Antibiotics Active Against Carbapenem-Resistant Gram-Negative Bacilli (including Enterobacterales and *P. aeruginosa)* **July 2021**

Cefiderocol (Fetroja™)	**Nonformulary**
Ceftazidime/avibactam (Avycaz™)	**Nonformulary**
Ceftolozane/tazobactam (Zerbaxa™)	**Formulary**
Imipenem/cilastatin/relebactam (Recarbrio™)	**Nonformulary**
Meropenem/vaborbactam (Vabomere™)	**Nonformulary**
Plazomicin (Zemdri™)	**Nonformulary**

Criteria for Formulary Consideration: Antibiotics Active Against Carbapenem-Resistant Gram-Negative Bacilli

Efficacy

Fifteen phase-3 trials, 1 phase-2 trial, and 1 guideline were reviewed. Clinical trials varied for each agent based on diagnosis, comparator, and pathogens included.

Cefiderocol
Compared to imipenem/cilastatin, cefiderocol is noninferior for the treatment of complicated urinary tract infections (cUTI), and superior in post-hoc analysis. Non-inferiority was driven by improved microbiologic eradication over the comparator (73% vs 56%), although clinical response was also numerically higher (90% vs 87%). This trial did not include resistant organisms. In the treatment of nosocomial pneumonia, cefiderocol was non-inferior in all-cause mortality at day 14 compared to high dose extended infusion meropenem (12.4% vs 11.6%). About 30% of isolates produced ESBL and outcomes were similar between cefiderocol and meropenem. 19% of patients were found to have a carbapenem-resistant organism and no significant differences in mortality were found except at very high meropenem MICs (increased in the meropenem arm), suggesting that cefiderocol may be useful for treating carbapenem resistant pathogens, but this subgroup was limited by small numbers. In a descriptive trial evaluating patients with serious carbapenem resistant infections, patients had similar clinical and microbiologic efficacy compared to best available therapies, but all-cause mortality at the end of the study was higher in the cefiderocol arm (34% vs 18%), primarily driven by Acinetobacter spp. Together, these trials suggest that cefiderocol in noninferior to carbapenems in the treatment of non-resistant urinary and pulmonary source infections, but may be associated with worse outcomes compared to best available therapies when treating carbapenem resistant pathogens.

Ceftazidime/avibactam
For the treatment of cUTI, ceftazidime/avibactam met noninferiority and had a numerically higher percentage of patients with symptom resolution at day 5 compared to doripenem (70.2% vs 66.2%) and met superiority for microbiologic eradication (71.1% vs 64.5%). Around 20% of pathogens were ceftazidime resistant/ESBL positive. For nosocomial pneumonia, 28-day all-cause mortality was noninferior to standard dose meropenem (9.6% vs 8.3%). ESBL and AmpC was prevalent in 30% of isolates, but carbapenem-resistant pathogens were excluded from the trial. Endpoints per pathogen were similar, generally numerically favoring meropenem. When used in combination with metronidazole for the treatment of complicated intraabdominal infections (cIAI), ceftazidime/avibactam was noninferior to meropenem for cure at test of cure (81.6% vs 85.1%). These trials suggest that ceftazidime/avibactam is noninferior compared to carbapenems for the treatment of ceftazidime resistant pathogens in cUTI, nosocomial pneumonia, and cIAI.

Ceftolozane/tazobactam
Ceftolozane/tazobactam is noninferior to levofloxacin in the treatment of cUTI with numerically higher microbiologic eradication (80.4% vs 72.1%) and clinical cure (92.0% and 88.6%). Patients with ESBL receiving ceftolozane/tazobactam had 62.3% composite cure vs levofloxacin 35.1%, but the difference in cure rate was likely due to greater prevalence of levofloxacin resistance. In the treatment of ventilator associated pneumonia, ceftolozane/tazobactam was noninferior (28-day all-cause mortality 24% vs 25.3%) compared to standard dose meropenem. This trial included resistant pathogens (ESBL, and MDR *P. aeruginosa*) and clinical cure did not significantly differ between pathogen or resistance mechanism. In combination with metronidazole for the treatment of cIAI, ceftolozane/tazobactam is noninferior to meropenem (clinical cure 83.0% vs 87.3%). In patients with an ESBL producing pathogen, clinical cure favored ceftolozane/tazobactam

(95.5% vs 88.5%). In summary, ceftolozane/tazobactam is noninferior to fluroquinolones and carbapenems in the treatment of cUTI, nosocomial pneumonia, and cIAI, including ESBL pathogens.

Imipenem/cilastatin/relebactam
The efficacy and safety of imipenem/cilastatin/relebactam for cUTI and cIAI was supported in-part by previous findings from imipenem/cilastatin as no phase-3 trials were completed for these indications. Phase 2 studies found that imipenem/cilastatin/relebactam was noninferior for these indications compared to imipenem/cilastatin. In the phase 3 trial evaluating imipenem/cilastatin/relebactam for nosocomial pneumonia, it was found noninferior compared to piperacillin/tazobactam (28-day all-cause mortality 15.9% vs 21.3%). Notably, in this trial 28-day-all-cause mortality caused by Enterobacterales was lower compared to piperacillin/tazobactam 11.8% vs 19.7%, but was increased in *P. aeruginosa* infections (33.3% vs 12.0%). Resistant organisms were excluded from this trial. A small descriptive trial found decreased 28-day all-cause mortality compared to colistin/imipenem in patients with serious, carbapenem resistant infections (9.5% vs 30.0%). In summary, imipenem/cilastatin/relebactam demonstrates non-inferiority compared to imipenem/cilastatin for cUTI, cIAI, non-inferiority to piperacillin/tazobactam in the treatment of nosocomial pneumonia, and decreased overall mortality compared to colistin in serious carbapenem-resistant infections.

Meropenem/vaborbactam
Meropenem/vaborbactam is noninferior to piperacillin/tazobactam for the treatment of cUTI with similar clinical cure (98.4% vs 95.6%) and microbial eradication (97.9% vs 95.6%). Notably, around 12% of pathogens were reported resistant to piperacillin/tazobactam at baseline, but there was no apparent relationship between MIC and overall success. This trial did not report the inclusion of any *P. aeruginosa* isolates, in which meropenem/vaborbactam would not be expected to have improved activity. A descriptive trial evaluating meropenem/vaborbactam compared to best available treatment for serious CRE infections demonstrated decreased 28-day all-cause mortality compared to best available treatment (15.6% vs 33.3%), but was limited by small numbers (n=32 vs 15). Together, these trials show that meropenem/vaborbactam is noninferior to piperacillin/tazobactam for cUTI, and may have decreased mortality compared to best available treatments in serious carbapenem-resistant infections.

Plazomicin
Compared to meropenem, plazomicin is noninferior for the treatment of cUTI with increased microbial eradication at test of cure (89.5% vs 74.6%) and similar clinical cure rates (89.0% vs 90.4%). Microbial eradication was increased in patients with ESBL and MDR pathogens treated with plazomicin (ESBL, 82.4% vs 75%; MDR 77.2% vs 70.3%). The trial evaluating plazomicin for the treatment of carbapenem resistant infections was stopped early due to low enrollment, limiting any major conclusions in the treatment of these pathogens, but provides some support of its use. Composite all-cause death at 28 days or clinically significant disease was lower in the plazomicin group compared to colistin based regimens (4/17 vs 10/20).

Safety
Cefiderocol and β-lactam/β-lactamase inhibitors have similar adverse effects compared to other cephalosporins. Data regarding allergenic cross-reactivity for β-lactams is limited, however; because of structural similarities the possibility of cross-sensitivity can not be ruled out. Caution should be used in patients with a history of sensitivity to β-lactams. In RECLAIM 1&2 and ASPECT-cIAI, patients with renal insufficiency (creatinine clearance 30-50 mL/minute) had decreased clinical cure rates. The dose of ceftazidime/avibactam used in this trial (1.25g every 12 hours) is lower than the currently approved dose for the same creatinine clearance (1.25 g every 8 hours). The dose of ceftolozane/tazobactam used in ASPECT-cIAI for creatinine clearance 30-50 ml/minute is the same as the currently approved dose (750 mg every 8 hours). Decreased clinical efficacy was not seen in this population in trials evaluating cUTI (ASPECT-UTI, RECAPTURE). Caution should be used when using these medications for the treatment of cIAI in patients with renal insufficiency.

Plazomicin has black box warnings for nephrotoxicity, ototoxicity, neuromuscular blockade, and pregnancy. In EPIC, overall adverse events were similar between plazomicin and meropenem. Adverse events related to renal function were higher in the plazomicin treatment group 11/303 (3.6%) vs 4/301 (1.3%).

In studies evaluating the treatment of carbapenem-resistant pathogens, cefiderocol, imipenem/cilastatin/relebactam, meropenem/vaborbactam, and plazomicin had decreased adverse events compared to best available therapies (colistin/polymyxin based combination therapies).

Uniqueness

Antibiotic resistance is a significant threat to public health. These novel antibiotics offer needed treatment options for resistant gram-negative infections. Each agent has unique pharmacology and varies in its spectrum of activity dependent on activity against mechanisms of resistance. Cefiderocol offers the broadest *in-vitro* activity and lowest propensity for resistance. Ceftazidime/avibactam utilizes a unique β-lactamase that confers activity against a number of carbapenemases and is the only agent with indications in pediatric patients. Ongoing studies have also suggested that the addition of aztreonam may expand activity of ceftazidime/avibactam to be effective against metallo-beta-lactamases. Ceftolozane/tazobactam does not offer activity against carbapenemases, but generally has higher percentages of susceptibility for difficult to treat *Pseudomonas aeruginosa* compared to other agents. Imipenem/cilastatin/relebactam extends imipenem's activity, giving broad susceptibility to a number of pathogens including KPC producing organisms. Meropenem/vaborbactam retains meropenem's spectrum with expanded activity against variant *K. pneumoniae* carbapenemases that may confer resistance against ceftazidime/avibactam, but does not have improved activity against *P. aeruginosa*. Lastly, plazomicin, a new aminoglycoside offers activity where traditional aminoglycosides may be resistant.

How Supplied/Cost

	Cefiderocol	Ceftazidime /avibactam	Ceftolozane/ tazobactam†	Imipenem/ cilastatin/ relebactam	Meropenem/ vaborbactam	Plazomicin*
Dosing						
Dose (grams)	2	2.5	3	1.25	4	1.2
Frequency (hour)	8	8	8	6	8	24
Infusion duration (hours)	3	4	1	0.5	3	0.5
Inpatient Cost						
Cost/Dose	460	430	300	330	396	910
Cost/Day	1370	1290	900	1320	1190	910
Cost/Course (7 day)	9560	9030	6310	9240	8330	6370
Products						
Supplied as	1 GM PWVL	2-0.5GM PWVL	1-0.5 GM PWVL	1.25 GM PWVL	2 GM PWVL	500 mg/10 mL

Average Wholesale Price (AWP) per Lexicomp, 08/20/2021

†currently unavailable for purchase

*Dose based on 80kg (15mg/kg)

Recommendations

- Keep ceftolozane/tazobactam on formulary
- Add ceftazidime/avibactam to formulary with antimicrobial restrictions.
    - Should only be used when there is documented or strong suspicion for infection due to multidrug-resistant Pseudomonas or carbapenem resistant Enterobacterales with no alternative treatment options.
    - For mixed infections, ceftazidime/avibactam must be used in combination with agents possessing gram-positive and/or anaerobic activity.
    - Any use will require review and approval by the Infectious Diseases Service. The ordering physician is responsible for contacting the ID service. The drug will be started with a 24-hour stop date unless approval for continued use is obtained; therefore, the approval must be received within 24 hours of the original order. If use is approved, the ID Service will relay this information to the ordering physician as well as to the pharmacy for continued administration of ceftazidime/avibactam. If ceftazidime/avibactam is thought to be inappropriate, the ID Service will provide alternative recommendations and communicate these recommendations to the physician originating the ceftazidime/avibactam order.

