



Carbapenem-Resistant Enterobacterales: Considerations for Treatment in the Era of New Antimicrobials and Evolving Enzymology

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Abstract

Purpose of Review Gram-negative resistance is a growing concern globally. Enterobacterales, formerly *Enterobacteriaceae*, have developed resistance mechanisms to carbapenems that leave very few antimicrobial options in the clinician's armamentarium.

Recent Findings New antimicrobials like ceftazidime-avibactam, meropenem-vaborbactam, imipenem-relebactam, cefiderocol, and plazomicin have the potential to overcome resistance mechanisms in Enterobacterales including different classes of carbapenemases.

Summary Novel β -lactam/ β -lactamase inhibitors, plazomicin, and cefiderocol give the clinician options that were once not available. Utilizing these options is of the utmost importance when treating carbapenem-resistant Enterobacterales.

Keywords Resistance · Carbapenemase · Enterobacterales · *Enterobacteriaceae*

Introduction

Antimicrobial resistance is one of the 2019 World Health Organization's (WHO) top ten threats to global health [1]. With increasing exposures to antimicrobials, organisms that were once easily treatable now harbor mechanisms of resistance that leave few treatment options for clinicians. Carbapenem-resistant Enterobacterales, formerly known as *Enterobacteriaceae*, are a group of organisms that are among the most difficult to treat; therefore, it is no surprise that the CDC considers them to be one of the top three most urgent

threats with resistance spreading rapidly in the USA and throughout the world [2]. As of 2018, the CDC has reported at least one type of carbapenemase in all 50 states, and rarer genotypic expressions are becoming more common [3]. Prior to the introduction of novel β -lactam/ β -lactamase inhibitors with activity against carbapenemase producers, mortality rates varied from 24% to as high as 74% [4, 5]. It is imperative that clinicians understand definitions of carbapenem-resistant Enterobacterales (CRE), local resistance patterns, and how to optimize treatment based on infection site.

There are major oversights when discussing carbapenem-resistant organisms (CRO) or CREs. For one, CRE's simplified definition of Enterobacterales resistant to carbapenems does an injustice to the complexities of developed mechanisms of resistance [6]. Combinations of extended spectrum β -lactamase (ESBL), overexpression of ampC and loss of porin channels may confer resistance to ertapenem but meropenem or imipenem may remain active [7–9]. While considered to be CRE using conventional definitions, these non-carbapenemase-producing organisms may be amenable to high-dose carbapenem therapy and do not pose the same potential for transmissibility due to their lack of plasmid conferred resistance [10]. In contrast to these non-carbapenemase-producing organisms, it is important to delineate if CRE are

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carbapenemase producers as differing enzymes will have variable phenotypic profiles to commercially available antimicrobials as well as a high degree of transmissibility due to their plasmid-mediated resistance profiles. OXA-48, a serine-based carbapenemase, may hydrolyze carbapenems, yet ceftazidime and cefepime will retain activity if no other mechanisms of resistance are expressed [11, 12]. Isolates may and often have additional mechanisms of resistance included with carbapenemase. Additional subtleties with carbapenem resistance occur demonstrating the need for more specific terminology. Moreover, the likelihood of different types of resistance varies between geographical regions. North America and Israel tend to have a higher prevalence of *Klebsiella pneumoniae* carbapenemase (KPC) whereas metallo- β -lactamase (MBL) can be found in India, Italy, and Greece [7, 13–17]. OXA carbapenemases are endemic to Europe, Northern Africa, and the Middle East [7, 11, 12, 14]. A potential treatment option for a KPC may not necessarily treat an MBL and can be overlooked using broad terminology like CRE. Table 1 highlights different groups and classifications of β -lactamase including potential carbapenemase producers.

Perhaps the greatest disservice when discussing treatment of CRE is assuming the clinician knows the organism prior to starting empiric therapy. Many risk factors associated with the development of CRE are associated with other multidrug-resistant nosocomial infections like *Pseudomonas aeruginosa* [18]. Empiric drug choice in an at-risk septic patient should take into account the roles and limitations of each therapy option. The remainder of this review will compare antimicrobials to treat CRE and discuss trends in treatment management of this infection entity.

Polymyxins

After the introduction of polymyxin B and colistin (polymyxin E) in the 1950s, they quickly fell out of favor due to their high risk of acute kidney injury (AKI) and unpredictable kinetics [19]. With the emergence of multidrug-resistant organisms like CRE, the polymyxin class has re-emerged as a backbone of salvage therapy prior to the clinical availability of novel β -lactam/ β -lactamase inhibitors (BL/BLI) targeted against carbapenemases. An international guideline on

polymyxin published in 2019 attempts to promote the optimal use of these drugs [20]. While this document presents a contemporary overview of the polymyxins and intends to promote strategies to improve outcome while minimizing the toxicodynamic profile of the class, it is important to note that a majority of guidance is based on small theoretical models, and for several pieces, such as polymyxin use in CRE, the committee did not reach a unanimous consensus.

