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Treatment Options for Carbapenem-Resistant Enterobacteriaceae Infections

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Summary: This article provides a comprehensive review of currently available treatment options for infections due to carbapenem-resistant enterobacteriaceae (CRE).

Abstract.

Antimicrobial resistance in Gram-negative bacteria is an emerging and serious global public health threat. Carbapenems have been used as the “last-line” treatment for infections caused by resistant enterobacteriaceae, including those producing extended spectrum ß-lactamases. However, enterobacteriaceae that produce carbapenemases, which are enzymes that deactivate carbapenems and most other ß-lactam antibiotics, have emerged and are increasingly being reported worldwide. Despite increasing burden, the most optimal treatment for carbapenem-resistant enterobacteriaceae (CRE) infections is largely unknown. For the few remaining available treatment options, there is limited efficacy data to support their role in therapy. Nevertheless, current treatment options include the use of older agents, such as polymyxins, fosfomycin, and aminoglycosides, which have been rarely used due to efficacy and/or toxicity concerns. Optimization of dosing regimens and combination therapy are additional treatment strategies being explored. CRE infections are associated with poor outcomes and high mortality. Continued research is critically needed to determine the most appropriate treatment.

Introduction.

Antimicrobial resistance is globally recognized as one of the greatest threats to public health. Of particular concern, are infections caused by resistant Gram-negative bacilli, which are increasingly being reported worldwide. The escalating burden of Gram-negative antimicrobial resistance is largely due to ß-lactamases, which are enzymes that bind and deactivate ß-lactam antibiotics, rendering them ineffective. For years, carbapenems have been used successfully to treat infections due to resistant enterobacteriaceae, such as *Escherichia Coli* and *Klebsiella pneumoniae*, including those producing extended spectrum ß-lactamases (ESBLs; a subset of ß-lactamase enzymes which confer broad resistance to penicillins, cephalosporins, and the monobactam aztreonam).

However, recently enterobacteriaceae producing carbapenemases (known as carbapenem-resistant enterobacteriaceae [CRE]) have emerged, which confer broad resistance to most ß-lactam antibiotics including “last-line” carbapenems. Carbapenem resistance can also be conferred when porin deficiencies, which allow decreased entry of the ß-lactam into the cell membrane, are combined with ESBLs.[1] The prevalence of CRE infections has incresed over the last decade, especially in healthcare settings and CRE have been recognized by the United States Centers for Disease Control and Prevention as an urgent public health threat.[2, 3] The Ceners for Disease Control and Prevention estimates that more than 9,000 healthcare-assocaited infections are caused by the two most common type of CRE, carbapenem-resistant *Klebsiella* species and carbapenem-resistant *Escherichia* species, each year in the United States.[3] CRE can cause a number of serious infection types (such as intra-abdominal infections, pneumonia, urinary tract infections, and device-associated infections) or asymptomatic colonization.[4-6] Each year approximtaley 600 deaths result from CRE infections. [3] CRE mortality rates are high and range from 18% to 60% depending on therapy.[7] This may be due to delayed time to active therapy, pharmacologic limitations of available treatment options, and that patients with CRE infections tend to be critically ill.

At this time there are a limited selection of treatment options for CRE infections. Clinicians have been forced to re-evaluate the use of agents, which have been historically rarely used due to efficacy and/or toxicity concerns, such as polymyxins, fosfomycin, and aminoglycosides. Additional CRE treatment strategies include optimization of dosing regimens and combination therapy. This review will focus on the current treatment options for CRE infections.

Overview of Carbapenem-resistant Enterobacteriaceae (CRE)Treatment.