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Class Review: Antibiotics Active Against Carbapenem-Resistant Gram-Negative Bacilli **July 2021**

Introduction

Antimicrobial resistance continues to be a significant threat to public health, with over 2.8 million antibiotic resistant infections and 35,000 associated deaths yearly in the United States.[1] Of particular concern is rising resistance to carbapenems and lack of effective and safe alternative treatment options. Clinically relevant resistant gram-negative bacteria include carbapenem-resistant Enterobacterales (CRE), difficult to treat *Pseudomonas aeruginosa* (DTR-*P*), and carbapenem-resistant *Acinetobacter baumannii* (CRAB). These pathogens have been designated urgent or serious threats by the CDC and cause a wide range of serious infections that carry significant morbidity and mortality (up to 50%).[1] A number of novel antibiotics have been approved in recent years with activity against these pathogens, however; resistance continues to be observed creating an ongoing need for the development of new agents.[2–4] Data regarding the clinical efficacy of new antibiotics specific to carbapenem-resistant infections continues to emerge, leading to uncertainty about the roles of new agents in clinical practice.[2–4] Table 1 provides an overview and comparison of these antibiotics. Traditional therapies including colistin/polymyxin-B are formulary but are considered more toxic and will not be reviewed in this document.

Table 1. Summary and comparison of novel agents

	Cefiderocol	Ceftazidime/ avibactam	Ceftolozane/ tazobactam	Imipenem/ cilastatin/ relebactam	Meropenem/ vaborbactam	Plazomicin
Current formulary status	Not yet considered	Non-formulary	Formulary	Not yet considered	Not yet considered	Not yet considered
Drug class	Siderophore-cephalosporin	β-lactam/β-lactamase inhibitor	β-lactam/β-lactamase inhibitor	β-lactam/β-lactamase inhibitor	β-lactam/β-lactamase inhibitor	Aminoglycoside
FDA approval year	2019	2015	2014	2019	2017	2018
FDA indicated for cIAI		X	X	X		
FDA indicated for cUTI	X	X	X	X	X	X
FDA indicated for HABP/VAP	X	X	X	X		
Dosing frequency	8 hours	8 hours	8 hours	6 hours	8 hours	Once daily
Infusion duration	3 hours	2 hours	1 hour	30 minutes	3 hours	30 minutes

Abbreviations: cIAI, complicated intra-abdominal infections; cUTI, complicated urinary tract infections including pyelonephritis; HABP/VABP, hospital-acquired bacterial pneumonia and ventilator associated bacterial pneumonia

The selection of antibiotics for the treatment of infections caused by CRE is challenging and requires careful consideration. They are not interchangeable as each agent varies in spectrum of activity, dependent on the mechanisms of resistance (Table 2). Agents also vary in their propensities for the selection of resistance and cross resistance. For example, treatment emergent resistance may develop after exposure to ceftazidime/avibactam in KPC producing *K. pneumoniae*, while meropenem/vaborbactam retains activity to the variant KPC.[4,5] Ceftolozane/tazobactam has been shown to generally have higher percentages of susceptibility against non-carbapenemase producing *P. aeruginosa* compared to other agents, but cross resistance with ceftazidime/avibactam may occur.[3,6] Additionally, cross resistance between meropenem/vaborbactam and ceftazidime/avibactam may occur up in up to 20% of isolates, but remains infrequent.[4,5] Clinical data varies based off indication and the pathogens included in each trial. Data supporting superiority over traditional colistin based combination therapies has been mostly positive with these novel agents; however, cefiderocol, while having broad *in-vitro* activity, had overall increased mortality against CRE.[7]

Table 2. General spectra of antimicrobial activity against organisms and enzymes with carbapenem resistance [2,4,5,8,9] †

Agent	Enterobacterales					Carbapenem-resistant Pseudomonas	Acinetobacter sp. (incl. CRAB)	S. maltophilia
	ESBL	AmpC	KPC	NDM	OXA-48-like			
Cefiderocol	✓	✓	✓	✓	✓	✓	✓	✓
Ceftazidime/avibactam	✓	✓	✓	x	✓	+/-	x	x
Ceftolozane/tazobactam	+/-	+/-	x	x	x	✓	x	+/-
Imipenem/cilastatin/relebactam	✓	✓	✓	x	x	✓	x	x
Meropenem/vaborbactam	✓	✓	✓	x	x	x	x	x
Plazomicin	✓	✓	✓	+/-	✓	+/-	x	x

Abbreviations: ESBL, extended spectrum beta-lactamase; AmpC, Ambler class C beta-lactamase; KPC, *Klebsiella pneumoniae* carbapenemases; NDM, New Delhi metallo-beta-lactamase; OXA-48; oxacillinase-48-like carbapenemases; CRAB, carbapenem-resistant *Acinetobacter baumanii*, S. maltophilia, *Stenotrophomonas maltophilia*

†Activity reflects general national trends; always defer to antimicrobial susceptibility testing and local antibiograms to support clinical decisions

Compared to other areas in the country, Nebraska has low prevalence of CRE. In 2018, there were 7 confirmed CRE cases according to the state health department. The prevalence of carbapenem-resistant gram-negative infections in the United States are driven by CRAB and *P. aeruginosa,* and non-carbapenemase mechanisms account for around 50% of CRE infections nationwide.[1,10–12] The incidence of CRE is low within the community, but in healthcare settings up to 30% of carbapenem resistant infections may carry a carbapenemase gene.[1] The most common carbapenemase in the U.S. is KPC, with less than 10% of isolates containing NDM or OXA-48-like. [1,10,11]

Table 3 depicts local antibiogram data including organisms commonly capable of producing resistance via ESBL, AmpC, or other mechanisms (porin mutations). The greatest need for alternative agents exists for *P. aeruginosa*, in which ≥10% of isolates were resistant to commonly used antimicrobials (cefepime, piperacillin/tazobactam, meropenem).

Table 3. Cumulative Antibiogram of Select Gram-Negative Organisms at Nebraska Medical Center

Organism	Cefepime	Ceftolozane/ Tazobactam	Ceftazidime/ Avibactam	Meropenem	Meropenem/ Vaborbactam	Piperacillin/ Tazobactam
Acinetobacter baumannii complex	84 (11)	-	-	100 (13)	-	-
Enterobacter cloacae	93 (152)	-	100 (1)	99 (161)	100 (117)	77 (125)
Escherichia coli	89 (906)	98 (581)	99 (582)	100 (906)	100 (581)	86 (906)
Klebsiella pneumoniae	89 (287)	98 (187)	100 (188)	98 (287)	100 (188)	87 (287)
Pseudomonas aeruginosa	90 (301)	98 (195)	96 (195)	86 (301)	-	90 (301)

Cumulative Antibiogram Nebraska Medical Center Jan 1 – Dec 31, 2020. Admitted patients only, first isolate per patient. Numbers represent % susceptible (# of isolates tested).

Nebraska Medicine's formulary currently includes ceftolozane/tazobactam. In December 2020, Merck issued a global recall for ceftolozane/tazobactam secondary to sterility concerns. This recall has resulted in manufacturer backorder with release not expected until early 2022, necessitating alternative therapies for the treatment of resistant infections.

Susceptibility Testing

FDA Susceptibility Interpretive Criteria and Clinical and Laboratory Standards Institute (CLSI) performance standards for antimicrobial susceptibility testing (CLSI M100) are available for all of the agents at this time.[42] Nebraska Medicine's Microbiology laboratory routinely tests susceptibility for ceftazidime/avibactam, ceftolozane/tazobactam, and meropenem/vaborbactam via automated MicroScan. Others are done manually or are sent to a reference laboratory. Meropenem/vaborbactam is not routinely tested in *P. aeruginosa* isolates as the FDA and CLSI does not have approved interpretative test criteria.

Pharmacology[2,4,13–18,25]

- Cefiderocol: is a siderophore cephalosporin with a catechol side chain that chelates extracellular iron. Utilizing bacterial siderophore iron uptake mechanism, it passively diffuses and is actively transported across the outer cell membrane of gram-negative organisms, bypassing resistance mechanisms. It is stable against a variety of carbapenemases including Ambler class A (KPC), class B (metallo-β-lactamase: NDM, VIM, IMP), and class D (OXA-48), resulting in broad susceptibility in gram-negatives organisms. It exerts bactericidal action by binding to penicillin-binding proteins (PBPs), primarily PBP3, inhibiting cell wall synthesis. It has no gram positive or anerobic activity. In vitro, MIC increases have been associated with a combination of β-lactamases, modification of PBPs, and mutations of transcriptional regulators that may impact siderophore expression and efflux pump expression.
- Ceftazidime/avibactam: is a cephalosporin/beta-lactamase inhibitor combination. Ceftazidime has activity against certain gram-negative bacteria. Its bactericidal action is mediated through binding to PBPs. The avibactam component is a diazabicyclooctane beta-lactamase inhibitor active against Ambler class A, C, and some D beta-lactamases. It is not active against class B beta-lactamases and may not have activity against organisms that overexpress efflux pumps or have porin mutations. Treatment emergent resistance has been documented in isolates of *K. pneumoniae* from mutations in the bla_{KPC} gene.
- Ceftolozane/tazobactam: is a cephalosporin/beta-lactamase inhibitor combination. Ceftolozane is a novel cephalosporin with activity against gram negative bacteria, gram positive bacteria (*S. anginosus, S. constellatus, S. salivarius)* and anerobic bacteria (*B.* fragilis) and is stable by itself against multiple resistance mechanisms. It is bactericidal through binding of PBPs, with high affinity binding to PBPs specific to *P. aeruginosa* (PBP1b, PBP1c, PBP3) and *E. coli* (PBP3). Tazobactam is a beta-lactamase inhibitor that has affinity for certain penicillinases and cephalosporinases and can bind to some chromosomal/plasmid mediated beta-lactamases. It does not have activity against carbapenemases. It generally has higher percentages of susceptibility for DTR-*P* compared to other agents. Resistance may occur with hyperproduction of AmpC, modification of PBPs, upregulation of efflux pumps, and loss of porins.
- Imipenem/cilastatin/relebactam: is a carbapenem/renal dehydropeptidase inhibitor/beta-lactamase inhibitor combination. It retains the activity that imipenem has with activity against a broad range of gram-negative, gram positive, and anerobic bacteria. Bactericidal action occurs from inhibition of PBPs. Relebactam is a novel beta-lactamase inhibitor structurally similar to avibactam and has activity against class A and class C β-lactamases but differs in that it does not inhibit class D beta-lactamases. It has been shown to restore activity to *P. aeruginosa* isolates that were imipenem resistant. Cilastatin limits the metabolism of imipenem which increases urinary concentrations. Resistance may occur with the hyperproduction of varying beta-lactamases and porin alterations.
- Meropenem/vaborbactam: is a carbapenem/beta-lactamase inhibitor combination. It has the same activity as meropenem plus activity against KPC. Vaborbactam is a boronic acid reversable beta-lactamase inhibitor that competitively inhibits class A beta-lactamases. Vaborbactam also inhibits class C beta lactamases, but meropenem is stable against these beta-lactamases by itself. It is not expected to improve activity against *P. aeruginosa.* Resistance may be due to production of beta-lactamases, changes in PBPs, upregulation of efflux pumps, or loss of outer membrane porin.
- Plazomicin: is an aminoglycoside with several structural changes that resist modification by aminoglycoside-modifying enzymes (AMEs), conferring broad activity against Enterobacterales that may be resistant to tobramycin, gentamicin, and amikacin. It that binds to bacterial 30S ribosomal subunit, inhibiting protein synthesis. It has concentration dependent bactericidal activity. Activity toward DTR-*P* and CRAB is comparable to existing aminoglycosides and is not predictable. Resistance occurs in isolates that produce 16S rRNA methyltransferases (prevalent in strains producing class B beta-lactamases), or via upregulation of efflux pumps.