Polymyxin B and colistin are fairly similar chemically even though their pharmacokinetic parameters differ substantially. Both agents have a similar mechanism of action by puncturing and disrupting the outer membrane integrity leading to bactericidal activity and possible synergy with other antimicrobials [19]. These agents also demonstrate AUC/MIC pharmacodynamics with a targeted average steady state ($C_{ss\ avg}$) of 2 mg/L [20].

Colistin is administered as pro-drug colistin methanesulfonate (CMS) or colistimethate, and the conversion from inactive to active drug is highly variable. It may take up to several hours to achieve adequate concentrations of drug even with appropriate loading doses. Unfortunately, inadequate rapid concentrations of colistin in the critically ill have demonstrated increased risk of 30-day mortality and may breed polymyxin resistance which is incredibly concerning considering patient frailty [19–24]. Both the active and non-active forms of colistin are highly excreted into the urine, and the inactivated CMS is partially converted to colistin allowing the drug to reach higher concentrations in the urine than Polymyxin B [19]. Colistin dosing units can be expressed as milligrams of colistin-based activity (CBA) or international units (IU) depending on country. Approximately one million IU is equivalent to 33 mg of CBA.

Polymyxin B is formulated in its active sulfate form, and it is not actively secreted in the urine. The preferable pharmacokinetics and decreased risk of AKI often make polymyxin B the preferred polymyxin for non-urinary systemic infections [19, 20, 25]. A loading dose of 2.0–2.5 mg/kg of total body weight followed by a maintenance dose of 1.25–1.5 mg/kg of total body weight divided into 2 dose 12 h apart is recommended without renal dosage adjustment [25, 26]. Neither parental polymyxin B nor colistin achieve adequate lung concentration and are suboptimal choices for the treatment of respiratory infection as monotherapy [19].

Table 1 Classification of β -lactamase

Ambler molecular classification	Busch-Jacoby functional groups	Active binding site	Common enzymes
A	2a, 2b, 2be, 2br, 2c, 2e, 2f	Serine	TEM, SHV, <i>KPC</i> , CTX-M, <i>GES</i>
B	3	Metallo	<i>VIM</i> , <i>NDM</i> , <i>IMP</i>
C	1	Serine	AmpC, P99
D	2d, 2de, 2df	Serine	<i>OXA</i>

Italicized enzymes represent carbapenemase production

The polymyxins should generally be given in combination with another susceptible or synergistic antimicrobial when treating CRE due to the high potential for failure, variable pharmacokinetics, and development of resistance observed on monotherapy. As novel therapies active against carbapenemase-producing organisms become more widely available, the use of polymyxins as the backbone of treatment for CRE should subside and the role of these agents should be reserved as salvage therapy when all other options have been exhausted.

Aminoglycosides

Similar to polymyxins, aminoglycosides were first clinically used in the 1940s and were a mainstay of therapy until the 1980s with the invention of safer antimicrobials like cephalosporins, carbapenems, and fluoroquinolones. Aminoglycosides carry an increased risk of nephrotoxicity and ototoxicity compared with the antimicrobials mentioned above [27]. Higher rates of adverse events occur with more frequent dosing, and a modified once-daily dosing regimen as demonstrated in the Hartford nomogram may mitigate these risks [28]. Aminoglycosides can play a crucial role in CRE because their mechanism of action is not affected by carbapenemases; however, many CRE organisms harbor aminoglycoside modification enzymes (AME) [29, 30]. As such, the therapeutic role of conventional aminoglycosides, like gentamicin and amikacin, can be highly variable based on the widespread geographic distribution of AMEs.

Plazomicin (Zemdri®) is a new aminoglycoside that is synthetically derived from sisomicin which remains stable against most AMEs and it has been shown to be synergistic when given in combination with β -lactams in vivo [31–33]. A phase III trial (CARE study) attempted to demonstrate efficacy of plazomicin combination therapy compared with polymyxin combination therapy for a multitude of carbapenem-resistant Enterobacterales infections [34]. Although the study did not reach an adequate power due to slow enrollment into the study, researchers reported a descriptive decrease in all-cause mortality. Fifteen patients who received plazomicin combination therapy were further evaluated to determine if adequate concentrations of each drug were achieved [35]. Of the 15 subjects treated with plazomicin combination, 0% treated with plazomicin and meropenem reached a meropenem $fT > MIC$ of 40%. Furthermore, only 75% of subjects treated with combination plazomicin and tigecycline reached tigecycline $fAUC/MIC$ concentrations of 0.9 mg/L or greater, yet 83% of subjects with inadequate meropenem or tigecycline concentrations achieved microbiological response. These data demonstrate the potential clinical utility of plazomicin in the treatment of CRE.

