Treatment for carbapenem-resistant *Enterobacterales* infections: recent advances and future directions

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Abstract

Carbapenem-resistant Enterobacterales (CRE) are a growing threat to human health worldwide. CRE often carry multiple resistance genes that limit treatment options and require longer durations of therapy, are more costly to treat, and necessitate therapies with increased toxicities when compared with carbapenem-susceptible strains. Here, we provide an overview of the mechanisms of resistance in CRE, the epidemiology of CRE infections worldwide, and available treatment options for CRE. We review recentlyapproved agents for the treatment of CRE, including ceftazidime-avibactam, meropenem-vaborbactam, imipenem-relebactam, cefiderocol, and novel aminoglycosides and tetracyclines. We also discuss recent advances in phage therapy and antibiotics that are currently in development targeted to CRE. The potential for the development of resistance to these therapies remains high, and enhanced antimicrobial stewardship is imperative both to reduce the spread of CRE worldwide and to ensure continued access to efficacious treatment options.

Keywords Carbapenem-resistant · Enterobacterales · CRE · Carbapenemase · Antimicrobial resistance

Introduction

The rise of antimicrobial-resistant (AMR) organisms worldwide is considered one of the biggest threats to global health by the World Health Organization (WHO) [1]. Carbapenem –esistant *Enterobacterales* (CRE) are defined by the US Centers for Disease Control and Prevention (CDC) as *Enterobacterales* (formerly *Enterobacteriaceae*) with in vitro resistance to at least one carbapenem [2]. Carbapenems are a potent class of broad-spectrum antibiotics that inhibit penicillin binding proteins, thereby preventing cell wall synthesis [3] and were once considered the "last resort" antibiotics in many hospitals. Resistance to carbapenems significantly limits the antibiotic armamentarium available to treat challenging infections. CRE have spread substantially in recent years [4–6] and are now endemic in certain regions of North America, Europe and the Mediterranean, and South Asia [7].

CRE are typically healthcare-associated infections, although community spread is becoming more common [8–11], with intestinal colonization and environmental sources as reservoirs of infection [12]. CRE are of particular concern due to the increased mortality [13, 14], length of hospital stay, and increased cost when compared with drug-susceptible infections [15]. An economic prediction model from the USA estimated a societal cost of between $59,692 and $86,940 for each CRE infection [16]. Additionally, CRE infections are often found in the most vulnerable patients—the elderly, those with underlying comorbidities, and those with indwelling catheters or permanent hardware in place [4, 17–19].

In October 2020, The Infectious Diseases Society of America (IDSA) released guidance for the treatment of multidrug-resistant Gram-negative bacterial infections, including CRE, and offers clinicians preferred and alternative treatment strategies for a variety of clinical scenarios [20]. The IDSA guidance is divided into infections inside and outside the urinary tract and assumes the organism and susceptibility profile are known. This guidance provides a current overview of treatment options for these challenging infections, albeit with a focus on variants that predominate in North America.

This review will focus on treatment strategies for infections with carbapenem-resistant *Enterobacterales*, including "traditional" antibiotics that have retained activity against

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CRE, newly approved antibiotics developed specifically for CRE, phage therapy, and antibiotics that are in development to target multi-drug resistant infections.

Mechanisms of carbapenem resistance in CRE

Resistance to carbapenems can be mediated via alterations to the penicillin binding protein of the bacterial cell wall, an increase in efflux pumps, or a decreases in membrane permeability [21, 22] as well as through the production of carbapenemase enzymes. Carbapenemases are a diverse family of β-lactamases that have the ability to hydrolyze and inactivate a variety of antibiotics including penicillins, cephalosporins, monobactams, and carbapenems [23]. These enzymes function by binding to the drug, breaking the amide bond of a four-membered azetidinone ring, and preventing it from binding to the penicillin-binding protein of the bacterial cell wall [24]. Carbapenemases are found in approximately 85% of CRE worldwide, with considerable variation between regions, ranging from 76% in Latin America to 90% in the Middle East and Africa found in a recent global survey [25]. Other studies have shown lower rates, with the recent CRACKLE-2 study finding carbapenemases in 59% of CRE from the USA [26]. Using the Ambler classification system, carbapenemases are found within class A, B, and D β-lactamases, with substantial geographic heterogeneity in classes between global regions and with various modes of transmission [7, 27] (Table 1).

Ambler class A carbapenemases use a serine residue to hydrolyze beta-lactams [28] and include the bla_{KPC}, bla_{NMC}/bla_{IMI}, and bla_{SME} [29] genes, *with* bla_{KPC} being the most common carbapenemase of the class [30]. It was first discovered in 1996 in a *Klebsiella pneumoniae* isolate from North Carolina, USA [31]; is plasmid-mediated; and is now endemic in much of the western hemisphere with the highest rates found in Eastern North America [25, 32, 33] and outbreaks reported in South America, including Columbia and Ecuador [34, 35]. Spread from the USA has led to outbreaks outside the hemisphere as well. An outbreak in Israel was traced to a strain from New York [36], and KPC enzymes have also been found in a variety of European countries including large outbreaks in Greece [37, 38], Portugal [39], and Poland [40], among other countries, where they can significantly impact regional resistance patterns [24, 25]. While found primarily in *Klebsiella pneumoniae*, KPC enzymes have also been found in a variety of other *Enterobacterales* including *Citrobacter freundii*, *Enterobacter cloacae*, *Escherichia coli*, and *Serratia marcescens*, among others, as well as in *Pseudomonas* species [29].