Pharmacokinetics and Pharmacodynamics[13–24]

	Absorption		Distribution		Metabolism	Excretion		PD Efficacy Parameter
	Cmax (mg/L)	AUC $_{0-24}$ (mg-hour/L)	Protein binding (%)	Vd (L)		Half-life (hours)	Excretion (%)	
Cefiderocol	91.4	1175	40-60	18	Minimally metabolized	2-3	98.6, urine	%*f*T > MIC
Ceftazidime/ avibactam	90.4 / 14.6	291 / 38.2	<10 / 5.7-8.7	10.8-17 / 12.3-22.2	Minimally metabolized	2.8 / 2.7	80-97, urine	%*f*T > MIC / %fT>C_T
Ceftolozane/ tazobactam	105 / 26.4[a]	392 / 73.3[a]	16-21 / 30	13.5 / 18.2	Minimally metabolized	3-4 / 2-3	80-95, urine	%*f*T > MIC / %fT>C_T
Imipenem/ cilastatin/ relebactam	122.7 / 80[b]	771 / 692.9[b]	20 / 40 / 22	24.3 / 13.8 / 19	Imipenem is metabolized renally by dehydropeptidase, cilastatin inhibits this enzyme resulting in increased urine concentrations. Relebactam is minimally metabolized.	1 / 1.2 [b]	63 / 77 / >90, urine	%*f*T > MIC / AUC_{0-24}:MIC
Meropenem/ vaborbactam[c]	57.3 / 71.3	650 / 835	2 / 33	20.2 / 18.6	Meropenem- 22% hydrolysis of beta-lactam ring, vaborbactam is minimally metabolized	2.30 / 2.25	40-60 / 75-95, urine	%*f*T > MIC / AUC_{0-24}:MIC
Plazomicin	73.7 Cmin 0.3	257	20	17.9 in healthy adults, 30 in cUTI patients	Minimally metabolized	3.5	97.5, urine	AUC_{0-24}:MIC

[a]Data from HABP/VABP patients after multiple 1-hour infusions of 3-gram doses every 8 hours with CrCl >50 ml/min
[b]Data for imipenem and relebactam from HABP/VABP patients after multiple 30 minute infusions of 500 mg/500 mg/250 mg every 6 hours in patients with CrCl > 90 ml/min
[c]Data from population pharmacokinetic parameters following 4-gram 3 hour infusion

FDA Approved Indications[13–18] †

	Cefiderocol	Ceftazidime/ avibactam	Ceftolozane/ tazobactam	Imipenem/ cilastatin/ relebactam	Meropenem/ vaborbactam	Plazomicin
Year of FDA approval	2019	2015	2014	2019	2017	2018
FDA Indication						
cIAI		X (in combination with metronidazole) Includes pediatric patients >3 months old	X (in combination with metronidazole)	X		
cUTI	X	X Includes pediatric patients >3 months old	X	X	X	X
HABP/VABP	X	X	X	X		
Microbiology (in vitro and in clinical infections)						
cIAI		*C. freundii complex* *E. cloacae* *E. coli* *K. oxytoca* *K. pneumoniae* *P. mirabilis* *P. aeruginosa*	*E. cloacae* *E. coli* *K. oxytoca* *K. pneumoniae* *P. mirabilis* *P. aeruginosa* *S. anginosus* *S. constellatus* *S. salivarius* *B. fragilis*	Broad number of gram negative aerobic and anerobic bacteria		

cUTI	*E. coli* *E. cloacae complex* *K. pneumoniae* *P. mirabilis* *P. aeruginosa*	*C. freundii complex* *E. cloacae* *E. coli* *K. pneumoniae* *P. mirabilis* *P. aeruginosa*	*E. coli* *K. pneumoniae* *P. mirabilis* *P. aeruginosa*	*K. aerogenes* *E. cloacae* *E. coli* *K. pneumoniae* *P. aeruginosa*	*E. cloacae species complex* *E. coli* *K. pneumoniae*	*E. coli* *K. pneumoniae* *P. mirabilis* *E. cloacae*
HABP/VABP	*A. baumannii complex* *E. coli* *E. cloacae complex* *K. pneumoniae* *P. aeruginosa* *S. marcescen*	*E. cloacae* *E. coli* *H. influenzae* *K. pneumoniae* *P. mirabilis* *P. aeruginosa* *S. marcescens*	*E. cloacae* *E. coli* *H. influenzae* *K. pneumoniae* *K. oxytoca* *P. mirabilis* *P. aeruginosa* *S. marcescens*	*A. calcoaceticus-baumannii complex* *E. cloacae* *E. coli* *H. influenzae* *K. aerogenes* *K. oxytoca* *K. pneumoniae* *P. aeruginosa* *S. marcescens*		
Microbiology (in vitro, clinical significance unknown)						
	Achromobacter spp. *Burkholderia cepacia complex* *C. freundii complex* *C. koseri* *K. aerogenes* *K. oxytoca* *M. morganii* *P. vulgaris* *P. rettgeri* *S. maltophilia*	*C. koseri* *E. aerogenes* *M. morganii* *P. rettgeri* *P. stuartii*	*C. koseri* *K. aerogenes* *M. morganii* *P. vulgaris* *P. rettgeri* *P. stuartii* *S. liquefaciens* *S. agalactiae* *S. intermedius*	Broad number of gram positive, gram negative bacteria similar to Imipenem	*C. freundii* *C. koseri* *E. aerogenes* *K. oxytoca* *M. morganii* *P. mirabilis* *Providencia spp.* *P. aeruginosa* *S. marcescens*	*C. freundii* *C. koseri* *E. aerogenes* *K. oxytoca* *M. morganii* *P. vulgaris* *P. stuartii* *S. marcescens*

Abbreviations: cIAI, complicated intra-abdominal infections; cUTI, complicated urinary tract infections including pyelonephritis; HABP/VABP, hospital-acquired bacterial pneumonia and ventilator associated bacterial pneumonia

†Each antibiotic has been shown to be active against different organisms both *in-vitro* and in clinical infections. FDA approved indications are for specific susceptible bacterial infections.

Clinical Trials and Guidelines

Studies evaluating the efficacy of cefiderocol[7,26,27]

<table>
<tr><th>Study Design</th><th>Methods</th><th>Results</th><th>Conclusions/Comments</th></tr>
<tr>
<td>Wunderink R. et al, 2021 (APEKS-NP)

Design:
Randomized multicenter phase 3, double-blind, non-inferiority trial evaluating Cefiderocol vs meropenem for the treatment <u>nosocomial pneumonia.</u>

Intervention/Comparator:
Cefiderocol 2 grams over 3 hours every 8 hours or meropenem 2 grams over 3 hours every 8 hours.

Doses were adjusted for renal function.

All patients received open label linezolid 600 mg IV every 12 hours for at least 5 days

Treatment duration was for 7-14 days, but could be extended up to 21 days

Number of patients:
N=148 assigned to cefiderocol, N=152 assigned to meropenem</td>
<td>Inclusion:
Adults with gram-negative pneumonia in the form of HAP, VAP, or HCAP

Exclusion:
Community acquired, atypical or viral pneumonia, chemical pneumonitis, known CRE pathogen before randomization, APACHE II score >35, refractory septic shock, concomitant mold infection, cystic fibrosis, bronchiectasis, and concomitant CNS infection

Power:
Assuming all-cause mortality of 10%, 12.5% noninferiority margin would have 90% power with α level of 0.025 (N=244, 122/arm) for primary outcome</td>
<td>Primary endpoint:
All-cause mortality at day 14 in the microbiologic modified intention to treat population

Secondary endpoint
All-cause mortality at 28 days, clinical cure, microbiological eradication
<table>
<tr><th></th><th>Cefiderocol N=145</th><th>Meropenem N=146</th></tr>
<tr><td>Primary endpoint</td><td>12.4%</td><td>11.6%</td></tr>
<tr><td colspan="3">Adjusted treatment difference=0.8%, 95% CI -6.6-8.2; met non-inferiority</td></tr>
<tr><td>Secondary endpoints</td><td></td><td></td></tr>
<tr><td>Mortality at 28 days</td><td>21.0% (30/143)</td><td>20.5% (30/146)</td></tr>
<tr><td>Clinical Cure</td><td>65%</td><td>67%</td></tr>
<tr><td>Microbiological eradication</td><td>41%</td><td>42%</td></tr>
<tr><td>Clinical cure per pathogen</td><td></td><td></td></tr>
<tr><td>K. pneumoniae</td><td>31/48 (65%)</td><td>29/44 (66%)</td></tr>
<tr><td>P. aeruginosa</td><td>16/24 (67%)</td><td>17/24 (71%)</td></tr>
<tr><td>A baumanni</td><td>12/23 (52%)</td><td>14/24 (58%)</td></tr>
</table>
ESBL producers were common (31% vs 29% in each arm). In patients with ESBL infections, no significant differences were found in mortality at 14 and 28 days.

Subgroup of patients with HCAP had numerically more patients die in the Cefiderocol group at 28 days (4/27) vs 1/23 (Table s15).

Adverse events:
Drug-related: Cefiderocol 9% vs meropenem 11%.
Drug related SAE 2% vs 3%.
Drug discontinuation due to drug related AE: 1% vs 1%</td>
<td>Author's Conclusion:
Cefiderocol was non-inferior to high dose extended infusion meropenem for 14-day all-cause mortality in critically ill patients with nosocomial pneumonia caused by Enterobacterales, A. baumannii, P. auerginosa.

Comments:
Did not include sufficient numbers of patients with CRE, carbapenem-resistant P. aeruginosa, or CRAB to define the role of Cefiderocol in the treatment of these infections.</td>
</tr>
<tr>
<td>Bassetti M. et al, 2021 (CREDIBLE-CR)

Design:
Randomized multicenter phase 3, open label, descriptive trial evaluating Cefiderocol vs best available therapy</td>
<td>Inclusion:
Adults with a serious infection defined as nosocomial pneumonia (NP), cUTI, and bloodstream infection (BSI), caused by a carbapenem-resistant gram-negative bacterium.</td>
<td>Primary endpoints:
In the microbiologic modified intention to treat population: patients with NP and BSI clinical cure at test of cure 7±2 days after the end of treatment and those with cUTI, microbiological eradication at test of cure.