There are numerous different types of carbapenemase enzymes, each conferring varying spectrums of resistance. An overview of the carbapenemase enzyme types with the greatest clinical importance can be found in Table 1. In general, the presence of a carbapenemase confers broad resistance to most ß-lactam antibiotics including penicillins, cephalosporins, and the monobactam aztreonam (excluding MBLs and OXAs).[1] *In vitro* activity of carbapenems in the setting of one of these enzymes is variable, and the exact role of carbapenems in infectious due to these organisms is controversial. To further complicate treatment, CRE often exhibit resistance to structurally unrelated antimicrobial classes such as aminoglycosides and fluoroquinolones.[8] However, aminoglycoside susceptibility can vary as a function of KPC strain type and co-existing aminoglycoside modifying enzymes, which are not tested in a traditional clinical laboratory. The emergence of resistance during therapy is another emerging concern.[9, 10]

Despite their increasing burden, the most optimal treatment for CRE infections is largely unknown. At this time, there is no published data from randomized controlled trials assessing antimicrobial treatment options for CRE infections. While important, in the United States at this time there may not be a sufficient amount of patients with serious CRE infections to conduct such a trial. Therefore, much of the existing evidence is from reviews of case reports, case series and small retrospective studies, which have a number of inherent limitations.[11, 12] A

potential CRE treatment algorithm and overviews of current treatment options can be found in Tables 2 and 3, respectively.

Carbapenems.

Pharmacokinetic data suggests that T>MIC targets can be achieved using high-dose prolonged-infusion carbapenems when carbapenem MICs are relatively low (<4μg/ml) or even moderately elevated (8-16μg/ml).[13-17] In a pharmacokinetic study of ten critically ill patients, high-dose meropenem (6000mg/day) administered by prolonged (over 4 hours)/continuous infusion had a high probability of target attainment (PTA) up to an MIC of 8-16μg/ml.[13] In another study, the PTA for an MIC of 4μg/ml increased with prolonged-infusion (over 3 hours) as compared to traditional-infusion (over 30 minutes); the PTA for prolonged-infusions were 100% (2000mg q8h) and 93% (1000mg q8h) as compared to 69% for traditional-infusion (1000mg q8h).[14] At an MIC of 8μg/ml, only high-dose prolonged-infusion meropenem had a high PTA(85%).

While pharmacokinetic data appears favorable, there is only limited clinical data assessing the efficacy of carbapenem monotherapy in the treatment of CRE infections. In a study that compiled data from eight clinical trials, in 44 patients treated with carbapenem monotherapy for infections due to carbapenemase-producing *K. pneumoniae,* treatment efficacy varied based on MIC.[17] The efficacy ranged from 69% (MIC $\leq$4μg/ml), 60% (MIC 8μg/ml), to only 29% (MIC >8μg/ml). Treatment efficacy when the MIC was $\leq$4μg/ml was similar to that observed in 22 patients with non-carbapenemase-producing *K. pneumoniae* infections (73%). The lowest mortality rate was observed in patients who received carbapenem-containing-combination treatment (MIC $\leq$4μg/ml). The mortality rate was lower for patients who received carbapenem-containing as compared to non-carbapenem regimens (12%[3/26] vs. 41%[46/112]; P=0.006).[17] In a recent review, the mortality rate associated with carbapenem monotherapy was unacceptably high (40.1%).[12] For patients with serious infections and/or

who are critically ill adding another active agent may increase the probability of clinical response.

Additionally, several retrospective studies have observed lower rates of mortality with carbapenem-based combination therapy as compared to non-carbapenem combination therapy.[17-20] The efficacy of carbapenem combination therapy also appears to be MIC dependent. In a large multi-center study where high-dose prolonged-infusion meropenem was used (2000mg administered over ≥3 hours q8h) mortality rates stratified by MIC were as follows: 13%(2/13) for <4μg/ml, 33% (1/3) for 8μg/ml, and 35.2%(6/17) for ≥16μg/ml.[19] In a large cohort study (see Table 4), the mortality rate associated with carbapenem-containing-combination therapy for carbapemase-producing *K. pneumoniae* bacteremia increased from 19.3% (MIC≤8μg/ml) to 35.5% (MIC>8μg/ml).[20]. In a review of 20 clinical studies, carbapenem-containing-regimens were associated with lower mortality than non-carbapenem-containing-regimens (18.8% vs. 30.7%).[12] While encouraging, it is important to note, that not all reports have focused on carbapenem-containing-regimens. A retrospective study conducted from a 10-bed intensive-care-unit (ICU) showed success in 24/26(92%) patients with KPC infections (16 ventilator-associated pneumonias [VAP], 7 bloodstream infections, 2 urinary tract infections [UTI], 1 peritonitis) with the use of carbapenem-sparing-combination therapy regimens.[21]