Class B metallo-β-lactamases (MBLs) are zinc-dependent [41] and include the bla_{VIM}, bla_{IMP}, and bla_{NDM} genes [41–43], all found on mobile genetic elements and capable of horizontal spread. [44] MBLs are able to hydrolyze a wide range of beta-lactams but cannot hydrolyze monobactams such as aztreonam. [45] The enzyme IMP was the first enzyme discovered in this class, isolated from an imipenem-resistant *Pseudomonas aeruginosa* isolate in Japan in 1991 [46] and it now accounts for as much as 15% of the CRE found in Japan, Australia and parts of Southeast Asia [25, 47, 48]. VIM, for Verona Integron-encoded Metallo-beta-lactamase, was first isolated in Italy in 1997 [49] and is responsible for approximately 15% of the CRE isolated from Europe [25], with the highest rates found in Greece, Italy, Spain, and Hungary [50]. More recently, the New Delhi Metallo-β-lactamases (NDM) were discovered in 2007 from a *Klebsiella pneumoniae* isolate of a Swedish patient who had previously been hospitalized in India with a urinary tract infection [51]. The highest burden of NDM remains in South Asia as well as the Middle East, where it accounts for up to a third of detected carbapenemases [25]. NDM is of particular concern given its rapid spread and limited treatment options [45].

The Class D carbapenemases include members of the OXA-encoding genes and are largely found in *Acinetobacter*; however the plasmid-encoded $bla_{OXA\text{-}48}$-like genes are found in *Enterobacterales* [52–55] and have been implicated in multiple nosocomial CRE outbreaks [56–59]. OXA-48-like enzymes encompass OXA-48 and related variants, including OXA-181, OXA-162, and OXA-232, among others, with distinct geographic distributions and co-occurring resistance

Table 1 Major carbapenemase enzymes

Ambler class	Major enzymes	Active site	Primary geographic distribution	Treatment notes
A	KPC	Serine	USA, Colombia, Greece	Inhibited by clavulanate, tazobactam
	NMC, SME		Rare	
B	VIM	Zinc	Spain, Italy, Greece	Do not hydrolyze monobactams*
	IMP		Japan, Taiwan	
	NDM		India, Pakistan, Romania, Poland	
D	OXA-48	Serine	Turkey, Mediterranean, Morocco	Low-level resistance against cephalosporins*

*Are often co-occurring with ESBL enzymes that confer resistance to these classes

genes [52, 54]. OXA-48-like enzymes are most commonly found in the Middle East and Europe, where over 27% of carbapenem-resistant isolates in each region were recently found to harbor OXA-48 [25], with endemic levels reported in Turkey, Malta, much of North Africa and the Middle East [54]. OXA-48 remains uncommon in North America, with only 52 cases reported in the USA between 2010 and 2015 [60] and only found in 1% of carbapenemase-producing CRE in the CRACKLE-2 study [26].

Previously approved antibiotics with CRE activity

Therapeutics for CRE are summarized in Table 2. There are several "traditional" antibiotics that have retained activity against some strains of CRE and are being deployed in new ways or in combination with other drugs for the treatment of severe CRE infections.

Table 2 Spectrum of Activity anti-CRE therapeutics

Agent	Therapeutic Class	Activity against Class A	Activity against Class B	Activity against Class D	Notes
Aztreonam	Monobactam	-	+	+	Not recommended. CRE often have co-occurring ESBL enzymes which render aztreonam ineffective
Colistin, Polymyxin B	Polymyxin	+/-	+/-	+/-	Limited efficacy, significant toxicities
Fosfomycin	Phosphoenolpyruvate analogue	+	+	+	Primarily used for urinary tract infections
Tigecycline	Tetracycline	+/-	+/-	+/-	Typically used as combination therapy
Ceftazidime-avibactam	β-lactam-β-lactamase inhibitor	+	-	+	Approved for cUTI, cIAI (with metronidazole), HAP/VAP. Can be used with aztreonam for treatment of NDM-producing infections
Meropenem-vaborbactam	β-lactam-β-lactamase inhibitor	+	-	-	Approved for cUTI, cIAI, HAP/VAP
Imipenem-relebactam	β-lactam-β-lactamase inhibitor	+	-	-	Approved for cUTI, cIAI by FDA. Approved for HAP/VAP, BSI, resistant GN infections by EMA
Plazomicin	Aminoglycoside	+	+	+	NDM-carrying CRE often resistant due to 16 s ribosomal methyltransferases. Approved for cUTI by FDA. Not approved by EMA
Eravacycline	Tetracycline	+	+	+	Approved for cIAI by FDA and EMA
Omadacycline	Tetracycline	+	+	+	Oral and IV formulations. Approved by FDA for ABSSSI and CABP. Not approved by EMA
Cefiderocol	Cephalosporin	+	+	+	Approved for cUTI and HAP/VAP by FDA. Approved for resistant GN infections by EMA. CREDIBLE-CR study showed increased all-cause mortality
Phage therapy	N/A	+	+	+	Few clinical trials showing efficacy for CRE at this time. Require specificity for infecting organism, often leading to significant lag time to start treatment
Zidebactam*	β-lactamase inhibitor	+	±	+	Combined with cefepime. Clinical trials pending
Taniborbactam*	β-lactamase inhibitor	+	+	+	Combined with cefepime. Currently in phase 3 trials for cUTI
LYS228*	Monobactam	+	+	+/-	No clinical trials currently underway
Nacubactam*	β-lactamase inhibitor	+	+/-	+	Combined with meropenem. Completed phase 1 clinical trials