Secondary endpoints:
All-cause mortality at days 28 and 49, mortality per pathogen</td>
<td>Author's Conclusion:
Cefiderocol had similar clinical and microbiological efficacy compared to BAT in patients with carbapenem resistant infections despite numerically more deaths in the Cefiderocol group, primarily in the subset with Acinetobacter NP and BSI infections.</td>
</tr>
</table>

<table>
<tr>
<td>for the treatment of carbapenem resistant infections.

Intervention/Comparator:
Cefiderocol 2 grams every 8 hours or best available therapy (BAT- max of 3 drug combination – Colistin and non-colistin based regimens).

For NP and BSI Cefiderocol could be combined with one adjunctive antibiotic (excluding polymyxins, cephalosporins including b-lactamse inhibitor combinations, and carbapenems)

Doses were adjusted for renal function.

Treatment duration was for 7-14 days, but could be extended up to 21 days

Number of patients:
N=101 assigned to cefiderocol
N=51 assigned to best available therapy</td>
<td>Exclusion:
Coinfection with molds, CNS infections, >3 weeks of antibacterial treatment, cystic fibrosis or moderate to severe bronchiectasis, refractory septic shock, severe neutropenia, peritoneal dialysis or , APACHE II score >30> Patients were excluded if they received a potentially effective treatment for >36 hours for pneumonia/bloodstream infection or >24 h for cUTI, requirement for more than 3 antibiotics for best available therapy at time of randomization, concomitant inhaled antibiotics

Statistics:
Designed as a descriptive analysis without hypothesis testing</td>
<td>
<table>
<tr><th></th><th>Cefiderocol N=101</th><th>BAT N=49</th></tr>
<tr><td>Primary Endpoint</td><td></td><td></td></tr>
<tr><td>NP</td><td>20/40 (50%)</td><td>10/19 (53%)</td></tr>
<tr><td>BSI</td><td>10/23 (43%)</td><td>6/14 (43%)</td></tr>
<tr><td>cUTI</td><td>25/80 (31%)</td><td>9/38 (24%)</td></tr>
<tr><td>Secondary endpoints</td><td></td><td></td></tr>
<tr><td>Overall all-cause mortality at end of study</td><td>34 (34%)</td><td>9 (18%)</td></tr>
<tr><td>All-cause mortality at the end of study by most common pathogens</td><td></td><td></td></tr>
<tr><td>Acinetobacter spp.</td><td>21/42 (50%)</td><td>3/17 (18%)</td></tr>
<tr><td>K. pneumoniae</td><td>6/28 (21%)</td><td>4/15 (27%)</td></tr>
<tr><td>P. aeruginosa</td><td>2/11 (18%)</td><td>2/11 (18%)</td></tr>
</table>
For the site of infection, all-cause mortality at the end of study was higher in the cefiderocol group when compared to best available therapy for pulmonary infections (42% vs 18%) and bloodstream infections (37% vs 8%) but not with complicated UTI (15% vs 20%)

Adverse events:
Drug-related: cefiderocol 10% vs BAT 22%.
Drug discontinuation due to drug related AE: 3% vs 4%</td>
<td>Comments:
Mortality was 50% in the Cefiderocol arm vs 18% for BAT in patients with CRAB. CRAB composed 46% of the study population.

These findings suggest that Cefiderocol may be associated with worse outcomes than BAT regimens for CRAB infections. There was no significant difference in mortality for other organisms between arms.</td>
</tr>
<tr>
<td>Portsmouth S. et al, 2018 (APEKS-cUTI)

Design:
Randomized multicenter phase 2, open label noninferiority trial evaluating cefiderocol vs imipenem/cilastatin for treatment of cUTIs

Intervention/Comparator:
cefiderocol 2 grams over 1 hour three times daily vs imipenem-cilastatin 1 gram three times daily.

Doses were adjusted for renal function.

Treatment duration was 7-14 days</td>
<td>Inclusion:
Adults admitted to the hospital with cUTI with or without pyelonephritis, or with acute uncomplicated pyelonephritis, allowed immunosuppressed patients

Exclusions:
≥2 uro-pathogens, fungal infection, pathogens known to be carbapenem resistant, CrCl <20 ml/min

Statistics:
Originally designed to have 90% power to detect a difference of greater than 20%(n=450) in the primary endpoint. This was amended to allow interpretation as a pivotal trial- 80% power with a noninferiority margin of 15%.</td>
<td>Primary endpoint:
Composite of clinical and microbiological outcomes at test of cure (7±2 days after end of treatment) in microbiologic modified intent to treat population

Secondary endpoints:
Safety, clinical and microbiologic response at different time points, outcome per diagnosis
<table>
<tr><th></th><th>Cefiderocol N=252</th><th>Imipenem/ cilastatin N=119</th></tr>
<tr><td>Primary endpoint</td><td>73%</td><td>65%</td></tr>
<tr><td colspan="3">Adjusted treatment difference=18.58%, 95% CI 8.23-28.92; met non-inferiority</td></tr>
<tr><td>Clinical response</td><td>90%</td><td>87%</td></tr>
<tr><td>Microbiologic eradication</td><td>73%</td><td>56%</td></tr>
</table>
</td>
<td>Author's Conclusion:
In patients with complicated UTI who are at risk of multidrug resistant infections, cefiderocol demonstrated noninferiority to imipenem/cilastatin. Post hoc analysis showed superiority.

Comments:
Patients with carbapenem resistant infections were excluded from this study, limiting conclusions for these pathogens.</td>
</tr>
</table>

Number of patients: N=303 assigned to cefiderocol N=149 assigned to imipenem/cilastatin		<table><tr><td>Secondary endpoints</td><td></td><td></td></tr><tr><td>Composite outcome for cUTI</td><td>129/187 (69%)</td><td>41/84 (49%)</td></tr><tr><td>Composite outcome for pyelonephritis</td><td>54/65 (83%)</td><td>24/35 (69%)</td></tr><tr><td>Sustained clinical response at follow up</td><td>81%</td><td>72%</td></tr></table> The median duration of treatment was 9 days for both arms. The most common pathogen was *E. coli*, 60.3% and 66.4%. *P. aeruginosa* was present in 7.1% and 4.2% in each arm. About 50% of pathogens in both arms had no resistance to other antimicrobials. **Adverse events:** Any: cefiderocol 122/300 (41%) vs imipenem 76/148 (51%) Drug related: 9% vs 11% Drug Discontinuation: 2% vs 2% Most common adverse events were diarrhea (4%, 6%), hypertension (4%, 5%), and constipation (3%, 4%).	

Studies evaluating the efficacy of ceftazidime/avibactam[28–32]

Study Design	Methods	Results	Conclusions/Comments
Torres A. et al, 2018 (REPROVE) Torres A. et al, 2019 (REPROVE): analyses per US FDA specified end points **Design:** Randomized multicenter phase 3, double-blind, non-inferiority trial evaluating ceftazidime/avibactam vs meropenem for the treatment of **nosocomial pneumonia, including VAP.** **Intervention/Comparator:** Ceftazidime 2000 mg/Avibactam 500 mg IV over 2 hours every 8 hours or	**Inclusion:** adults 18-90 years with HAP defined as pneumonia with onset 48 hours or longer after admission or less than 7 days after discharge from inpatient facility. VAP was defined as lung infection with onset 48 hour or longer after intubation. **Exclusions:** Infections caused by gram positive pathogens or pathogens not expected to respond to ceftazidime/avibactam or meropenem, or both (polymicrobial were permitted if they included a target gram negative pathogen), infection requiring >14 days of treatment	**FDA Specified Primary endpoint:** 28-day all-cause mortality in intent to treat population **Secondary endpoints:** Clinical cure, 28-day all-cause mortality in modified microbiologic intent to treat population (ceftazidime non-susceptible), favorable response per pathogen <table><tr><td></td><td>Ceftazaidime/ Avibactam N=436</td><td>Meropenem N=434</td></tr><tr><td>Primary endpoint</td><td>9.6%</td><td>8.3%</td></tr><tr><td colspan="3">Treatment difference=1.5%, 95% CI -2.4-5.3; met noninferiority</td></tr><tr><td>Secondary endpoints</td><td></td><td></td></tr></table>	**Author's Conclusion:** Ceftazidime/avibactam demonstrated noninferiority to meropenem in the treatment of HAP/VAP. **Comments:** Excluded patients with resistant pathogens, therefore unable to estimate efficacy for those bacteria. Noninferior results, but favored meropenem numerically in regards to 28-day all cause mortality and clinical cure. Meropenem was not given as an extended infusion vs ceftazidime/avibactam which was.

<table>
<tr>
<td>meropenem 1000 mg over 30 minutes every 8 hours

Doses were adjusted for renal function.

Treatment duration was for 7-14 days.

Number of patients:
N=436 assigned ceftazidime/avibactam
N= assigned 434 meropenem</td>
<td>Statistics:
FDA Specified endpoint: noninferiority margin of <10% for primary endpoint. Had 90% power to detect 10% difference (note noninferiority margin originally 12.5%), n=790</td>
<td>
<table>
<tr><td>Clinical Cure</td><td>67.2%</td><td>69.1%</td></tr>
<tr><td colspan="3">Met-noninferiority for this secondary endpoint based on margin of 10%.</td></tr>
<tr><td>28-day all-cause mortality (mITT) – ceftaz non-suspetible</td><td>4/49 (8.2%)</td><td>5/59 (8.5%)</td></tr>
<tr><td>Clinical Cure per pathogen</td><td></td><td></td></tr>
<tr><td>Aerobic gram-negative</td><td>126/187 (67.4%)</td><td>143/195 (73.3%)</td></tr>
<tr><td>P. aeruginosa</td><td>38/64 (59.4%)</td><td>37/51 (72.5%)</td></tr>
<tr><td>Ceftazidime non-susceptible pathogens</td><td>37/49 (75.5%)</td><td>42/59 (71.2%)</td></tr>
</table>
More patients in the ceftazidime/avibactam arm had P. aeruginosa infections.

ESBL and AmpC was prevalent in 30.1% of isolates in the micro intent to treat population.

Adverse events:
Significant AE: ceftazidime/avibactam 18.1% vs 13.6% for meropenem
Discontinuation of study drug: 3.7% vs 3.0%.

Most common adverse events were diarrhea 15% vs 15%, hypokalemia 11% vs 8%, anemia 6% vs 4%
</td>
<td>Numerically higher adverse events in ceftazidime/avibactam group.</td>
</tr>
<tr>
<td>Carmeli Y. et al, 2016 (REPRISE)

Design:
Randomized, multicenter, open label phase 3 trial evaluating <u>ceftazidime/avibactam vs best available therapy (BAT) for the treatment of cUTI and cIAI.</u>

Intervention/Comparator:
Ceftazidime 2000 mg/Avibactam 500 mg IV over 2 hours every 8 hours or best available therapy (mostly carbapenems- 97%)
Patients with cIAI who received ceftazidime/avibactam also received metronidazole 500 mg IV every 8 hours

Doses were renally adjusted.

Treatment duration was 5-21 days.</td>
<td>Inclusions: Adult patients with cUTI with or without pyelonephritis or cIAI caused by ceftazidime-resistant gram-negative pathogens (Enterobacteriaceae and <i>P. aeruginosa</i>).