While plazomicin utilizes the once-daily dosing regimen to improve efficacy and minimize toxicity, dose adjustments are required in patients with decreased renal function. Asempa and colleagues evaluated a group of 37 enrolled patients being treated for CRE bloodstream infections or pneumonia, who were originally enrolled in the CARE study [36]. Plazomicin blood samples were collected 10 h post dose to determine an appropriate dosing interval based on the Hartford nomogram. Afterwards, the information was simulated to predict toxic trough concentrations greater than 3 mg/L and an efficacious interval-normalized AUC. Use of the nomogram reduced the incidence of potentially toxic trough concentrations while maintaining similar target AUCs. Additionally, the application of the Hartford nomogram appears useful in less sick patients with UTIs [37].

While limited clinical data exist thus far, the microbiologic potency, pharmacokinetic, and pharmacodynamic profiles of plazomicin suggest that this agent is a viable option for CRE in combination with conventional compounds or the novel BL/BLIs. Other examples of plazomicin's utility include in combination to treat an MBL producer where novel BL/BLIs lack in vitro activity, patients with a hypersensitivity to ceftazidime and carbapenems, or patients requiring a once-daily injection being treated in an outpatient antimicrobial treatment program.

Double Carbapenem

As mentioned above, KPC is the most prevalent carbapenemase produced in the USA, and antimicrobial options were often scarce prior to the introduction of novel β -lactam/ β -lactamase inhibitors. Bulik and Nicolau proposed the use of combination ertapenem and high-dose doripenem or meropenem as a method to combat CRE [38]. The theoretical mechanism uses ertapenem as a suicide molecule with high affinity for KPC enzymes, allowing meropenem or doripenem to treat the organism. Both their in vitro model and murine thigh model demonstrated bacterial reduction with a roughly 3 log and 1 log reduction, respectively. Clinical studies and case reports have also demonstrated an increase in microbiological cure and a decrease in all-cause mortality compared with other options like polymyxins [39–42]. While the clinical utility of double carbapenem therapy has demonstrated in patients with CRE, it is important to recognize that the efficacy of this regimen is restricted to KPC-based infections.

B-Lactam/B-Lactamase Inhibitors

Novel β -lactam/ β -lactamase inhibitors are a revolutionary treatment option for carbapenemase-producing

Enterobacterales. Ceftazidime-avibactam (Avycaz®), meropenem-vaborbactam (Vabomere®), and the new BL/BLI imipenem-relebactam (Recarbrio®) have brought welcomed treatment options to clinicians treating these MDR organisms. It is important to note that these drugs do not all cover the same carbapenemase. Table 2 highlights the differences in activity against Ambler classification of carbapenemases and the Clinical Laboratory and Standards Institute (CLSI) MIC breakpoints for novel BL/BLIs as well as novel antimicrobials that will be discussed.

Avibactam, a novel diazabicyclooctane β -lactamase inhibitor, restores ceftazidime activity against group A, and some D (OXA-48) serine carbapenemases [43, 44]. There is no ceftazidime restoration against class B metallo- β -lactamases; however, there are several successful case reports of using ceftazidime-avibactam with aztreonam for the treatment of New Delhi metallo- β -lactamase (NDM), and aztreonam-avibactam is currently in clinical development [45–47]. Ceftazidime-avibactam has displayed consistently improved outcomes relative to polymyxin-based regimens as numerous reports show decreased all-cause mortality, increased microbiologic cure, and reduced toxicity [48–53].

At present the vast majority of clinical and microbiologic outcome data with these new BL/BLIs for CRE-based infections accumulated during the clinical utilization of ceftazidime-avibactam, where this new agent is often being used as salvage therapy in patients failing polymyxin-based regimens. As a result, it is not surprising that treatment failure and the development of resistance on therapy have been observed in these pre-selected salvage use scenarios. Specifically, the emergence of a mutant KPC-3 variant has been noted during therapy [54]. While resistant to ceftazidime-avibactam, the organism's genotype reverted to resemble that of an ESBL testing susceptible to meropenem and not surprisingly to other BL/BLIs like meropenem-vaborbactam [55]. Shields and colleagues also proposed ceftazidime-avibactam treatment

failure correlates to patients treated for healthcare-associated pneumonias and continuous renal replacement therapy [56]. Their single-center retrospective study looked at treatment failure with ceftazidime-avibactam and found that 60% of clinical failures were treated for pneumonia compared with 29% of successes ($p = 0.045$, OR 3.09, 1.03–9.34). Similar success and failure trends were seen with continuous renal replacement therapy at 7% and 37% respectively ($p = 0.046$, OR 4.78, 95% CI 1.03–22.2). This raises the question whether resistance and treatment failure were observed because of inappropriate dosing in these critically ill patients. This controversy with ceftazidime-avibactam highlights that it is crucial that patients receiving these novel BL/BLIs are aggressively dosed with optimal exposures to achieve clinical cure.