cUTI complicated urinary tract infection, *cIAI* complicated intraabdominal infection, *HAP/VAP* hospital acquired pneumonia/ventilator-associated pneumonia, *GN* gram negative, *ABSSSI* acute bacterial skin and skin structure infection, *CABP* = community acquired bacterial pneumonia; *FDA* = United States Food and Drug Administration, *EMA* European Medicines Agency

* antibiotic currently in development

Aztreonam

The monobactam antibiotic Aztreonam is effective against bacteria-producing Class B and D carbapenemases in isolation; however these bacteria often carry concomitant ESBL genes that hydrolyze aztreonam rendering it ineffective and thus it is often of limited clinical utility as monotherapy [61, 62]. The combination of aztreonam with the novel β-lactam-β-lactamase inhibitor ceftazidime-avibactam is a promising treatment option for MBLs and is discussed in detail below. Notably, aztreonam does not have activity against bacteria-producing Class A carbapenemases, including bacteria producing the highly prevalent KPC carbapenemases [61].

Polymyxins

The polymyxin antibiotics colistin and polymyxin B have long been used for resistant Gram-negative bacteria, including CRE [63]; however there is emerging resistance developing to these drugs. This is notable, as several studies have shown an association between polymyxin resistance and an increase in mortality [64, 65], although these studies occurred prior to the development of newer CRE-active agents which are now available. Resistance to polymyxins can occur via chromosomal point mutations leading to changes in the bacterial lipopolysaccharide membrane or an increase in efflux pumps or it can be plasmid-mediated, via several *mcr* genes that change lipid A present in the lipopolysaccharide membrane and prevent the target drug from binding [66]. There is also evidence that heteroresistance arising from minor resistant subpopulations in a culture may make colistin resistance difficult to detect in vitro and lead to subsequent treatment failure [67, 68]. Additionally, polymyxins have significant nephrotoxicity, with several studies having shown their inferiority compared with newer drugs against isolates carrying Class A carbapenemases [69–71], and as such they are not currently recommended for the treatment of CRE by the IDSA [20]. Despite this, they are often the only available antibiotic for CRE infections in certain regions despite increasing resistance levels [72, 73] and thus are considered to be a "highest priority" critically important antimicrobial by the WHO [74, 75].

Fosfomycin

Fosfomycin, an antibiotic first discovered in 1969, inhibits cell wall synthesis in a variety of Gram-positive and Gram-negative bacteria [76], including *Enterobacterales*, and has retained activity against some CRE isolates [77]. Resistance to fosfomycin is mediated primarily through the *fosA* genes which encode fosfomycin hydrolases and are found in many *Enterobacterales* with the exception of E. coli [78, 79]. Traditionally, fosfomycin has primarily been used as an oral formulation for lower urinary tract infections [76, 80]; however there is growing interest in intravenous use for MDR organisms, including CRE [81–83]. Fosfomycin does not have sufficient renal parenchymal penetration and thus should not be used for upper urinary tract infections [84, 85].

Tigecycline

The tetracycline antibiotic tigecycline has a broad spectrum of activity against gram positive and gram negative infections and global surveillance data from the TEST study shows that the majority of *Enterobacterales* isolates collected worldwide between 2014 and 2016 remain susceptible ($\leq 1.3\%$ resistance in all regions) [86]. Tigecycline has been used for CRE infections with success; however several recent studies have shown monotherapy to be of limited benefit [87] and combination therapy is likely more efficacious [88, 89]. Resistance to tigecycline in *Enterobacterales* can arise from upregulation of the AcrAB efflux pump [90, 91] or via the plasmid-mediated *tet*(X4) gene, which encodes a flavin-dependent monooxygenase that modifies tigecycline [92, 93]. Using "traditional" CRE-active antibiotics in combination with antibiotics with other mechanisms of action or with "repurposed" drugs from other classes has also shown some promise for the treatment of CRE infections [94]. For example, there are in vitro studies showing synergistic effects of combining colistin with other antibiotics including clarithromycin or rifamycin [95] or the HIV drug azidothymidine (AZT) [96] for the treatment of CRE that are colistin-resistant. Other combinations that have shown in vitro activity against CRE include AZT and tigecycline [97]; pentamidine in combination with rifampicin, tobramycin, tigecycline, or amikacin [98]; and polymyxin B with citalopram, sertraline, or spironolactone [99]. Animal studies and clinical trials are needed to determine in vivo efficacy of these combination treatments in true clinical infections, and thus the utility of these combination regimens remain theoretical at this time.