Exclusions: Crcl <6ml/min, evidence of abnormal LFTs, infection due to gram negative bacterial species unlikely to respond (<i>Acinetobacter spp, Stenotrophomonas spp)</i>, infection unlikely to respond 5-21 days of study treatment, APACHE II score >30, or previously undergone a liver, pancreas, or small bowel transplant

Statistics: 200 patients per treatment group was expected to provide sufficient data. No formal power calculations or formal statistical comparisons were done for treatment groups.</td>
<td>Primary Endpoint:
Clinical response at the test of cure 7-10 days after last infusion of study therapy in microbiologic modified intention to treat population
<table>
<tr><td></td><td>Ceftazidime/ Avibactam N=154</td><td>BAT N=148</td></tr>
<tr><td>Primary outcome</td><td>91% (95% CI 85.6-94.7)</td><td>91% (95% CI 85.9-95.0)</td></tr>
<tr><td>Clinical cure at test of cure</td><td></td><td></td></tr>
<tr><td>cUTI</td><td>132/144 (92%)</td><td>129/137 (94%)</td></tr>
<tr><td>cIAI</td><td>8/10 (80%)</td><td>6/11 (55%)</td></tr>
</table>
The most common pathogen identified was E. coli and K pneumoniae for both cUTI and cIAI.

The proportion of patients with a favorable microbiological response at the test of cure for cUTI was higher with ceftazidime/avibactam 82% vs BAT 64%.</td>
<td>Author's Conclusion:
REPRISE provides evidence for the safety and efficacy of ceftazidime/avibactam in the treatment of cUTI and cIAI as an alternative to carbapenems in patients with ceftazidime resistant Enterobacterales and P. aeruginosa.
Comments:
This trial did not include CRE but did include pathogens that have multidrug resistance, showing efficacy in these bacteria.

Larger trials were completed for cIAI and cUTI indications below.</td>
</tr>
</table>

<table>
<tr>
<td>Number of patients:
N=165 assigned to ceftazidime-avibactam (153 with cUTI, 12 with cIAI)
N=168 assigned to BAT (153 with cUTI, 15 with cIAI)</td>
<td>Utilized corresponding CIs for the efficacy of best available therapy to provide a context for descriptive estimates of ceftazidime/avibactam efficacy.</td>
<td>Median duration of treatment was 10 days for cUTI in both arms and 10.5 and 12 days for cIAI.

Adverse events:
Any AE: cUTI 28% in ceftazidime/avibactam group vs 35% in BAT. cIAI-67% vs 80%.
Treatment discontinuation: 1 patient in each arm

Most common AE were nausea, vomiting, and diarrhea.</td>
<td></td>
</tr>
<tr>
<td>Wagenlehner F. et al, 2016 (RECAPTURE)

Design:
Two identical phase 3, randomized, multicenter, double blind, parallel group noninferiority trials evaluating ceftazidime/avibactam vs doripenem for cUTI including pyelonephritis.

Intervention/comparator:
Ceftiazidime/avibactam 2000 mg/500 mg over 2 hours every 8 hours or doripenem 500 mg over 1 hour every 8 hours.

Doses were adjusted for renal function.

Patients meeting prespecified clinical improvement criteria after 5 days of IV therapy could be switched to oral therapies. Total study duration was 10-14 days.

Number of patients:
N=516 randomized to ceftazidime/avibactam
N=517 randomized to doripenem</td>
<td>Inclusion: adult patients hospitalized with cUTI or acute pyelonephritis

Exclusion: complete obstruction of any portion of the urinary tract, perinephric or intrarenal abscess or prostatitis, UTI symptoms attributable to another process, urinary diversion or vesicoureteral reflux, CrCl <30

Statistics: Data from the 2 studies were analyzed as a single dataset. Sample size across the combined study data base ensured 90% power for a 10% noninferiority margin</td>
<td>FDA coprimary endpoint:
(1) proportion of patients with symptomatic resolution of symptoms at day 5 (2) the proportion of patients with microbiological eradication and symptom resolution at test of cure 21-25 days after randomization in microbiologic modified intention to treat population

Secondary endpoints:
Per patient microbiologic response at end of treatment and late follow up (45-52 days post randomization), per patient and per pathogen microbiological response at test of cure
<table>
<tr><th></th><th>Ceftazidime/ Avibactam N=393</th><th>Doripenem N=417</th></tr>
<tr><td>Coprimary endpoint (1)</td><td>70.2%</td><td>66.2%</td></tr>
<tr><td colspan="3">Difference 4.0%, (95% CI -2.39% to 10.42%), met noninferiority</td></tr>
<tr><td>Coprimary endpoint (2)</td><td>71.1%</td><td>64.5%</td></tr>
<tr><td colspan="3">Difference, 6.7% (95% CI 0.30-13.12), met noninferiority</td></tr>
<tr><td>Secondary endpoints</td><td></td><td></td></tr>
<tr><td>Microbial eradication at test of cure (EMA endpoint)</td><td>77.4%</td><td>71.0%</td></tr>
<tr><td colspan="3">Difference 6.4% (95% CI 0.33-12.36%), met noninferiority</td></tr>
<tr><td>Per pathogen favorable microbiologic response</td><td></td><td></td></tr>
<tr><td>Enterobacterales</td><td>299/382 (78.3%)</td><td>281/398 (70.6%)</td></tr>
<tr><td>P. aeruginosa</td><td>12/18 (66.7%)</td><td>15/20 (75.0%)</td></tr>
</table>
The most common pathogen in both arms was E. coli, 78.4% and 71.9%. 18.6% of patients in the ceftazidime/avibactam arm had ESBL positive Enterobacterales, vs 19.7% in the doripenem arm.</td>
<td>Author's Conclusion:
Compared to doripenem, ceftazidime/avibactam is an noninferior for the treatment of cUTI including acute pyelonephritis.

Ceftazidime/avibactam had numerically higher percentage of patients with symptomatic resolution at day 5 and met superiority for microbiologic eradication at test of cure compared to doripenem.

Around 20% of the pathogens in both arms were ESBL positive.</td>
</tr>
</table>

<table>
<tr><td></td><td></td><td>Adverse events:
Serious AE: 21 (4.1%) in ceftazidime/avibactam arm vs 12 (2.4%) in doripenem arm.
Discontinuation of study drug: 7 (1.4%) vs 6 (1.2%)

Most common AE were headaches, nausea, diarrhea, and constipation.</td><td></td></tr>
<tr><td>Mazuski J. et al, 2016 (RECLAIM 1 & 2)

Study design:
2 identical prospective, randomized, multicenter, double blind phase 3 studies noninferiority studies evaluating ceftazidime/avibactam plus metronidazole compared with meropenem for cIAI.

Doses were adjusted for renal function.

Intervention/comparator:
Ceftazidime/avibactam 2000mg/500 mg over 2 hours every 8 hours followed by metronidazole 500 mg IV every 8 hours or meropenem 1000 mg over 30 minutes every 8 hours.

Total duration of treatment was 5-14 days.

Number of patients:
N=532 randomized to ceftazidime/avibactam plus metronidazole
N=534 randomized to meropenem.</td><td>Inclusion:
Adults hospitalized with cIAI requiring surgical intervention or percutaneous drainage within 24 hours before or after randomization

Exclusion:
Diagnosis of traumatic bowel perforation managed operatively within 24 hours , perforation of gastroduodenal ulcers managed operatively within 24 hours, intra-abdominal processes in which the primary cause was unlikely infectious, abdominal wall abscess, bowel obstruction, ischemic bowel without perforation, simple cholecystitis, gangrenous cholecystitis without rupture, simple appendicitis, acute suppurative cholangitis, infected necrotizing pancreatitis or abscess

Statistics:
90% power for a 10% noninferiority margin</td><td>Primary endpoint:
Cure at test of cure 28-35 days after randomization in the microbiologic modified intention to treat population, noninferiority margin of 10%.

<table><tr><th></th><th>Ceftazidime/ Avibactam N=413</th><th>Meropenem N=410</th></tr><tr><td>Cure at test of cure</td><td>81.6%</td><td>85.1%</td></tr><tr><td colspan="3">Difference -3.5% (95% CI -8.64-1.58), met noninferiority</td></tr></table>
Appendiceal perforation/abscess was the most common site of infection and E. coli was the most common pathogen identified (58%). 90% of ceftazidime resistant pathogens had an ESBL, and 3% harbored a metallo beta lactamase.

Patients with moderate renal impairment, CrCl >30 to <50 response trend favored meropenem over ceftazidime/avibactam.

Adverse events:
Serious AE: 5.7% vs 6.8%
Discontinuation of study drug: 2.6% vs 1.3%

Most common AE were wound infections, anemia, headache, diarrhea/nausea</td><td>Author’s Conclusion:
Ceftazidime/avibactam plus metronidazole is an effective treatment for cIAI demonstrated by non-inferiority to meropenem.

Comments:
Patients with moderate renal impairment may have decreased clinical cure compared to meropenem.</td></tr>
</table>

*Two trials not reviewed here have been completed in pediatric patients with cIAI and cUTI, leading to FDA approval for their respective indications.

Studies evaluating the efficacy of ceftolozane/tazobactam[33–35]

Study Design	Methods	Results	Conclusions/Comments
Kollef M. et al, 2019 (ASPECT-NP) **Study design:** Multicenter randomized controlled double-blind phase 3 noninferiority trial evaluating Ceftolozane/tazobactam vs	**Inclusion:** Adults who were intubated/mechanically ventilated and had ventilator associated pneumonia or ventilated hospital acquired pneumonia (at least 48 hours of mechanical ventilation prior)	**Primary endpoint:** All-cause mortality at 28 days in microbiologic modified intention to treat population. **Secondary endpoint:** Clinical response at the test of cure visit (7-14 days after the end of therapy).	**Author’s Conclusion:** High dose Ceftolozane/tazobactam is noninferior to meropenem for critically ill patients with nosocomial pneumonia caused by *P. aeruginosa,* Enterobacteriaceae, and other gram negative lower respiratory tract pathogens. **Comments:**

<table>
<tr>
<td>meropenem for patients with nosocomial pneumonia.

Intervention/comparator:
Ceftolozane/tazobactam 3 g/1g every 8 hours or meropenem 1 gram every 8 hours, both given as 1-hour infusions for 8-14 days.

Adjunctive empiric linezolid 600 mg IV every 12 hours was given to all patients until lower respiratory tract cultures showed the absence of S. aureus.

Adjunctive empiric therapy with amikacin 15mg/kg was permitted for up to 72 hours after the first dose of study drug at sites where >15% of P. aeruginosa isolates were resistant to meropenem.

Doses were adjusted for renal function.

Treatment duration was at the discretion of investigators, but 14 days was recommended for patients with P. aeruginosa.

Number of patients:
N=362 assigned to Ceftolozane/tazobactam group
N=364 assigned to meropenem group</td>
<td>Exclusion:
Baseline gram stain with only gram-positive pathogens, more than 24 hours of treatment within the past 72 hours with active, systemic, or inhaled antibacterial with gram negative activity (included if persistent worsening despite 48 hours of active therapy), more than 24 hours of a carbapenem in the past 7 days, growth of a gram negative pathogen resistant to meropenem or Ceftolozane/tazobactam from a respiratory or blood culture obtained within the past 15 days, diagnoses or comorbidities that could interfere with outcomes (viral pneumonia, lung cancer), active immunosuppression including patients with HIV, transplant patients, continuous renal replacement therapy, or end stage renal disease requiring hemodialysis.