Double-carbapenem combination treatment may be an effective option for infections caused by pan-drug-resistant CRE, however data is limited to selected case reports.[22, 23] Experimental data has shown that the KPC enzyme may have increased affinity for ertapenem than other carbapenems, therefore when given together; KPC preferentially deactivates ertapenem, which hinders degradation and improves the activity of the concomitant carbapenem.[24, 25] In case reports, ertapenem plus either doripenem or meropenem has been used successfully to treat select pan-drug-resistant and colistin-resistant KPC-producing *K. pneumoniae* infections (bacteremia, VAP, and UTI). Double-carbapenem combination

treatment is a promising option, which may be most effective in combination with a third drug.[26]

Polymyxins. Colistin (polymyxin E) and polymyxin B are considered to be the most active *in vitro* agents against CRE.[27] Polymyxin B and colistin differ by a single amino acid. A comparison of the two drugs can be found in Table 5. There are several potential advantages to the use of polymyxin B over colistin, many of which stem from the fact that colistin is administered as the inactive prodrug colistimethate (CMS). Only a small fraction of CMS is converted to colistin and this conversion is slow, with maximum concentrations occurring $\geq$7 hours after administration.[28] As the conversion of CMS to colistin is slow and inefficient in patients with normal renal function the majority of CMS is cleared prior to conversion to colistin. Therefore, despite being dosed at a lower mg/kg/day dose, polymyxin B can achieve higher peak serum concentrations which are achieved much more rapidly than with colistin.[28, 29]

Renal dose adjustments are necessary for colistin/CMS but are not required polymyxin B.[26] The reason for this is that there is minimal renal clearance of colistin, but the prodrug CMS is predominately cleared renally.[26] As with colistin, polymyxin B undergoes extensive renal tubular reabsorption and is eliminated by mostly nonrenal clearance. Importantly, however, polymyxin B package insert dosing recommendations include vague renal dosing adjustments that have been followed in all of the polymyxin B literature to date. The efficacy and safety of non-renally adjusted polmyxin B remains unclear. The renal clearance of CMS allows an advantage over polymyxin B that a higher concentration of active drug in the urine is reached which would make colistin/CMS a viable UTI treatment alternative.[26, 30] Despite the potential advantages of polymyxin B use, the majority of clinical data to date for CRE infections has focused on the use of colistin.

The ideal dosages of colistin and polymyxin B are largely unknown, especially in the case of renal failure, renal replacement therapy, and critical illness.[31] Scientifically based

dosing recommendations can be found in Table 5.[28, 29] For serious infections caused by resistant Gram-negative pathogens, high total daily doses of colistin appear to be important to maximize treatment efficacy.[28, 32] In a retrospective study of 258 ICU patients treated with CMS, 21.7% of patients on the highest total daily dose (9 million IU/day) died as compared to 27.8% and 38.6% patients on lower doses of 6 and 3 million IU/day, respectively (p=0.0011).[33] In a retrospective study of 67 patients with Gram-negative bacteremia, the median colistin dose was higher in patients who achieved microbiological success (2.9 vs. 1.5mg/kg/day; P=0.011) and 7-day survival (2.7 vs 1.5mg/kg/day; P=0.007).[32] Another retrospective study found similar results with polymyxin B treatment.[34]