β-lactam-β-lactamase inhibitor combinations

Ceftazidime-avibactam

In the last several years, β-lactam-β-lactamase inhibitor combinations have been developed and approved specifically to target multidrug resistant organisms, including CRE. The first of these, avibactam, was developed in 2011 and is a synthetic diazabicyclooctane (DBO) non-β-lactam that

covalently and reversibly binds to serine β-lactamases and has activity against class A (KPC*)* [100, 101] and class D (OXA-48-like) [100–103] carbapenemases, but not MBLs (NDM, VIM, IMP). When compared with polymyxin antibiotics, multiple observational studies have shown ceftazidime/avibactam to be superior for the treatment of CRE infections possessing Class A carbapenemases with fewer side effects and toxicities [71, 104–106]. Ceftazidime-avibactam was approved by the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) in 2015 for complicated urinary tract infections (cUTI) and for complicated intra-abdominal infections (cIAI) in combination with metronidazole [107]. Approval was granted following the RECLAIM [108] trials, which showed non-inferiority for ceftazidime/avibactam when compared with meropenem for cIAI and the RECAPTURE trial, which showed non-inferiority compared with doripenem for cUTI [109]. Approval has since been expanded to include hospital-acquired and ventilator-associated pneumonia following the REPROVE trial, a phase-III trial conducted across 23 countries which showed non-inferiority of ceftazidime-avibactam compared with meropenem for nosocomial pneumonia [110]. It is important to note all three of these studies leading to approval for ceftazidime-avibactam used clinical inclusion criteria and did not select specifically for CRE. Microbiological analysis showed that 13.5% of patients in the RECLAIM trials, 19.6% of patients in the RECAPTURE trial, and 28% in the REPROVE trial had a ceftazidime-resistant organism at baseline. Only the RECLAIM trials reported the rate of MBL infection, at approximately 3% [108].

In isolates from hospitalized patients collected worldwide during the INFORM global surveillance survey for AMR resistance, in vitro susceptibility to ceftazidime-avibactam has remained high for CRE; among 816 non-MBL CRE isolates collected between 2012 and 2014, only 19 (2.3%) were resistant, and 97.7% were susceptible to ceftazidime-avibactam [111]. Subsequent testing of isolates collected between 2015 and 2017 showed a similarly high rate of 99.8% susceptibility for ceftazidime-avibactam [112].

Although overall high rates of susceptibility to ceftazidime-avibactam remain, a number of mutations have been seen clinically that confer resistance, primarily in carriers of KPC-2 and KPC-3 enzymes. The sequence type 258 *Klebsiella pneumoniae* with KPC-3 has been shown to be resistant to ceftazidime-avibactam due to transposition of KPC-3 onto a second plasmid with subsequent alterations in the porin channels OmpK35 and OmpK36 and upregulation of efflux pumps [113–115]. Concerningly, mutations in $bla_{KPC\text{-}3}$ conferring resistance to avibactam have been reported in patients while on ceftazidime-avibactam therapy via single amino acid substitutions at D179Y/T243M, D179Y, and V240G leading to alterations in the Ω-loop in KPC-3; however these mutations restore meropenem susceptibility in some isolates [116]. More recently, a KPC-3 variant named KPC-50 was recovered from a *Klebsiella pneumoniae* isolate in a Swedish patient and found to contain a three-amino-acid insertion that conferred increased affinity to ceftazidime and decreased activity of avibactam leading to resistance [117]. KPC-2 variants arising from single amino acid substitutions at the Ω-loop have also been found to confer resistance to ceftazidime-avibactam, likely through increased affinity of the enzyme for ceftazidime, thereby preventing the binding of avibactam [118]. While most of the above resistance mechanisms have been documented in Klebsiella pneumoniae isolates, point mutations leading to insertion of TIPY in penicillin binding protein 3 of an E. coli isolate containing KPC-3 have been documented, which prevents the binding of ceftazidime and cannot be overcome by avibactam [119, 120].