Statistics:
90% power with a 10% noninferiority margin, assuming a 28-day all-cause mortality rate in both groups. Noninferiority would be determined if the lower bound of the 95% CI did not cross the -10% bound for the primary outcome, and -12.5% for the secondary efficacy endpoint.</td>
<td>
<table>
<tr><th></th><th>Ceftolozane/ Tazobactam N=362</th><th>Meropenem N=364</th></tr>
<tr><td>All cause 28-day mortality</td><td>24%</td><td>25.3%</td></tr>
<tr><td colspan="3">Difference 1.1% (95% CI -5.1-7.4), met noninferiority</td></tr>
<tr><td>Secondary endpoints</td><td></td><td></td></tr>
<tr><td>Clinical cure at test of cure</td><td>54.4%</td><td>53.3%</td></tr>
<tr><td colspan="3">Difference 1.1% (95% CI -6.2-8.3), met noninferiority</td></tr>
<tr><td>Per pathogen clinical cure at test of cure</td><td></td><td></td></tr>
<tr><td>ESBL-producing enterobacteriacea</td><td>48/84 (57.1%)</td><td>45/73 (61.6%)</td></tr>
<tr><td>MDR P. aeruginosa</td><td>13/24 (54.2%)</td><td>6/11 (54.5%)</td></tr>
<tr><td>Extensively drug resistant P. aeruginosa</td><td>4/10 (40%)</td><td>2/5 (40%)</td></tr>
</table>
Adverse events:
Serious treatment related adverse events occurred in 8 patients (2%) in the Ceftolozane/tazobactam arm vs 2 (1%) in the meropenem arm.
Leading to study drug discontinuation: 4 (1%) vs 5 (1%)

Most frequent adverse events included C. difficile colitis (1%), diarrhea, LFT abnormalities</td>
<td>Similar outcomes in patients with resistant infections when using higher doses of Ceftolozane/tazobactam including ESBL and multidrug resistant P. aeruginosa. Numerically higher number of patients had test of cure with meropenem in ESBL producing pathogens vs Ceftolozane/tazobactam, despite lower dosing of meropenem (no extended infusion either).</td>
</tr>
<tr>
<td>Solomkin J. et al, 2015 (ASPECT-cIAI)

Study design:
Two identical multicenter, prospective, randomized, double blind placebo-controlled phase 3 noninferiority trials evaluating Ceftolozane/tazobactam plus metronidazole vs meropenem for the treatment of cIAI.

Intervention/comparator:</td>
<td>Inclusion:
Adult with clinical evidence of cIAI, operative or percutaneous drainage of an infectious focus was either planned or had been recently performed (24 hours) confirming the presence of cIAI.

Exclusion:
Staged abdominal repair in which the fascia was not closed, Crcl <30 ml/min, use of systemic antibiotics for >24 hours prior to the first dose of study drug (unless the treatment failed)</td>
<td>Primary endpoint:
Clinical cure at the test of cure (24-32 days from start of therapy) in the microbiologic modified intention to treat population.

Secondary endpoints:
Clinical cure rates in ESBL producing pathogens (supplementary tables).
<table>
<tr><th></th><th>Ceftolozane/ Tazobactam N=389</th><th>Meropenem N=417</th></tr>
<tr><td>Primary outcome</td><td>83.0%</td><td>87.3%</td></tr>
<tr><td colspan="3">Difference -4.2% (95% CI -8.91 – 0.54), met noninferiority</td></tr>
</table>
</td>
<td>Author's Conclusion:
Ceftolozane/tazobactam plus metronidazole is noninferior to meropenem for the treatment of cIAI, especially when resistant Enterobacteriaceae or P. aeruginosa are suspected.

Comments: Only 7.2% of isolates were ESBL producing and 5.7% of pseudomonas was classified as MDR.

In subgroup analysis in patients with renal insufficiency, ceftolozane/tazobactam plus</td>
</tr>
</table>

<table>
<tr>
<td>Ceftolozane/tazobactam 1 gram/500 mg plus metronidazole 500 mg IV every 8 hours or meropenem 1 gram every 8 hours plus placebo.

Doses were adjusted for renal function.

Treatment duration was 4-14 days.

Number of patients:
N=489 in Ceftolozane/tazobactam arm
N=506 in meropenem arm</td>
<td>Statistics:
Analysis was planned based on the pooled data from the 2 trials, meeting 90% power to demonstrate noninferiority at a 10% margin.</td>
<td>
<table>
<tr><td>Secondary endpoint</td><td></td><td></td></tr>
<tr><td>Clinical cure in ESBL producing Enterobacteriacae</td><td>23/24 (95.5%)</td><td>23/26 (88.5%)</td></tr>
</table>
The most common origin of infection was the appendix (46%, 49.2%)

Adverse events:
Any: 212 (44%) vs 212 (42.7%).

Most common adverse events were nausea, diarrhea, vomiting, pyrexia</td>
<td>metronidazole resulted in a lower clinical cure rate of 69% (69/100) compared to 82.4% (70/85) in the meropenem arm.</td>
</tr>
<tr>
<td>Wagenlehner F. et al, 2015 (ASPECT-UTI)

Study design:
Two identical phase 3 multicenter, prospective, randomized, double blind, noninferiority trials evaluating ceftolozane/tazobactam vs levofloxacin for cUTI.

Intervention/comparator:
Ceftolozane/tazobactam 1.5 grams IV every 8 hours vs levofloxacin 750 mg IV daily

Doses were adjusted for renal function.

Treatment duration was 7 days.

Number of patients:
N=543 assigned to ceftolozane/tazobactam
N=540 assigned to levofloxacin</td>
<td>Inclusion:
Adults with pyuria, a diagnosis of pyelonephritis or complicated lower UTI, hospital admission, pretreatment baseline urine culture obtained within 36 hours before the first dose of study drug

Exclusion:
Concomitant infections that required treatment with non-study drugs or require a duration of treatment >7 days, or received non-study antibiotic within 48 hours before baseline urine culture

Statistics:
Analysis based on pooled data from the 2 trials, meeting 90% power to show a noninferiority margin of 10%</td>
<td>Primary endpoint: composite of microbiological eradication and clinical cure 5-9 days after treatment in the modified intention to treat population, noninferiority margin 10%.

Secondary endpoints:
composite cure in subgroups
<table>
<tr><td></td><td>Ceftolozane/ Tazobactam N=398</td><td>Levofloxacin N=402</td></tr>
<tr><td>Primary outcome</td><td>76.9%</td><td>68.4%</td></tr>
<tr><td colspan="3">Difference 8.5% (95% CI 2.3-14.6), met noninferiority</td></tr>
<tr><td>Microbiologic eradication</td><td>80.4%</td><td>72.1%</td></tr>
<tr><td>Clinical Cure</td><td>92.0%</td><td>88.6%</td></tr>
<tr><td>Secondary endpoints</td><td></td><td></td></tr>
<tr><td>Composite cure per diagnosis</td><td></td><td></td></tr>
<tr><td>cUTI</td><td>47/70 (67.1%)</td><td>35/74 (47.3%)</td></tr>
<tr><td>Pyelonephritis</td><td>259/328 (79.0%)</td><td>240/328 (73.2%)</td></tr>
<tr><td>Composite cure in patients with ESBL</td><td>38/61 (62.3%)</td><td>20/57 (35.1%)</td></tr>
</table>
Adverse events:
Any: 185/533 (34.7%) vs 184/535 (34.4%).
Most common adverse events were headache, constipation, nausea, and diarrhea</td>
<td>Author’s conclusions:
Ceftolozane/tazobactam was superior to levofloxacin for composite cure rates in patients with cUTI.

Comments:
Most patients had pyelonephritis (82%), few patients with P. aeruginosa (2.9%)

The difference in cure rates was likely due to a greater prevalence of levofloxacin resistance</td>
</tr>
</table>

Studies evaluating the efficacy of imipenem/cilastatin/relebactam[36,37]

Study Design	Methods	Results	Conclusions/Comments
Motsche J. et al, 2020 (RESTORE-IMI 1)	**Inclusion:** hospitalized adults requiring IV antibacterial treatment for HAP/VAP, cUTI, or cIAI caused	**Primary endpoint:**	**Author’s conclusions:**

<table>
<tr>
<td>Study design:
Randomized, controlled, double-blind, non-inferential descriptive phase 3 trial evaluating <u>imipenem/relebactam vs colistin based therapies for imipenem non susceptible serious infections.</u>

Intervention/comparator:
Imipenem/cilastatin/relebactam (IMI/REL) 500/500/250 mg every 6 hours over 30 minutes vs imipenem 500 mg every 6 hours and colistin.

Doses were adjusted for renal function.

Minimum treatment duration was 5 days for cIAI and cUTI, or 7 days for HAP/VAP, with a 21-day duration maximum.

Number of patients:
N=31 imipenem/relebactam
N=16 colistin/imipenem</td>
<td>by imipenem non-susceptible, imipenem/relebactam-susceptible and colistin-susceptible pathogens and lacking clinical improvement on any prior therapy

Exclusion:
APACHE 2 score >30, CrCl<15 ml/min, requiring hemodialysis or peritoneal dialysis, concomitant systemic/inhaled agents active against Enterobacterales, Pseudomonas spp., and gram-negative anaerobic bacilli, prior colistin based therapy, pulmonary obstructions, and complete obstruction of any portion of the urinary tract in cUTI

Statistics:
Descriptive trial without formal statistical testing for efficacy endpoints</td>
<td>Overall response in the modified intent to treat population (HAP/VAP-28 day all cause mortality, cIAI day 28 clinical response, cUTI-composite clinical and microbiologic response early follow up).

Secondary endpoints:
28-day clinical response, 28 day all cause mortality, treatment emergent nephrotoxicity

<table>
<tr><th></th><th>Imipenem/ Relebactam N=21</th><th>Colistin/ Imipenem N=10</th></tr>
<tr><td>Primary outcome</td><td>71.4% (49.8,86.4)</td><td>70.0% (39.2, 89.7)</td></tr>
<tr><td>NP</td><td>7/8 (87.5%)</td><td>2/3 (66.7%)</td></tr>
<tr><td>cIAI</td><td>0/2 (0%)</td><td>0/2 (0%)</td></tr>
<tr><td>cUTI</td><td>8/11 (72.7%)</td><td>5/5 (100%)</td></tr>
<tr><td>Secondary endpoints</td><td></td><td></td></tr>
<tr><td>Favorable clinical response at day 28</td><td>71.4%</td><td>40.0%</td></tr>
<tr><td>28-day all-cause mortality</td><td>9.5%</td><td>30.0%</td></tr>
<tr><td>Treatment-emergent nephrotoxicity</td><td>3/29 (10.3%)</td><td>9/16 (56.3%)</td></tr>
<tr><td>Most common pathogens</td><td></td><td></td></tr>
<tr><td>P. aeruginosa</td><td>16 (76.2%)</td><td>8 (80%)</td></tr>
<tr><td>K. pneumoniae</td><td>3 (14.3%)</td><td>1 (10%)</td></tr>
</table>

Adverse events
Drug related: 5/31 (16.1%) vs 5/16 (31.3%)
Discontinued drug: 0/0 (0%) vs 3/16 (18.8%)
Most common treatment emergent adverse events were pyrexia, increased LFTs, nausea, decreased CrCl.</td>
<td>Imipenem/relebatam is efficacious and well tolerated in the treatment of carbapenem-non susceptible infections

Comments:
Overall 28-day all-cause mortality was lower in the imipenem/relebactam group 9.5% compared to colistin/imipenem 30%, but these results are limited by small sample sizes.