Vaborbactam, another non- β -lactam/ β -lactamase inhibitor, restores meropenem against Ambler group A and C β -lactamase [55, 57]. The addition of a boron structure allows for higher affinity for KPC-producing Enterobacterales, but has no effect on other MDR like *Acinetobacter baumannii* or *P. aeruginosa*. Vaborbactam, furthermore, does not restore meropenem activity against group B or D carbapenemases.

Targeting Antibiotic Non-susceptible Gram-negative Organisms (TANGO-II) trial evaluated meropenem-vaborbactam against best available therapy (either monotherapy or combination of polymyxin, colistin, high-dose meropenem, ceftazidime-avibactam ($n = 1$), or aminoglycoside) for the treatment of CRE infections [58]. Eligible patients were enrolled from 8 countries where KPC is prevalent. It is important to note that a majority of isolates grew *Klebsiella pneumoniae* (87.2%), and the major sites of infection were bacteremia (46.8%), followed by complicated urinary tract infection (34%), healthcare- and ventilator-associated pneumonia (10.6%), and complicated intra-abdominal infection (8.6%). All patients with previous antimicrobial failure were placed in the meropenem-vaborbactam group. Meropenem-vaborbactam had statistically significant

Table 2 Novel antimicrobial Ambler class activity

Drug	Ambler group A	Ambler group B	Ambler group C	Ambler group D	2019 CLSI Enterobacterales MIC breakpoint
β -lactam/ β -lactamase inhibitor					
Ceftazidime-avibactam	+	-	+	+ (OXA-48)	8/4
Meropenem-vaborbactam	+	-	+	-	4/8*
Imipenem-relebactam	+	-	+	-	1/4**
Other novel antimicrobials					
Plazomicin	+	+	+	+	2**
Cefiderocol	+	+	+	+	2**
Fosfomicin	+	+	+	+	N/A

*Higher than meropenem breakpoint, avoid use in OXA endemic areas

**FDA minimum inhibitory concentration breakpoint

OXA, oxacillinase; CLSI, Clinical and Laboratory Standards Institute

improvement for clinical cure at end of treatment (ARR 32.3%, 95% CI 3.3–61.3, $p = 0.03$) and at test of cure (ARR 32.7%, 95% CI 4.6–60.8, $p = 0.02$). There was no difference in 28-day all-cause mortality; however, when previous treatment failure was removed, meropenem-vaborbactam did show statistical difference (absolute reduction 29%, 95% CI 54.3–3.7, $p = 0.02$). Drug-related adverse events, including nephrotoxicity, were seen less often in the meropenem-vaborbactam-treated patients (24%) than in best available therapy (44%).

Of concern with meropenem-vaborbactam is that the current CLSI/FDA-approved breakpoint for Enterobacterales is $\leq 4/8$. This encompasses 30–40% of the MIC distribution for OXA-producing organisms despite the designation of no in vitro activity for this class of carbapenemases as mentioned in the package insert of the commercially available product. Despite no activity and no clinical data, the elevated breakpoint relative to that of meropenem at ≤ 1 is due solely to the nuances in dosing between the products [59]. As a result, caution should be exercised when using meropenem-vaborbactam for the treatment of susceptible carbapenemase-producing Enterobacterales when OXA-based enzymes are in the differential and genotypic profiling has not confirmed the enzymologic driver of resistance.

Relebactam, like avibactam, is a diazabicyclooctane β -lactamase inhibitor restoring imipenem against group A and C β -lactamases [60, 61]. In vitro and animal models show efficacy with imipenem-relebactam, and it has recently been approved for complicated urinary tract infections and complicated intra-abdominal infections [60–66]. Motsch and colleagues recently published a randomized controlled trial comparing imipenem-relebactam to imipenem and colistin for imipenem non-susceptible bacterial infections [67]. Out of the 31 modified microbiologic intent to treat population, a majority of isolates were *P. aeruginosa*, (77%) followed by *Klebsiella* spp. (16%) and other Enterobacterales (6%). Imipenem-relebactam was considered non-inferior for microbiological cure (71%) compared with imipenem and colistin (70%) and had a significant 28-day favorable response (71% vs. 40%, 90% CI 1.3–51.5). The authors further described a non-significant reduced 28-day all-cause mortality of 10% with imipenem-relebactam compared with 30% of imipenem and colistin subjects. Notably, CRE specific data demonstrated only one out of four carbapenem-resistant Enterobacterales showing a microbiological cure compared with one out of one imipenem and colistin treated subject. Authors attributed microbiologic failure of imipenem-relebactam to organisms harboring several group A and C extended β -lactamases. The therapeutic niche of imipenem-relebactam remains unclear as it may be used as an additional option for CRE or it may be more useful in treating multidrug-resistant *P. aeruginosa* including those producing carbapenemases [62]. Similarly to ceftazidime-avibactam, the additional pseudomonal coverage

may make imipenem-relebactam an appropriate option for empiric therapy in a septic patient with high risk of CRE and pseudomonal infection. Unlike the two previously approved β -lactam/ β -lactamase inhibitors which are recommended to have each dose administered over 2–3 h, imipenem-relebactam is given via a 30-min infusion. Shorter infusion durations may be advocated in some institutional settings.