Historically, neurotoxicity was an important concern with the use of polymyxins, however with current formulations this side effect is reported less frequently. Patients discussed in the recent literature are more critically ill, ventilated, and sedated which might significantly limit the ability to detect neurotoxicity, which primarily manifested as parasthesias and ataxia. However, nephrotoxicity remains a concern as it continues to occur in ≥40% patients treated with polymyxins.[35] While nephrotoxicity has been reported with both colistin and polymyxin B use, recent evidence suggests that nephrotoxicity rates might be higher with colistin use than polymyxin B (50-60% vs. 20-40%).[35, 36] The use of colistin and polymyxin B at higher doses, which may be necessary for CRE infections, may be associated with a higher risk of nephrotoxicity.[32, 34] The better outcomes associated with high dose colistin, may come at the cost of worsening renal function.[32] In a retrospective study, a colistin dose of >5mg/kg of ideal body weight/day was independently predictive of the development of renal insufficiency.[37] For polymyxin B, a retrospective cohort study of 276 patients demonstrated that high doses (≥200mg/day) were independently associated with lower mortality (adjusted OR 0.43; 95% CI 0.23–0.79).[34] However, the use of ≥200mg/day was associated with a significantly higher risk of severe renal impairment (adjusted OR 4.51; 95% CI 1.58–12.90; $P = 0.005$). Even when controlling for the development of moderate to severe renal

dysfunction, multivariate analyses showed that doses ≥200mg/day were still associated with decreases in mortality.

Another concern with the use of polymyxins is on-treatment resistance development. Blood isolates from one patient infected with carbapenem-resistant *K. pneumoniae* and treated with polymyxin B monotheray, showed a significantly increased polymyxin B MIC in just 5 days (0.75μg/ml to 1,024μg/ml).[9] Additionally, there have been reports of colistin-resistant, carbapenem-resistant *K. pneumoniae* outbreaks.[38, 39] Therefore, polymyxins may be most effective as part of a combination for serious CRE infections.[31, 40] In a recent review which used compiled data on 889 patients with CRE infections (bacteremia, pneumonia, intra-abdominal infections, UTIs, and surgical site infections), the mortality rate for colistin monotherapy was 42.8%.[12] A review of 55 studies found that clinical success was lower for colistin monotherapy as compared to colistin combination therapy for treatment of infections caused by KPC-producers (14% [1/7] vs. 73% [8/11]).[41] In a recent cohort study of 36 patients with blood stream infections due to CRE (all but two yielded both OXA-48 and CTX-M ESBLs), colistin based combination therapy was associated with better 28-day survival than non-colistin regimens (33.3% vs. 5.5%; p=0.018).[42]

Tigecycline. The majority of CRE isolates remain active against tigecyline *in vitro*, however resistance to tigecycline is increasing.[43-45] There are only limited clinical data to support use of tigecycline monotherapy for infections caused by CRE that demonstrate *in vitro* susceptibility.[19, 20, 41, 46, 47] In a small number of patients with carbapenem-resistant *K. pneumoniae,* 71.4% (5/7) patients had a favorable outcome with tigecycline treatment.[41] High mortality rates have been reported with the use of tigecycline monotherapy in the treatment of bloodstream infections due to carbapenem-resistant *K. pneumoniae* in two separate cohort studies (see Table 4).[19, 20] Additionally, despite *in vitro* susceptibility, on-treatment resistance emergence has been described.[10, 40, 48]

Tigecycline may be most effective when used at higher doses and/or in combination for serious CRE infections, and depending on the source of the infection.[40, 49, 50] However, high dose tigecycline may only transiently lead to increased plasma concentrations, as higher doses may lead to increased intracellular accumulation and tissue distribution.[49] In 30 complex patients with severe intra-abdominal infections due to KPC-producing *K. pneumoniae,* high dose tigecycline in combination with colistin was associated with lower mortality as compared to approved dose tigecycline plus colistin.[51] In a review which used compiled data on patients with various types of CRE infections, the mortality rate with tigecycline monotherapy was 41.1%.[12] A carbapenem-sparing regimen of tigecycline plus either gentamicin or colistin was effective in 92%(24/26) of ICU patients treated for KPC infections.[21]