Although ceftazidime-avibactam alone does not have activity against MBLs, there is significant in vitro synergy between ceftazidime-avibactam and aztreonam that confers activity against these isolates [121]. This is of particular importance, given that although aztreonam is active against class B carbapenemases, it is often hydrolyzed by other β-lactamases that co-occur with MBLs [122]. As a result, only 29.2% of MBLs from a recent global survey were found to retain susceptibility to aztreonam monotherapy [123]. When tested against the combination of aztreonam-avibactam, all MBL isolates in that study were inhibited by the combination [123]. A clinical case series evaluating this combination treatment in 10 patients with infections caused by NDM-producing MBLs during an outbreak found 6 of 10 patients had clinical success at 30 days, suggesting the combination of ceftazidime-avibactam plus aztreonam may be a useful clinical option for extensively drug resistant *Enterobacterales* infections that contain both class B carbapenemases as well as ESBL enzymes [124]. Additional reports of combined ceftazidime-avibactam plus aztreonam treatment have replicated these early findings [125], including in pan-resistant isolates [126]. Given that the combination of aztreonam plus avibactam alone, without the addition of ceftazidime, appears efficacious, this two-drug combination is currently being tested in a Phase III clinical trial for the treatment of complicated infections caused by MBL-containing gram negative bacteria [127]. An earlier Phase II pharmacokinetic trial (the REJUVENATE study) showed the combination of aztreonam-avibactam to have similar safety and tolerability to aztreonam monotherapy [128]. As a result of these findings, the IDSA currently recommends ceftazidime-avibactam alone as the preferred treatment for OXA-48-producing CRE outside the urinary tract and in combination with aztreonam for NDM-producing CRE infections [20].

Meropenem-vaborbactam

Meropenem-vaborbactam was approved by the FDA in 2017 for the treatment of complicated urinary tract infections (cUTI) [129] and by the EMA in 2018 with an expanded authorization that includes cUTI, cIAI, and hospital-acquired or ventilator-associated pneumonia (HAP/VAP) [130]. Meropenem-vaborbactam was designed to target multidrug-resistant organisms and specifically the class A KPC carbapenemases [131]. The drug combines the carbapenem antibiotic meropenem with a novel β-lactamase inhibitor containing a cyclic boronic acid pharmacophore that restores the activity of meropenem against serine carbapenemases [132]. While it has broad activity against class A carbapenemases (as well as class C β-lactamases conferring cephalosporin resistance), it notably does not have activity against the class B metallo β-lactamases (NDM, VIM, IMP) nor class D (OXA-48-like) carbapenemases [133]. A survey of meropenem-vaborbactam susceptibility against global-lycollected CRE showed the lowest MIC values for isolates from the Americas, consistent with the predominance of KPC-producers in this region [134]. Given this, meropenem-vaborbactam may be of more limited utility in regions where MBLs and OXA-48-like enzymes predominate, including parts of Asia, the Middle East, and North Africa.

Approval for meropenem-vaborbactam was obtained following the TANGO I trial which showed non-inferiority of meropenem-vaborbactam for cUTI when compared with piperacillin-tazobactam [135]. TANGO I did not select for patients with CRE organisms, and in fact, nearly all baseline uropathogens were susceptible to meropenem. This was later followed by the TANGO II trial to test meropenem-vaborbactam in complicated CRE infections including bloodstream infections (BSI), pyelonephritis, VAP, and cIAI [70]. While a descriptive study, TANGO II evaluated 47 patients across 8 countries and found an increase in clinical and microbiologic cure and reduction in death with fewer adverse events compared with best alternative therapy. Vaborbactam enters cells via the membrane porin channels OmpK35 and OmpK36 [133], and resistance to vaborbactam can develop via downregulation or alteration of these porin channels [136–138]

Imipenem-relebactam

The most recent drug combination in this class is imipenem-relebactam, a non-β-lactam bicyclic DBO β-lactamase inhibitor that is structurally similar to avibactam, but with the addition of a piperidine ring [139]. It is believed to reversibly acylate β-lactamases [140]. Imipenem-relebactam is active against class A carbapenemases but not the metallo-β-lactamases and has little to no activity against the class D OXA-48-like enzymes [141]. Information from the SMART surveillance study on *Enterobacterales* isolates collected in Europe showed the addition of relebactam restored imipenem susceptibility in 67% of isolates carrying KPC enzymes, but that nearly all isolates with MBLs or OXA-48-like enzymes remained nonsusceptible, primarily occurring in isolates from countries with endemic levels of these enzymes [142]. This highlights the importance of determining the underlying mechanism of carbapenem resistance and carbapenemase epidemiology when selecting treatment options.

Imipenem-relebactam was approved for use by the US FDA in 2019 [143] and is available with the carbapenem imipenem/cilastatin for clinical use [144]. The RESTORE-IMI-1 trial evaluating the safety and efficacy of imipenem-relebactam in a variety of severe imipenem-resistant gram negative infections found higher favorable clinical response rate (71.4 vs 40%), lower 28-day mortality rates (9.5 vs 30%), and lower treatment-associated nephrotoxicity (10.3 vs 56.3%) with imipenem-relebactam compared with imipenem plus colistin [69]. Notably, most of the isolates in this study were *Pseudomonas* spp. (77.4%) with the remainder *Enterobacterales*. The RESTORE-IMI-II trial was a non-inferiority study of imipenem-relebactam compared with piperacillin-tazobactam for HAP/VAP infection and found imipenem-relebactam was non-inferior for both 28-day mortality and favorable clinical response [145]. When looking specifically at the microbiologic modified intent-to-treat population, mortality rates for intubated patients with HAP/VAP were 12.2% lower for those in the imipenem-relebactam group compared withs the piperacillin-tazobactam group. Given the potential for resistance with all of the β-lactam-β-lactamase inhibitor combinations, enhanced antibiotic stewardship will be crucial to ensuring ongoing efficacy of these agents [146].