Zidebactam, a novel diazabicyclooctane β -lactamase inhibitor, serves two functions by preventing broad spectrum hydrolysis of cefepime and binding PBP2 [68, 69]. Currently it is in phase I of development. The combination theoretically works against A, C, and D β -lactamase Enterobacterales with additional in vitro restored function to some group B β -lactamase Enterobacterales, drug-resistant *P. aeruginosa*, and drug-resistant *A. baumannii* [69]. In vivo cefepime-zidebactam has shown 1 to greater than 3 log reductions of growth, and 1.6 log reductions in growth for Enterobacterales and *P. aeruginosa*, respectively [68]. Further research is warranted for zidebactam as it may be the next breakthrough novel antimicrobial.

There are limited data comparing β -lactam/ β -lactamase inhibitors in the treatment of CRE which makes it difficult to determine a superior drug with overlapping susceptibilities. At least one BL/BLI which covers carbapenemase-producing Enterobacterales and *P. aeruginosa* should be on each hospital formulary. Local resistance patterns to Enterobacterales and *Pseudomonas aeruginosa* as well as the availability of microbiologic testing should be taken into account when making formulary decisions.

Cefiderocol

Coined as the “Trojan horse” antimicrobial, cefiderocol uses a siderophore to hijack bacteria’s iron uptake system and enter the cell to disrupt cell wall synthesis [70–72]. Cefiderocol is stable and potent against all Ambler group β -lactamases in vitro, including MBLs, without the addition of a β -lactamase inhibitor [70, 73, 74]. In vivo and healthy volunteer studies have demonstrated adequate tissue concentration into epithelial lining fluid making it a promising therapy in bacterial pneumonia [73, 75]. Cefiderocol responded well against Gram-negative isolates of *Klebsiella* spp., *P. aeruginosa*, and *A. baumannii* with a greater than 3 log bacterial growth reduction in a rat lung model. Similar results were seen in an immunocompromised murine thigh infection model with greater than 3 log bacterial growth reduction against various Enterobacterales [74]. Cefiderocol is currently approved for complicated urinary tract infections as it was non-inferior to imipenem in a phase II trial. It is important to note that carbapenem-resistant isolates were excluded from this trial [76]. Cefiderocol is a welcomed novel antimicrobial for a

