agent is recommended according to the source of infection and the pathogen's susceptibility profile (Daikos et al. 2014; Tumbarello et al. 2012). As previously discussed, in confirmed CRE infections, a PK/PD optimized, MIC-driven approach is advisable for meropenem use, especially in critically ill patients (Cojutti et al. 2017; Giannella et al. 2018). Carbapenem use may also be beneficial when the combination of other in vitro active drugs is suboptimal according to the source of infection (e.g. use of tigecycline for cUTI and tigecycline or an aminoglycoside for VAP, due to poor drug concentrations at the sites) or because of increased nephrotoxicity (e.g. colistin and aminoglycosides). Limitations in the use of carbapenems are represented by their controversial efficacy against non-KPC carbapenemase producers and non-carbapenemase-producing CRE (Hagihara et al. 2013; Wiskirchen et al. 2013). Furthermore, AMS programs should consider the negative ecological effects of an increased use of carbapenems to treat CRE, which may lead to further selection of resistance.

A double carbapenem regimen, including ertapenem plus doripenem or meropenem, has been used for the treatment of pandrug-resistant CRE with some evidence of efficacy in small observational studies (Bulik and Nicolau 2011). The rationale for the combination is the high affinity of ertapenem for the KPC enzymes, allowing the binding of another carbapenem to the penicillin binding protein (Bulik and Nicolau 2011). Although some reports have documented successful outcomes with this approach, its efficacy may be simply attributable to the overall high dose of carbapenem administered, and the strategy remains limited against organisms with OmpK36 porin mutations, known to increase carbapenem MICs (Bulik and Nicolau 2011; Oliva et al. 2016; Wang et al. 2009). Therefore, a double carbapenem combination should be considered only when there are no other available options.

7.2.2.2. Polymyxins. Polymyxins are still frequently used as backbone for the treatment of CRE, despite concerns raised over dosing uncertainties and toxicity, especially among renally compromised and elderly patients (Poulakou et al. 2014). Current data suggest that colistin-containing combination therapy is more beneficial than colistin monotherapy for high-risk patients with CRE infections (Bergen et al. 2015; Gutiérrez-Gutiérrez et al. 2017; Hirsch and Tam 2010; Zusman et al. 2017). A loading dose of 9 MU followed by 9 MU q24h divided in two or three doses is currently recommended, with dose adjustments performed according to renal function (EMA 2017; Poulakou et al. 2014). Due to its potential toxicity and suboptimal PK, colistin should be used when other options are limited (e.g. meropenem MIC >8 mg/L and susceptibility only to colistin and another agent) and preferentially in combination (Fig. 1). Co-administration of colistin and aminoglycosides has high nephrotoxic potential and should be avoided whenever possible.

7.2.2.3. Aminoglycosides. Aminoglycosides show variable - but often significant - in vitro susceptibility against CRE (Tumbarello et al. 2015; van Duin et al. 2018). Although studies comparing the outcomes for patients treated with and without aminoglycosides are scarce, gentamicin (5–7 mg/kg/day) or amikacin (15 to 20 mg/kg/day) have been frequently used, especially in combination, in the management of infections caused by CRE (Daikos et al. 2014; Qureshi et al. 2012;Tumbarello et al. 2012, 2015). Specifically, the use of aminoglycosides was associated with better outcomes in cUTI (Satlin et al. 2011; van Duin et al. 2018). As a general rule, dose adjustments based on therapeutic drug monitoring are recommended during therapy with aminoglycosides (van Duin et al. 2015). The optimal dose of these drugs in severe infections, however, is still not well established. Some studies employing high doses of amikacin (>25 mg/kg/day) have been linked with higher probability of reaching PK/PD targets especially in critically ill patients, although further data are needed to recommend the use of these doses in CRE infections (Allou et al. 2016; Zazo et al. 2013).

7.2.2.4. Tigecycline. Tigecycline may be useful as part of treatment regimens based on susceptibility tests and source of infection (Daikos et al. 2014; Qureshi et al. 2012; Tumbarello et al. 2012, 2015). Tigecycline concentrations in urine are low, and this drug has been evaluated in this indication only in few reports (Brust et al. 2014). Tigecycline has been associated with a lower rate of KPC-*Kp* clearance in patients with bacteriuria or cUTI compared with aminoglycosides (Satlin et al. 2011; van Duin et al. 2015). Tigecycline use in cUTI appears therefore suboptimal and should not be considered as first line treatment. More generally speaking, we do not recommend the use of tigecycline as monotherapy for CRE (Tumbarello et al. 2012). Increased tigecycline doses are suggested for severe infections, such as HAP, and may be considered for other infections with suboptimal drug concentrations, such as BSI and cUTI (De Pascale et al. 2014; Geng et al. 2018; Pournaras et al. 2011; Ramirez et al. 2013). More clinical data, however, are required to support the use of high-dose tigecycline regimens for the treatment of HAP and other types of infections.

7.2.2.5. Fosfomycin. Because of the paucity of data associated with the use of fosfomycin in CRE infections, fosfomycin should not be considered as a first option when other active drugs are available. Similar to tigecycline, fosfomycin could be useful as part of combination regimens when other options are limited (Tumbarello et al. 2012, 2015) and to avoid emergence of resistance (Karageorgopoulos et al. 2012). Fosfomycin dose of 16 to 24 g a day given intravenously is recommended (Pontikis et al. 2014).

8. Conclusions

Carbapenem resistance represents one of the biggest challenges for clinicians managing severe infections. The optimal treatment for CR GNB infections, however, is still not well established. New agents for the treatment of CRE have been recently approved or are in late-stage development and displayed promising results. Several concerns about the use of new antibiotics remain, including some gaps in their activity, in particular against MBL producers, and limited availability of real-world studies assessing their efficacy in clinical practice. In the current scenario, clinicians and antimicrobial stewards have to rely on available antimicrobials and try to optimize the use of novel available compounds to avoid the selection of further resistances. Careful use of currently available options along with adequate infection prevention procedures and optimized AMS programs remain key points to manage severe infections caused by MDR GNB.

Declarations

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