Fosfomycin. Limited data has demonstrated fosfomycin has activity against KPC-producing *K. pneumoniae* and NDM-1-producing enterobacteriaceae.[52, 53] Fosfomycin achieves high urinary concentrations for prolonged time periods (after a single 3 gram dose peak urine concentrations of >4000µg/ml are obtained and above MIC concentrations persist for 72 hours).[54] Select case reports have demonstrated success of oral fosfomycin for treating UTIs caused by fosfomycin susceptible KPC- and NDM-producing enterobacteriaceae.[55, 56] Two patients with OXA-48-producing *K. pneumoniae* UTIs were successfully treated with oral fosfomycin and colistin.[57]

In Europe an intravenous fosfomycin formulation is available. In a small (n=11) European study, intravenous fosfomycin (2-4 g q6h) in combination was associated with good bacteriological and clinical outcomes in all patients for various carbapenem-resistant *K. pneumoniae* infections (bacteremia, VAP, UTI, wound infections).[58] In a report of three cases of KPC-producing *K. pneumoniae* bacteremia, intravenous fosfomycin was used as an adjunct "last-resort" treatment which initially led to bacteremia control, however ultimately all three patients failed treatment due to relapse and resistance development.[59] The use of

intravenous fosfomycin monotherapy for the treatment of systemic infections may be limited due to the potential for the development of drug resistance during treatment.[60]

Aminoglycosides. Gentamicin is generally the most active aminoglycoside *in vitro* against carbapenem-resistant *K. pneumoniae,* however amikacin can be most active against other CRE.[46, 61, 62] Data on the use of aminoglycosides as monotherapy is limited and aminoglycosides monotherapy appears to be most efficacious in the treatment of UTIs.[12, 41, 63] In a retrospective cohort study of cases of carbapenem-resistant *K. pneumoniae* bacteriuria, treatment with an *in vitro* active aminoglycoside was associated with a significantly higher rate of microbiologic clearance as compared to either polymyxin B or tigecycline.[63] In multivariate analysis, aminoglycoside treatment was independently associated with microbiologic clearance.

Aminoglycoside therapy may be most appropriate as a component of combination therapy for infections, especially UTIs, caused by CRE.[64-66] In the largest CRE bacteremia cohort study to date, similar mortality rates were observed for aminoglycoside monotherapy (22.2%) and combination therapy (26.5%), however only a small number of patients (n=9) were treated with monotherapy as compared to 68 patients treated with aminoglycoside combination therapy.[20] In a review of 24 cases of aminoglycoside combination therapy (most often with colistin, carbapenems, fluoroquinolones, and tigecycline), all patients who failed aminoglycoside based combination therapy had bloodstream infections.[66] In a review of 20 clinical studies, the combination of an aminoglycoside and a carbapenem had the lowest mortality rate (11.1%).[12]

Combination Therapy. Combination therapy for CRE infections may decrease mortality as compared to monotherapy. It is also an important empiric consideration when a CRE is suspected.[18, 19, 31] Benefits of combination therapy include reduction of initial inappropriate

antimicrobial therapy, potential synergistic effects, and suppression of emerging resistance.[31] As monotherapy options all have significant limitations (pharmacokinetics, toxicity, emergence of resistance), combination therapy can be an attractive option to optimize therapy. However, with combination therapy there is the potential for an increased risk for the development of *Clostridium difficile* infection, colonization/infection with other resistant bacteria, and adverse effects such as nephrotoxicity.[11, 31] Combination therapy leads to increased antimicrobial pressure and may potentiate the development of antimicrobial resistance. The benefits of combination therapy may outweigh the risks, and many experts recommend combination therapy as opposed to monotherapy for the treatment of severe CRE infections.[31, 40]