Treatment emergent nephrotoxicity was lower in the imipenem/relebactam group 10% compared to colistin/imipenem 56.3%.</td>
</tr>
<tr>
<td>Titov I. et al, 2020 (RESTORE-IMI 2)

Study design:
Randomized, controlled, double blind, multicenter phase 3 noninferiority trial evaluating <u>Imipenem/relebactam vs piperacillin/tazobactam for HABP/VABP.</u>

Intervention/comparator:
Imipenem/cilastatin/relebactam (IMI/REL) 500/500/250 mg or piperacillin/tazobactam (PIP/TAZ)</td>
<td>Inclusion:
Adults with HABP/VABP

Exclusion:
>24 hours of effective antibiotic therapy for the current episode within 72 hours prior to randomization (unless they failed therapy), baseline culture with only gram positive cocci, CrCl <15 ml/min or need for dialysis, confirmed or suspected community acquired, viral, fungal, or parasitic pneumonia, pneumonia caused by any airway obstructive process including lung cancer, immunosuppression, expected survival <72 hours, concurrent conditions including</td>
<td>Primary endpoint:
28-day all-cause mortality in the modified intention to treat population

Secondary endpoints:
Favorable clinical response at early follow up (resolution of baseline HABP/VABP signs/symptoms and no non-study antibacterial therapy, 7-14 days after end of therapy)

<table>
<tr><th></th><th>Imipenem/ Relebactam N=264</th><th>Piperacillin/ tazobactam N=267</th></tr>
<tr><td>28-day all-cause mortality</td><td>15.9%</td><td>21.3%</td></tr>
<tr><td colspan="3">Difference -5.3 (95% CI -11.9-1.2), met noninferiority</td></tr>
</table>
</td>
<td>Author’s conclusions:
Imipenem/cilastatin/relabactam is noninferior to piperacillin/tazobactam for treating HABP/VABP in adults. Both agents appeared well tolerated.

Comments:
Did not include resistant pathogens.</td>
</tr>
</table>

4g/500 mg IV over 30 minutes every 6 hours All patients received empiric linezolid 600 mg IV every 12 hours until baseline respiratory cultures confirmed the absence of MRSA; if MRSA was present, linezolid was continued for ≥7 days, ≥14 days for bacteremia. Doses were adjusted for renal function. Duration of treatment was 7-14 days. 14 days was required if infection was due to *P. aeruginosa* or concurrent bacteremia. **Number of patients:** N=268 randomized to IMI/REL N=269 randomized to PIP/TAZ	tuberculosis, cystic fibrosis, or endocarditis, anticipated need for specific medications including non-study antibiotics: valproate, selective serotonin reuptake inhibitors, serotonin-norepinephrine reuptake inhibitors, or monoamine oxidase inhibitors **Statistics:** 90% power to detect 10% noninferiority margin for primary endpoint, 84% power for 12.5% noninferiority margin for secondary endpoints	Secondary endpoint Favorable clinical response at early follow up: 61.0% vs 55.8% Difference 5.0 (95% CI -3.2-13.2), met noninferiority 28-day all-cause mortality per pathogen Enterobacterales: 8/68 (11.8%) vs 13/66 (19.7%) *P. aeruginosa*: 5/15 (33.3%) vs 3/25 (12.0%) **Adverse events:** Drug related:31/266 (11.7%) vs 26/269 (9.7%) Drug discontinuation due to AE: 15/266 (5.6%) vs 22/269 (8.2%)	

Studies evaluating the efficacy of meropenem/vaborbactam[38,39]

Study Design	Methods	Results	Conclusions/Comments
Wunderink R. et al, 2018 (TANGO II) **Study design:** Phase 3, randomized, multicenter, open label, descriptive trial evaluating meropenem/vaborbactam compared to best available treatment (BAT) for serious **CRE infections.** **Intervention/comparator:** Meropenem/vaborbactam 2g/2g over 3 hours every 8 hours or BAT (mono/combination therapy with polymyxins, carbapenems, aminoglycosides, tigecycline, or ceftazidime/avibactam alone).	**Inclusion:** Adults with cUTI/AP, HABP/VABP, bacteremia, cIAI and confirmed or suspected CRE pathogen. Patients on HD and immunosuppression were allowed. **Exclusion:** History of hypersensitivity to beta-lactams, confirmed infection with CRE producing metallo, Verona integron-encoded, or Oxa-48 beta-lactamases, APACHE 2 >30, immediately life-threatening disease, CRRT **Statistics:** Descriptive study, no formal power or sample size calculations. Ad hoc inferential testing was performed for select outcomes utilizing Wald test of equality.	**Primary endpoint:** The proportion of patients in the microbiologic CRE modified intention to treat population that achieved overall success (composite of clinical cure and microbiologic eradication) at test of cure (7 days after) in the cUTI/AP subgroup, all cause mortality in the combined HABP/VABP and bacteremia subgroups, and the proportion of patients with clinical cure at test of cure at end of treatment in the cIAI subgroup. **Secondary endpoints:** Adverse events, exploratory risk/benefit analyses of composite clinical failure and nephrotoxicity Meropenem/vaborbactam N=32 vs Best available treatment N=15 Day-28 All-cause Mortality Bacteremia/HABP Combined: 4/20 (22.2%) vs 4/9 (44.4%) Bacteremia: 4/14 (28.6%) vs 3/8 (37.5%)	**Author's conclusions:** Monotherapy with meropenem/vaborbactam for serious CRE infections was associated with increased clinical cure, decreased mortality, and reduced nephrotoxicity compared to BAT. **Comments:** First trial evaluating monotherapy of intervention vs BAT. Included immunocompromised patients (40.4%), representing real world practice. Small numbers of patients for each infection type. Most common was bacteremia. Only 1 patient received ceftazidime/avibactam. More patients with prior antibiotic failure were randomized to meropenem/vaborbactam arm (28.1% vs 0%). Sensitivity analyses excluding these patients was done showing increased treatment effect of meropenem/vaborbactam over

Doses were adjusted for renal function. Duration of treatment was 7-14 days **Number of patients:** N=52 randomized to meropenem/vaborbactam N=25 randomized to BAT		<table><tr><td>HABP/VABP</td><td>0/4 (0%)</td><td>1/1 (100%)</td></tr><tr><td>Overall success at test of cure cUTI</td><td>4/12 (33.3%)</td><td>2/4 (50.0%)</td></tr><tr><td>Clinical cure at test of cure cIAI</td><td>2/2 (100%)</td><td>0/2 (0.0%)</td></tr><tr><td>Overall mCRE-MITT Population</td><td></td><td></td></tr><tr><td>Day-28 all-cause mortality</td><td>15.6%</td><td>33.3%</td></tr><tr><td>Clinical cure at end of treatment</td><td>65.6%</td><td>33.3%</td></tr><tr><td>Clinical cure at test of cure</td><td>59.4%</td><td>26.7%</td></tr><tr><td>Microbiologic cure at end of treatment</td><td>65.6%</td><td>40.0%</td></tr><tr><td>Microbiologic cure at test of cure</td><td>53.1%</td><td>33.3%</td></tr></table> A trend towards significance was found for clinical cure at end of treatment and test of cure (p= 0.03, 0.02). Day 28 mortality was not significantly different (p=0.20), but under the sensitivity analyses excluding prior antibiotic failure it was (p=0.02). The most common infection types: bacteremia 43% vs 53% The most frequent pathogen was *K. pneumoniae* (87.2%, 72.7% of isolates KPC producing) **Adverse events:** Drug related: 24% vs 44% Drug discontinuation: 10% vs 12% Renal related treatment emergent: 4% vs 24%	BAT (clinical cure at test of cure 69.6% vs 26.7, all cause mortality 4.3% vs 33.3%).
Kaye K. et al, 2017 (TANGO I) **Study design:** Phase 3, randomized, multicenter, double-blind, non-inferiority trial with patients stratified by infection type and geographic region evaluating meropenem/vaborbactam compared to piperacillin/tazobactam for **cUTI.** **Intervention/comparator:** Meropenem/vaborbactam 2g/2g over 3 hours every 8 hours or piperacillin/tazobactam 4g/0.5 g over 30 minutes every 8 hours	**Inclusion:** Adults 185 kg or less who needed 5 or more days of IV antibiotics and had documented or suspected cUTI or pyelonephritis. **Exclusion:** Requirement of an antibiotic in addition to study drug or antifungal therapy, received antibiotics within 48 hours before randomization (except for single dose of short actin goral or IV antibiotic), CrCl <30 ml/min. Patients who received more than 48 hours of an antibiotic could be included if they had treatment failure.	**Primary endpoint:** FDA endpoint: overall success as a composite of clinical cure (resolution of symptoms) and microbial eradication at the end of intravenous treatment in the microbiologic modified intention to treat population. **Secondary endpoints:** Proportion of patients with overall success at end of treatment per infection type, microbial eradication at test of cure (7 days after end of treatment), outcomes by pathogen and MIC <table><tr><td></td><td>Meropenem/ vaborbactam N=192</td><td>Piperacillin/ tazobactam N=182</td></tr></table>	**Author's conclusions:** In patients with cUTI, meropenem/vaborbactam vs piperacillin/tazobactam resulted in a composite outcome of complete resolution or improvement of symptoms along with microbial eradication that met noninferiority. **Comments:** Was not designed to evaluate therapy for the treatment of CRE. Meropenem/vaborbactam was administered as an extended infusion, piperacillin/tazobactam was not. ≈12% of Enterobacteriaceae were resistant to piperacillin/tazobactam at baseline, there was no

Doses were adjusted for renal function. After 15 or more doses of IV therapy and criteria for improvement were met, patients could be switched to oral levofloxacin to complete 10 days of total treatment (14 days if bacteremia present). **Number of patients:** N=274 randomized to meropenem/vaborbactam N=276 randomized to piperacillin/tazobactam	**Statistics:** 90% power for noninferiority margin of 15% for primary end point. Was not powered to demonstrate noninferiority for secondary endpoints.			apparent relationship between MIC and overall success, clinical cure, or microbial eradication.

Primary endpoint	98.4%	94.0%
Difference 4.5 (95% CI 0.7-9.1), met noninferiority		
Clinical Cure	98.4%	95.6%
Microbial eradication	97.9%	95.6%
Secondary endpoints		
Microbial eradication at test of cure	68.8%	62.1%
Overall success at end of treatment		
Acute pyelonephritis	97.5%	94.1%
cUTI, removable source of infection	100%	92.1%
cUTI, nonremovable source of infection	100%	95.3%

85.9% of patients in the meropenem/vaborbactam group and 84.6% in the piperacillin/tazobactam group had Enterobacterales as a baseline pathogen. No isolates of *P. aeruginosa* were reported.

Mean duration of treatment IV therapy was 8.0 days in both groups. Mean duration of IV and oral step-down therapy was 10.1 days vs 9.9 days.

93.6% of patients in the meropenem/vaborbactam group and 95.1% in the piperacillin/tazobactam group received levofloxacin step down therapy. 9.9% and 8.2% of isolates in each group were resistant to levofloxacin.