Novel aminoglycosides

Plazomicin

Plazomicin is a novel semisynthetic aminoglycoside that was derived from the antibiotic sisomicin, a naturally occurring aminoglycoside discovered in 1970, and works by binding to the 30 s subunit of bacterial ribosomes, inhibiting protein synthesis [147]. Plazomicin has a broad spectrum of activity against *Enterobacterales*, including those with ESBL enzymes and multiple classes of CRE, including class A (KPC), class B (VIM, IMP), and class D (OXA-48) [148–150]. It has shown variable activity against the metallo-beta lactamase NDM-1, largely because NDM-1 often co-produces 16 s ribosomal methyltransferases, which modify the 30 s ribosomal subunit and prevent aminoglycoside

binding [148]. Given this, it may be of limited clinical utility in regions where NDM-1 are endemic.

Plazomicin was approved by the US FDA in 2018 for cUTI [151] following a non-inferiority trial comparing plazomicin to meropenem for cUTI including pyelonephritis caused by *Enterobacterales* [152]. This was later followed by the CARE trial, comparing plazomicin to colistin in combination with adjunctive meropenem or tigecycline in patients with CRE-causing BSI or VAP and found a 26% reduction in death or clinically significant disease-related complications at 28 days in those who received plazomicin and with fewer adverse events [153]. The trial was small, however, and the drug was therefore not granted expanded approval for use in BSI [154]. Plazomicin has not been approved by the European Medicines Agency, and the application for approval has since been withdrawn due to financial reasons [155], following the parent manufacturer of plazomicin declaring bankruptcy [156].

Resistance to aminoglycosides most often occurs via aminoglycoside-modifying enzymes (AMEs) that reduce the binding affinity for the ribosomal target [157]. Plazomicin has several structural modifications that prevent the activity of most AMEs, thereby reducing the risk of AME-mediated resistance [158]. As noted above, plazomicin cannot overcome modifications caused by 16 s ribosomal methyltransferases and bacteria that possess these enzymes are resistant to plazomicin, a concerning finding given that these genes can be transferred horizontally via plasmids [159].

Tetracyclines

Eravacycline

Eravacycline is a fully synthetic tetracycline developed in 2011 [160] that is structurally similar to tigecycline and inhibits bacterial protein synthesis by binding to the ribosomal 30 s subunit resulting in broad gram positive and gram negative activity against both aerobic and anaerobic organisms, with the exception of *Pseudomonas* [161]. Eravacycline has activity against CRE including class A (KPC), class B (VIM, NDM-1), and class D (OXA-48) enzymes [162, 163] with consistently lower MICs than for tigecycline [162–164]. While it has reasonably high oral bioavailability, only IV formulations are available currently.

A pooled analysis of two-phase III trials evaluating eravacycline for cIAI showed non-inferiority compared with ertapenem and meropenem, although with higher levels of nausea, vomiting, and diarrhea compared with the carbapenems [165]. The results of these studies led to approval for the drug in 2018 by both the EMA and the US FDA for use in cIAI [166, 167]. While initially promising as a potential option for urinary tract infections given in vitro activity against biofilms of uropathogenic *E. coli* [168], a phase 3 trial comparing eravacycline to levofloxacin for cUTI failed to show noninferiority and thus it was not approved for this indication [166, 169].

Resistance to tetracycline antibiotics most often occurs via active drug efflux pumps encoded via *tet* genes, and ribosomal protection proteins [170]. Eravacycline evades these resistance mechanisms via a modified D ring side chain that maintains the drug's efficacy [160, 171]. Notably, the enzyme Tet(X) is a tetracycline destructase that enzymatically inactivates tetracyclines and is active against eravacycline [172]. This enzyme can be located on mobile genetic elements and has been shown to confer resistance to eravacycline. It has been found in various organisms, including *E. coli*, and can be found as asymptomatic carriage in human gut flora [92, 173], indicating the potential for spread of eravacycline resistance.

Omadacycline

Omadacycline is a semisynthetic tetracycline that most closely resembles tigecycline but with an aminomethyl group at the C9 position [174]. Similar to eravacycline, this substitution results in broad gram positive and gram negative activity and resistance to the activity of the *tet* efflux pumps and ribosomal protection proteins [174, 175]. Two phase-3 trials showed IV omadacycline to be noninferior to IV linezolid and IV moxifloxacin for acute bacterial skin and skin structure infection (ABSSSI) and community acquired bacterial pneumonia (CABP), respectively [176, 177]. Subsequently, the OASIS-2 trial showed noninferiority of oral omadacycline to oral linezolid for ABSSTI [178]. Approval was obtained from the FDA in 2018 for both oral and IV formulations for ABSSSI and CABP [179]. Approval was sought from the EMA for the same; however the agency requested additional studies for an indication for CABP and the manufacturer of omadacycline subsequently withdrew the application for financial reasons [180].