As previously described, emerging clinical evidence suggests that treatment with combination therapy may be beneficial for serious CRE infections.[12, 18-21, 41, 42, 67-69] In the most comprehensive review to date, which included data on 889 patients with CRE infections, combination therapy with two or more *in vitro* active agents was associated with lower mortality than treatment with a single *in vitro* active agent (27.4%[121/441] vs. 38.7%[134/346], $p<0.001$).[12] Monotherapy resulted in mortality rates that were not significantly different from those in patients treated with inappropriate therapy with no *in vitro* active agents (46.1%[48/102]). Another comprehensive review found similar mortality results (18.3% vs. 49.1%).[31] Several observational studies have assessed the efficacy of combination therapy versus monotherapy in the treatment of bloodstream infections due to carbapenemase-producing *K. pneumoniae* (mostly KPC-producers).[18-20, 67] A summary of these studies can be found in Table 4. In the first study, all patients who received combination therapy had favorable outcomes, while 46.7% patients who received active monotherapy died.[67] The next retrospective cohort study also demonstrated lower mortality rate with combination treatment (usually a carbapenem with colistin or tigecycline) compared with monotherapy.[18] A larger multi-center retrospective cohort study also found similar results.[19] Interestingly, meropenem, colistin, tigecycline combination was associated with a significant

reduction in mortality even in patients who received inappropriate empiric therapy (14% vs. 61%). In the most recent and largest cohort study to date, combination therapy again was associated with lower mortality than monotherapy (27.2% vs. 44.4%).[20] Combination therapy was an independent predictor of survival; which was mostly due to the effectiveness of carbapenem-containing regimens.

Emerging treatment. An overview of emerging treatment options can be found in Table 6. The Food and Drug Administration approved ceftazidime-avibactam in February 2015 for the treatment of complicated intra-abdominal infections (cIAI) and complicated urinary tract infections (cUTI).[70] It is expected that ceftazidime-avibactam will be available in the second quarter of 2015, however ceftazidime-avibactam received a priority review based on Phase II data, and as such should be reserved for patients with limited or no alternative treatment options.[70]

Ceftazidime-avibactam is combination of an established broad-spectrum cephalosporin (ceftazidime) and a novel β-lactamase inhibitor (avibactam) with activity against class A, class C, and some class D β-lactamases.[71, 72] Avibactam has activity against KPC-type carbapenemases and some OXA enzymes, however it has no activity against metallo- β -lactamases (such as NDM-1).[71, 72] In two Phase II trials, efficacy and safety rates were similar for ceftazidime-avibactam versus comparator drugs for the treatment of cIAI and cUTI.[73, 74] For cIAI, favorable clinical response rates were observed for ceftazidime-avibactam (2000/500 mg IV q8h) plus metronidazole (500 mg IV q8h) as compared to meropenem (1000 mg IV q8h; 91.2% [62/68] vs. 93.4% [71/76], p=0.06).[74] For cUTI, favorable clinical response rates were observed for ceftazidime-avibactam (500/125 mg IV q8h) as compared to imipenem (500 mg IV q6h; 85.7% [24/28] vs. 80.6% [29/36], p=0.06).[73] The most common adverse drug reactions (>10%) in trials were vomiting, nausea, constipation, and anxiety.[70] In a Phase III trial, clinical cure rates for ceftazidime-avibactam were lower for

patients with a creatinine clearance between 30 to 50 ml/min.[70] Additionally, seizures have been reported with the use of ceftazidime and as with other β-lactam antibiotics there is a risk for serious hypersensitivity.[70] Phase III trails are underway assessing ceftazidime-avibactam for the treatment of cIAI, cUTI, and nosocomial pneumonia and results will likely be available in late 2015.[70]

Conclusions. The burden of antimicrobial resistance among Gram-negative pathogens, particularly carbapenem-resistant enterobacteriaceae is increasing rapidly worldwide. Treatment options for serious CRE infections remains extremely limited at this time. Optimization of dosing of currently available agents and combination therapy may be the most appropriate treatment strategies at this time. However, continued research is desperately needed, in particular randomized controlled trials, to determine the most appropriate treatment for serious CRE infections.

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