Table 3 Summary of BL/BLI vs. BAT for treatment of CRE

Author and year	Description of study	Study arms	Patient characteristics	Outcome	Conclusion
Wunderink 2018	<ul style="list-style-type: none"> Phase III Open Label Randomized Control Trial KPC-CRE infection <i>n</i> = 47 	<ul style="list-style-type: none"> Meropenem 2 g-vaborbactam 2 g infused over 3 h every 8 hours Best available therapy (monotherapy or in combination) <ul style="list-style-type: none"> Colistin/polymyxin Carbapenems Tigecycline Ammoglycoside Ceftazidime-avibactam (<i>n</i> = 1) 	<ul style="list-style-type: none"> Age, 62 years old Region <ul style="list-style-type: none"> North America (29.8%) Europe (57.4%) Infection type <ul style="list-style-type: none"> BSI (46.8%) HABP/VABP (10.6%) cUTI/AP (34%) clAI (8.5%) ICU admission (17%) 	<ul style="list-style-type: none"> Clinical cure at end of treatment <ul style="list-style-type: none"> M-V, 21 (65.6%) BAT, 5 (33.3%) <i>P</i> = 0.03 Clinical cure at test of cure <ul style="list-style-type: none"> M-V, 19 (59.4%) BAT, 4 (26.7%) <i>P</i> = 0.02 28-day mortality <ul style="list-style-type: none"> M-V, 5 (15.6%) BAT, 5 (33.3%) <i>P</i> = 0.20 Renal adverse event <ul style="list-style-type: none"> M-V, 2 (4.0%) BAT, 6 (24%) 30-day clinical success <ul style="list-style-type: none"> C-A, 11 (85%) CB-COL, 12 (48%) CB-AG, 12 (40%) Other, 15 (37%) <i>P</i> = 0.02 Acute kidney injury at 7 days <ul style="list-style-type: none"> C-A, 1 (9%) CB-COL, 3 (17%) CB-AG, 10 (43%) Other, 4 (12%) <i>P</i> = 0.02 Multivariate analysis of factors for 30-day clinical success <ul style="list-style-type: none"> Receiving C-A, <i>P</i> = 0.01 All-cause 30-day mortality <ul style="list-style-type: none"> C-A, 3 (8%) CO, 33 (33%) IPTW all-cause 30-day mortality <ul style="list-style-type: none"> C-A, 9% CO, 32% <i>P</i> = 0.001 IPTW adjusted better outcome with C-A, 62% (95% CI, 52–72%) 	<p>Meropenem-vaborbactam monotherapy is more efficacious than best available therapy for the treatment of CRE with less descriptive renal adverse events</p>
Shields 2017	<ul style="list-style-type: none"> Retrospective, single center CR-KP Bacteremia <i>n</i> = 109 	<ul style="list-style-type: none"> Ceftazidime-avibactam ± gentamicin Best available therapy <ul style="list-style-type: none"> Colistin Carbapenem Ammoglycoside Other 	<ul style="list-style-type: none"> Age, 61 years old ICU at time of bacteremia, 50% APACHE-II score, 18 Pitt score, 4 Source <ul style="list-style-type: none"> Primary, 26% Abdominal, 46% Respiratory, 13% Urinary, 13% Soft tissue, 3% 	<ul style="list-style-type: none"> Ceftazidime-avibactam increases clinical success compared with best available therapy and is an independent clinical factor for success 	
Van Duin 2017	<ul style="list-style-type: none"> Multi-center, prospective, observational study CRE Infection <i>n</i> = 137 	<ul style="list-style-type: none"> Ceftazidime-avibactam Colistin 	<ul style="list-style-type: none"> Age, 61 years old Charlson comorbidity index, 3 Critical illness at time of culture, 47 (34%) Type of infection <ul style="list-style-type: none"> BSI, 63 (46%) HABP/VABP, 30 (22%) UTI, 30 (22%) Wound, 14 (10%) Other, 11 (8%) Age, 60 years old Charlson comorbidity index ≥ 3–38 (36.5%) Median before ceftazidime-avibactam start, 7 days Pitt Score, 4 Monotherapy, 22 (21.2%) 	<ul style="list-style-type: none"> Ceftazidime-avibactam leads to better outcomes than colistin for the treatment of CRE 	
Tumbarello 2019	<ul style="list-style-type: none"> Multi-center, retrospective, observational study CR-KP Bacteremia <i>n</i> = 208 	<ul style="list-style-type: none"> Ceftazidime-avibactam ± antimicrobial as salvage therapy Best available therapy (control) 	<ul style="list-style-type: none"> Age, 60 years old Charlson comorbidity index ≥ 3–38 (36.5%) ICU admission, 39 (37.5%) Median before ceftazidime-avibactam start, 7 days Pitt Score, 4 Monotherapy, 22 (21.2%) 	<ul style="list-style-type: none"> Ceftazidime-Avibactam is associated with improved clinical success regardless of additional therapeutic agents 	
Moisch 2019	<ul style="list-style-type: none"> Multi-center, multi-national, randomized double blind trial Imipenem-non-susceptible isolates <i>n</i> = 31 	<ul style="list-style-type: none"> Imipenem 500 mg-relebactam 250 mg every 6 h Imipenem 500 mg every 6 h and colistin 300 mg CBA loading dose + 150 mg every 12 h 	<ul style="list-style-type: none"> Age, 59 years old APACHE-II > 15–9 (29%) Infection type <ul style="list-style-type: none"> HABP, 2 (6.5%) VABP, 9 (29%) 	<ul style="list-style-type: none"> Imipenem-relebactam has similar favorable response to imipenem non-susceptible Gram-negative organisms compared with imipenem and colistin. Significantly less renal 	

Table 3 (continued)

Author and year	Description of study	Study arms	Patient characteristics	Outcome	Conclusion
			<ul style="list-style-type: none"> ○ cUTI, 8 (25.8%) ○ cUTI + AP, 8 (25.8%) ○ cIAI, 4 (12.9%) • Pathogen <ul style="list-style-type: none"> ○ <i>P. aeruginosa</i>, 24 (77.4%) ○ Enterobacterales, 7 (22.6%) • KPC producing, 5 (16.1%) 	<ul style="list-style-type: none"> ○ IMI + CO, 3 (30%) • Treatment emergent nephrotoxicity <ul style="list-style-type: none"> ○ I-R, 10.3% ○ IMI + CB, 56.3% ○ Adjusted difference, -45.9% (90% CI -69.1, -18.4) 	adverse events occur with imipenem-relebactam

C-A, ceftazidime-avibactam; M-V, meropenem-vaborbactam; I-R, imipenem-relebactam; BAT, best available therapy; CO, colistin; CB, carbapenem; AG, aminoglycoside; Tigc, tigecycline; Fos, fosfomycin; IMI, imipenem; Gent, gentamicin; HABP, healthcare-associated bacterial pneumonia; VABP, ventilator-associated bacterial pneumonia; BSI, bloodstream infection; cUTI, complicated urinary tract infection; cIAI, complicated intra-abdominal infection; AP, acute pyelonephritis; CR-KP, carbapenem-resistant Klebsiella pneumoniae; KPC, Klebsiella pneumoniae carbapenemase; CRE, carbapenem-resistant Enterobacterales; ICU, intensive care unit; IPTW, inverse probability of treatment weighting

clinician’s repertoire. Not only is this a novel mechanism of delivery, but also it may be one of the first monotherapy agents to effectively treat metallo-β-lactamase with minimal adverse events. Further clinical development will help determine the exact niche for cefiderocol.