As with eravacycline, omadacycline is deactivated by the Tet(X) destructase enzyme [172]. A recent study of NDM-producing *Enterobacterales* from the USA found that 59.6% were susceptible to omadacycline, indicating this may be a possible oral treatment option for selected patients infected with CRE [181].

Cephalosporins

Cefiderocol

Cefiderocol is a novel siderophore cephalosporin that acts through a "trojan horse" mechanism that uses the bacterial iron transport system to facilitate antibiotic uptake and evade

bacterial defense systems [182]. Once inside the bacterium, cefiderocol has high affinity for several penicillin binding proteins, inhibiting peptidoglycan synthesis and ultimately causing cell death [183]. Modifications in the C3 and C7 side chains of cefiderocol render it highly stable against a variety of β-lactamases, including carbapenemases [184, 185]. Cefiderocol has a similar safety profile to other cephalosporins, with the most common adverse reactions being gastrointestinal disturbance, rash, and fever [186].

In vitro studies show activity of cefiderocol against a variety of CRE, including those harboring class A (KPC), class B (NDM, VIM, IMP), and class D (OXA-48-like) enzymes [184, 187, 188]. Cefiderocol was approved by the FDA in 2019 [189] for cUTI and HAP/VAP following a phase 2 non-inferiority trial comparing cefiderocol to imipenem-cilastatin for treatment of cUTI caused by gram negative uropathogens [190] and a phase 3 non-inferiority trial comparing cefiderocol to meropenem for gram negative nosocomial pneumonia [191]. The EMA authorization is broader and includes gram negative aerobic infections in patients with limited treatment options [192]. The CREDIBLE-CR study was subsequently undertaken to evaluate cefiderocol in serious carbapenem-resistant infections [193]. It found that cefiderocol had comparable clinical and microbiologic effectiveness when compared with the best alternative therapy; however there was an increase in all-cause mortality in the cefiderocol group in those treated for BSI, nosocomial pneumonia, and sepsis [193]. This increase was not seen for cUTI and appeared to be driven largely by *Acinetobacter* infections. The clinical efficacy of cefiderocol against CRE remains to be determined in practice, and the FDA approval now includes a warning for increased all-cause mortality as a result of the trial [189].

There is some evidence of emerging resistance to cefiderocol; however it remains rare [194–196]. In vitro studies suggest that cefiderocol resistance among *Enterobacterales* is likely due to the co-production of both serine and metallo-beta lactamases and may be able to be overcome with the addition of avibactam [197].

Phage therapy

As bacteria become increasingly resistant to chemical antibiotics through mutations and horizontal gene transfer, an area that is gaining increasing attention and promise as a therapeutic option for multidrug resistant organisms is phage therapy. Phage therapy is derived from naturally occurring bacteriophages that use lytic viruses to infect and ultimately lyse bacteria [198]. Phages attach to receptors on the surface of target bacteria and deliver viral genomic material into the bacterial cell. The bacteria then use that genetic material to produce viral copies and package new viral particles which then escape the bacterium via cell lysis. This kills the infected bacterial cell and releases new phage particles to infect other susceptible bacteria, making the process potentially self-amplifying [198], although in clinical practice repeated ongoing dosing is likely required [199].

The use of bacteriophages to treat human infections was first pioneered at the turn of the twentieth century and used successfully in several human infections including cholera, plague, and conjunctivitis; however their use was limited and phages soon fell out of favor with the advent of chemical antibiotics in the mid-twentieth century [200]. Phages have several advantages over antibiotics, including specificity for the infecting organism, self-amplification, self-destruction when the bacterial infection is cleared, ability to penetrate biofilms, and preservation of the commensal human microbiota [201]. However, phages may induce inflammatory immune response [202] and antiviral immunity [203] in humans. The requirement for strain-specific phages may also limit the timely administration and scaling of phage therapy. As antibiotic resistance has increased at an alarming rate, there has been a renewed interest in phage therapy for treatment of multidrug resistant infections.

While the use of phage therapy continued in the twentieth century in Georgia, Poland, and Russia [200, 204], the first randomized controlled phase I/II trial that met guidelines of good manufacturing practice for phage therapy was the PhagoBurn trial [205]. It was conducted between 2015 and 2017 and enrolled 27 individuals with burn wounds infected with *Pseudomonas aeruginosa* to receive topical therapy with a lytic phage cocktail or standard dressing [205]. The study showed a slower decrease in bacterial burden with phage therapy compared with standard of care, but the study authors note that a low concentration of phage was used. Since then, several case reports have shown efficacy of phages for treating multidrug-resistant infections. A case series of 10 patients with highly resistant infections from a single center in the USA showed success with phage therapy in 7 of 10 cases, failure in 2, and uninterpretable results in 1 with few adverse effects [206]. These infections were primarily MDR *Acinetobacter*, *Pseudomonas*, and *S. aureus*, with one case of a persistent ESBL *E. coli* infection.