Fosfomycin

IV fosfomycin is a treatment gaining interest in the USA for the treatment of various MDR organisms due to high rates of susceptibility and tolerability [77, 78]. A small prospective study including 11 critically ill patients evaluated the use of IV fosfomycin in combination against hospital-acquired carbapenem-resistant Enterobacterales and found that all-cause mortality rates (18.2%) were lower than other best available therapies [79]. A potential fail point of this therapy is development of resistance during treatment when used as monotherapy [80]. The USA lags behind a majority of other countries as oral fosfomycin is the only formulation available at this moment; however, an IV formulation is currently under development [81]. Fosfomycin will likely be combined with additional agents for its additive and synergistic effects. Avery and colleagues evaluated combination fosfomycin against various CPE isolates using the E-test method [82]. Fosfomycin had no antagonism against any tested antimicrobial and had at least one isolate that was additive making it a potential option for treating multidrug-resistant organisms.

Monotherapy vs. Combination and Colistin or BL/BLI as Backbone of Therapy

The treatment of a non-metallo carbapenemase-producing Enterobacterales with monotherapy or combination has been a topic of interest for many clinicians now that novel β-lactam/β-lactamase inhibitors have been introduced into clinical practice. Historically, the high mortality rates of polymyxins due to poor microbiologic potency and less than optimal drug exposures that have been limited by toxicity have mandated the use of combination therapy in severely ill patients. A large retrospective cohort study evaluated the treatment of bloodstream infections either with monotherapy or combination therapy [83]. Three hundred forty-three subjects were stratified into groups based on severity of illness with a primary endpoint of overall mortality. There were no statistical differences among combined cohorts (HR 0.76, 95% CI 0.53–1.08) and the low mortality score cohort (HR 1.18, 95% CI 0.62–2.23); however, subjects identified as a high risk of mortality had a statistically significant decrease in overall mortality (HR 0.6, 95% CI 0.39–0.93). It is important to note the above study did not include novel therapies like BL/BLIs which should take over as the mainstay of CPO therapy. The shift away from

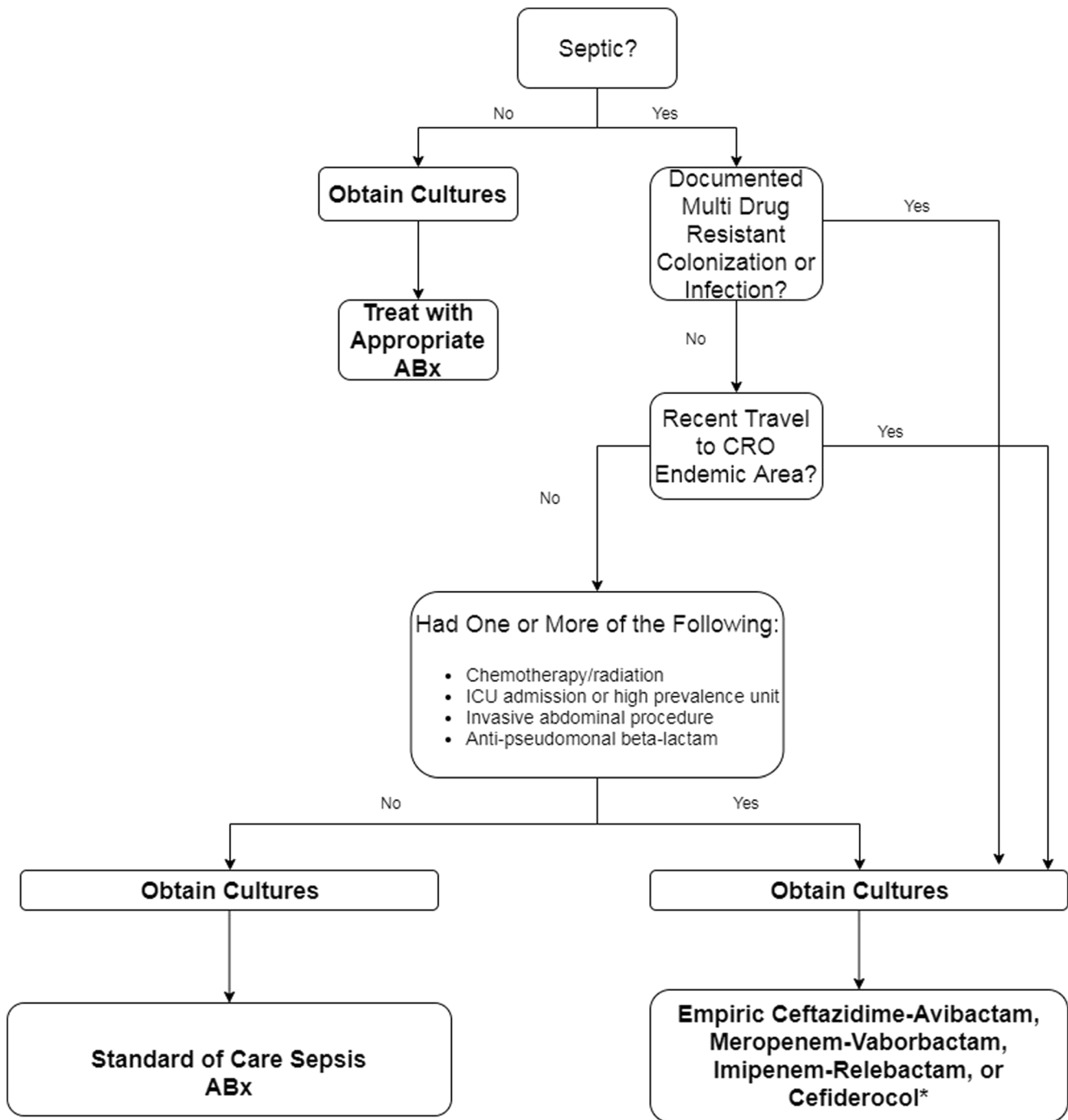


Fig. 1 Algorithm for the empiric therapy of the critically ill septic patient. Choose empiric coverage based on patient specific factors, local epidemiology, and concordant resistance. ABX, antimicrobial, CRO, carbapenem-resistant organism

using nephrotoxic agents with unpredictable pharmacokinetics has reopened the debate of which agent is superior. There is a growing amount of literature demonstrating ceftazidime-avibactam, imipenem-relebactam, and meropenem-vaborbactam lead to better treatment outcomes with less adverse events compared with polymyxin best available therapy regimens [49, 52–54, 58, 67]. A summary comparing BL/BLI therapy to traditional colistin-based therapy can be seen in

Table 3. If an organism is susceptible to a novel β -lactam/ β -lactamase inhibitor, then that agent may be considered for monotherapy because these compounds have demonstrated efficacy in the setting of severe infections. Even with novel agents demonstrating superiority over colistin, prescribing habits are slow to change. A recent publication by Clancy and colleagues show that polymyxin and colistin are still the most prescribed antimicrobials for CRE infections which is

deeply concerning [84]. Gaining access to novel agents to treat CRE should be a priority for all clinicians as these β -lactam/ β -lactamase inhibitors have been shown to improve outcomes and reduced toxicities relative to polymyxin-based regimens.

Empiric Therapy

Another carbapenemase treatment dogma often overshadowed in literature is when to use empiric therapy which covers carbapenemase. A prospective observational cohort study conducted by Gianella and colleagues evaluated risk factors for development of CRE bloodstream infection from previously colonized subjects and found ICU admission, invasive abdominal procedures, chemotherapy/radiation, and multiple CRE colonization sites independently increased risk [85]. Another study conducted in Israel demonstrated that clinically significant increased risks in carbapenem-resistant colonized patients developing infection were treated with anti-pseudomonal penicillins [86]. In an effort to maximize the probability of early appropriate therapy in patients at risk for resistant pathogens, clinicians need to become increasingly comfortable with the antimicrobial spectrum, pharmacokinetic and toxicodynamic profiles of the novel therapies discussed so that optimal empiric therapy can be initiated at the onset of infection (Fig. 1). Unfortunately a single source of antimicrobial susceptibility data for the agents included in this review is not available and thus comparative assessments based on percent susceptible collated from multiple sources are potentially misleading for CRE due to differing genotypic profiles across the globe. As such, these challenges highlight the importance of local susceptibility testing to determine the most suitable agent(s) for clinical practice in any given region. While the use of novel broad-spectrum antimicrobial agents may be warranted in the setting of initial empirical therapy for the septic patient, great effort should be taken to utilize the available diagnostic techniques (i.e., invasive sampling strategies, molecular tests) to identify the causative pathogen(s) and thus allow a rapid, narrow targeted approach to treatment.

Conclusion

The rapid emergence of carbapenemase-producing organisms is a major concern for human health. It is of utmost importance that clinicians are familiar with what antimicrobials can be used to treat serious infections like carbapenem-resistant Enterobacteriales as well as the evolving enzymology associated with these pathogens. With the introduction of new β -lactam/ β -lactamase inhibitors and the improved clinical outcomes associated with these compounds, a shift away from the less efficacious, more toxic polymyxin-based regimens

appears completely warranted. While the β -lactam/ β -lactamase inhibitors will play an important role moving forward, other parenteral agents such as plazomicin, fosfomycin, and cefiderocol show great promise and are welcomed options for treating multidrug-resistant organisms.

Compliance with Ethical Standards

Conflict of Interest MJL has no conflicts of interest to declare.

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