Although clinical trials of phage therapy specifically for CRE treatment are lacking, there is promising data from in vitro studies. Phages have recently been discovered that show in vitro activity against MDR *E. coli* isolates [207], carbapenem-resistant *Citrobacter freundii* [208], and there have been several phages discovered with activity against various strains of carbapenem-resistant *Klebsiella* isolates [209–212]. Additional studies in mouse models show success using phages to treat CRE *Klebsiella* infections [213]. These provide promising options for future studies targeting infections caused by CRE, where few antibiotic options remain or where toxicities preclude their use [198].

As with antibiotics, phages are not immune to the development of bacterial resistance. A variety of resistance mechanisms have been described, including blocking phage attachment and adsorption, cutting phage DNA via the CRISPR system, and mechanisms to block phage transcription, translation, and cell lysis [214]. Combining phages with traditional antibiotics has proven efficacious in some cases [206, 215] as a way to overcome these challenges.

Future directions: antibiotics in the pipeline

The World Health Organization has identified CRE as a critical priority pathogen for prioritizing new drug development [216] and there are several drugs currently undergoing clinical trials that are promising candidates for increasing the armamentarium against CRE. Zidebactam (WCK 5222) is a DBO that functions as both a direct antibacterial and a beta lactamase inhibitor that, when combined with cefepime, has activity against KPC, OXA-48, and several class B carbapenemases [217, 218]. Isolates of *Enterobacterales*, *Acinetobacter spp.*, and *Pseudomonas* spp. collected worldwide showed high levels of susceptibility to the zidebactam/cefepime combination [219], making this a promising drug for clinical trials. Phase 1 pharmacokinetic studies have shown high plasma concentrations as well as good pulmonary penetration of the drug [220] and it is well-tolerated in individuals with renal impairment, although it requires dose-adjustment [221].

Taniborbactam (VNRX-5133) is a boronic-acid-containing pan-spectrum β-lactamase inhibitor that restores the activity of beta-lactam antibiotics against ESBL and CRE and is considered the first pan-spectrum β-lactamase inhibitor in clinical development [222]. The boronic acids and esters bind to the active-site serine residue of enzymes, including β-lactamases, thereby inhibiting their function, and bicyclic boronates are able to inactivate serine- and metallo-beta lactamases [223]. When combined with the β-lactam drug cefepime, taniborbactam restored in vitro activity against all *Enterobacterales* tested, including CRE with class A, B, and D enzymes, as well as ESBL-*Enterobacterales* containing class C enzymes [224]. Studies in animal models showed high in vitro activity of cefepime/taniborbactam against *Enterobacterales* [225], and there is currently a phase 3 trial underway testing cefepime/taniborbactam for cUTI (clinical trials.gov NCT03840148).

LYS228 is a monobactam antibiotic, similar to aztreonam, that retains activity against metallo-β-lactamases but with structural changes that also provide activity against the serine β-lactamases [226] by targeting penicillin binding protein 3. In vitro studies have shown potent activity against class A (KPC) and class B (NDM) carbapenemases [227, 228]. Pharmacokinetic studies showed good safety and tolerability [229]. Two phase 2 trials of LYS228 were underway when Novartis, the parent company that developed LYS228, licensed the drug to Boston Pharmaceuticals for further development [230]. The proposed clinical trials were halted and as of publication there are no additional trials for LYS228/BOS228 yet registered with clinicaltrials.gov.

Nacubactam is a bridged diazabicyclooctane β-lactamase inhibitor that inactivates class A and class C β-lactamases and functions both as an independent antibiotic as well as providing "enhancement" when combined with β-lactam antibiotics with potent activity against *Enterobacterales* [231]. When combined with meropenem, nacubactam has shown strong in vitro activity against class A and class D carbapenemases as well as class C ESBL enzymes [232] and has shown some activity against the metallo-β-lactamases [233]. Phase 1 pharmacokinetic trials showed it to be well-tolerated without significant adverse reactions [234].

Conclusion

The spread of carbapenem-resistant *Enterobacterales* is an urgent public health issue and represents a threat to antibiotic efficacy worldwide. There are several treatment classes currently available to clinicians to treat these infections including "traditional" antibiotics that have retained anti-CRE-activity, novel β-lactam-β-lactamase inhibitor combinations that have come on the market in the last decade, and novel aminoglycosides, tetracyclines, and cephalosporins. Local resistance patterns and the regional prevalence of specific carbapenemase enzymes are important to consider when selecting therapy, as not all agents have activity against all classes of enzymes. Phage therapy represents a promising alternative therapy for highly drug-resistant infections; however the applicability of this technology to a broad range of clinical scenarios remains to be seen. With all these treatments, enhanced antimicrobial stewardship will be paramount to ensuring the continued efficacy of these therapies for years to come.

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