Adverse events:
Drug related: 15.1% and 12.8%
Severe AE: 2.6% and 4.8%
Drug discontinuation due to AE: 2.6% and 5.1%

Studies evaluating the efficacy of plazomicin[40,41]

Study Design	Methods	Results	Conclusions/Comments
Wagenlehner F. et al, 2019 (EPIC) **Study design:**	**Inclusion:** Adults less than 150 kg with CrCl >30 ml/min, pyuria, clinical symptoms of cUTI or acute pyelonephritis that would require at least 4	**Primary endpoint:** Composite of (1) clinical cure and microbiologic eradication at day 5 and (2) at the test of cure visit (15-19 days after initiation of therapy) in the microbiologic modified intention to treat population.	**Author's conclusions:** Plazomicin is noninferior to meropenem in the treatment of patients with cUTIs including pyelonephritis, with higher rates of microbiologic eradication and composite cure observed at the test

Phase 3, randomized, multicenter, double blind, noninferiority study evaluating Plazomicin vs meropenem for the treatment of **cUTI.**

Intervention/comparator:
Plazomicin 15 mg/kg (adjusted body weight) once daily or meropenem 1 g every 8 hours.

Optional oral step-down therapy (levofloxacin preferred, others allowed) after at least 4 days IV therapy was allowed.

Doses were adjusted for renal function.

Total duration of treatment was 7-10 days.

Number of patients:
N=306 randomized to plazomicin
N=303 randomized to meropenem

days of IV therapy, pretreatment baseline urine culture

Exclusion:
perinephric abscess, prostatitis, obstruction of urinary tract, receipt of a therapeutic agent 48 hours prior to randomization, fungal infection, known colonization with gram positive pathogens, pathogens resistant to meropenem, immunocompromised, pathogens that were resistant to the comparator.

Statistics: 85% power to show noninferiority with a margin of 15% for primary outcomes.

Secondary endpoints:
Composite cure according to patient subgroup, composite cure at late follow up (24-32 days), microbiologic response at test of cure according to pathogen

	Plazomicin N=191	Meropenem N=197
Composite at day 5	88.0%	91.4%
Difference -3.4 (95% CI -10-3.1), met noninferiority		
Clinical Cure	89.5%	92.4%
Microbial eradication	98.4%	98.0%
Composite at test of cure	81.7%	70.1%
Difference 11.6 (95% CI 2.7-20.3), met noninferiority		
Clinical cure	89.0%	90.4%
Microbial eradication	89.5%	74.6%
Secondary endpoints		
Composite cure at test of cure		
cUTI	82/119 (68.9%)	84/107 (78.5%)
Acute pyelonephritis	56/78 (71.8%)	72/84 (85.7%)
Composite cure at late follow up	77.0%	60.4%
Microbial eradication at test of cure		
ESBL	42/51 (82.4%)	45/60 (75%)
MDR	44/57 (77.2%)	45/65 (70.3%)

The majority of patients had cUTI 56.0% and 60.4%.

The mean duration of IV therapy was 5.5 days in each group. Combined with oral therapy, mean duration was 9.2 days and 8.9 days. Most patients received oral step-down therapy 80.6% and 76.6%.

Adverse events:
Any AE: 19.5% vs 21.6%
Drug discontinuation: 2% in each arm

Most frequent adverse events were diarrhea, hypertension, headache, nausea, vomiting, hypotension.

Adverse events related to renal function:

	Plazomicin N=303	Meropenem N=301
AE related to renal function	11 (3.6%)	4 (1.3%)
Increase in Scr >0.5 mg/dl	21/300 (7.0%)	12/297 (4.0%)

of cure in the Plazomicin arm, suggesting that Plazomicin has greater clinical benefit.

Comments:
This is the only trial that excluded patients from the modified intention to treat population who had pathogens that were resistant to the comparator (not biased toward Plazomicin)

Therapeutic drug monitoring was not done.

High number of resistant pathogens included (MDR/ESBL, lower number of carbapenem resistant)

Risk factors for decreased renal function were consistent with drug accumulation.

No pseudomonas isolates reported.

<table>
<tr><td></td><td></td><td><table><tr><td>Full recovery at last follow up</td><td>9/11 (81.8%)</td><td>9/9 (100%)</td></tr></table>
Potentially ototoxic events occurred in 1 patient in each group.</td><td></td></tr>
<tr><td>McKinnell J. et al, 2019 (CARE)

Study design:
Phase 3, randomized, multicenter, double blind, study evaluating Plazomicin vs best available treatment (BAT) for serious CRE infections.

Intervention/comparator:
Plazomicin 15 mg/kg or colistin in combination with meropenem or tigecycline.

Duration of treatment was 7-14 days.

Number of patients:
N=18 plazomicin
N=21 colistin</td><td>Inclusion:
Adults with bacteremia, HABP/VABP or cUTI with suspected CRE infection

Exclusion:
APACHE II score >30, receipt of potentially effective therapy >72 hours before randomization, HD/CRRT

Statistics:
Secondary to the small sample size, no formal hypothesis testing was performed.</td><td>Primary endpoint:
Composite of death from any cause at 28 days or clinically significant disease related complications in the microbiologic modified intention to treat population.

Secondary endpoints:
Time to death.

<table><tr><th></th><th>Plazomicin N=17</th><th>Meropenem N=20</th></tr><tr><td>Composite endpoint</td><td>4 (24%)</td><td>50%</td></tr><tr><td>Bacteremia</td><td>2/14 (14%)</td><td>8/15 (53%)</td></tr><tr><td>HABP/VABP</td><td>2/3 (67%)</td><td>2/5 (40%)</td></tr><tr><td>Composite at test of cure</td><td>81.7%</td><td>70.1%</td></tr><tr><td colspan="3">Difference 11.6 (95% CI 2.7-20.3), met noninferiority</td></tr></table>
Numerically fewer deaths at day 14 in the plazomicin arm compared to BAT.

Adverse events:
Serious AE: 9/18 (50%) vs 17/21 (81%)
Increase in Scr >0.5 mg/dL 2/12 (16.7%) vs 8/16 (50%)</td><td>Author’s conclusions:
Combined with evidence from EPIC, this trial provides information about the use of Plazomicin in patients with serious infections caused by CRE who have limited treatment options.

Comments:
The trial was stopped prematurely because of slow enrollment limiting any conclusions.</td></tr>
</table>

Guideline[3]	Recommendations

Infectious Diseases Society of America Antimicrobial Resistant Treatment Guidance: Gram-Negative Bacterial Infections
 	
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	CRE:
	• **Cystitis**
	  ○ Preferred: Ciprofloxacin, levofloxacin, trimethoprim/sulfamethoxazole, nitrofurantoin, or a single-dose of an aminoglycoside, meropenem only if ertapenem resistant, meropenem susceptible, and carbapenemase negative.
	  ○ Alternative: Ceftazidime/avibactam, meropenem/vaborbactam, imipenem/cilastatin/relebactam, cefiderocol, colistin (if no alternatives)
	• **Pyelonephritis or cUTI**
	  ○ Preferred: Ceftazidime/avibactam, meropenem/vaborbactam, imipenem/cilastatin/relebactam, cefiderocol, meropenem extended infusion if ertapenem resistant, meropenem susceptible and carbapenemase negative
	  ○ Alternative: once daily aminoglycosides
	• **Infections outside of the urinary tract:**
	  ○ Preferred: (resistant to meropenem): Ceftazidime/avibactam, meropenem/vaborbactam, imipenem/cilastatin/relebactam
	  ○ Alternative: cefiderocol, tigecycline, eravacycline
	• **KPC positive:**
	  ○ Preferred: Ceftazidime/avibactam, meropenem/vaborbactam, imipenem/cilastatin/relebactam
	  ○ Alternative: Cefiderocol, tigecycline, eravacycline
	• **Metallo-β-lactamase positive:**
	  ○ Preferred: Ceftazidime/avibactam + aztreonam, cefiderocol

	○ Alternative: tigecycline, eravacycline • **Oxa-48-like positive** ○ Preferred: Ceftazidime/avibactam ○ Alternative: cefiderocol, tigecycline, eravacycline **DTR-*P*** • **Cystitis** ○ Preferred: Ceftolozane/tazobactam, ceftazidime/avibactam, imipenem/relebactam, cefiderocol, or a single-dose of an aminoglycoside ○ Alternative: Colistin • **Pyelonephritis or cUTI** ○ Preferred: Ceftolozane/tazobactam, ceftazidime/avibactam, imipenem/relebactam, cefiderocol ○ Alternative: once daily aminoglycosides • **Infections outside of the urinary tract:** ○ Preferred: Ceftolozane/tazobactam, ceftazidime/avibactam, imipenem/relebactam ○ Alternative: cefiderocol, aminoglycoside monotherapy limited to uncomplicated BSI with source control

Safety: Warnings, Precautions, and Adverse Effects [13–24]

	Cefiderocol	Ceftazidime/ avibactam	Ceftolozane/ tazobactam	Imipenem/ cilastatin/ relebactam	Meropenem/ vaborbactam	Plazomicin
Contraindications	Hypersensitivity to β-lactams	Hypersensitivity to β-lactams	Hypersensitivity to β-lactams	Hypersensitivity to β-lactams	Hypersensitivity to β-lactams	Hypersensitivity to aminoglycosides
Warnings/Precautions						
Adverse effects	Neurotoxicity *C. difficile* associated diarrhea	Neurotoxicity *C. difficile* associated diarrhea	*C. difficile* associated diarrhea	Neurotoxicity *C. difficile* associated diarrhea	Neurotoxicity *C. difficile* associated diarrhea	*C. difficile* associated diarrhea **Boxed Warnings:** Nephrotoxicity Ototoxicity Neuromuscular blockade Pregnancy
Disease-related	Increase in all-cause mortality in patients with CRE	cIAI: adults with CrCl 30-50 ml/min had lower cure rates. Dose that is approved is higher than what was used in trial. No clinical difference in patients with cUTI	cIAI: adults with CrCL 30-50 ml/min had lower cure rates. No clinical difference in patients with cUTI	Increased seizure potential due to interaction with valproic acid	Increased seizure potential due to interaction with valproic acid	Caution in patients with hearing loss, neuromuscular disorders (myasthenia gravis), or renal impairment
Use in special populations						
Pregnancy	Not established, animal models have not demonstrated toxicity	Not established, animal models have not demonstrated toxicity	Not established, animal models have not demonstrated toxicity	Not established, embryonic loss and fetal abnormalities observed in animal models	Not established, fetal malformations observed in animal models	Can cause fetal harm
Lactation	Not established, present in animal models	Ceftazidime is excreted. Significance is unestablished	Not established	Not established, relebactam present in animal models	Meropenem is excreted. Unknown if vaborbactam is. Significance unestablished	Not established, present in animal models
Pediatric	Not established	Approved in patients 3 months-18 years for cUTI and cIAI. Safety similar to adults	Not established	Not established	Not established	Not established
Geriatric	No overall differences in safety or efficacy. Monitor renal function	Increased avibactam AUC. Decreased efficacy for cIAI in renal impairment	Increased adverse events noted. Decreased efficacy for cIAI in renal impairment	No overall differences in safety or efficacy. Monitor renal function	No overall differences in safety or efficacy. Monitor renal function	Increased adverse events noted. Increased toxicity in renal impairment
Renal Impairment	Dosage adjustment required for CrCl <60 ml/min	Dosage adjustment required for CrCl <50 ml/min	Dosage adjustment required for CrCl <50 ml/min	Increased seizure risk with renal impairment. Dose adjustment required for CrCl <90 ml/min	Increased seizure risk and thrombocytopenia with renal impairment. Dose adjustment required for CrCl <50 ml/min	For CrCl > 15 - <90 ml/min, therapeutic drug monitoring is recommended
Hepatic Impairment	Not expected to alter elimination	Not expected to alter elimination	Not expected to alter elimination	Not expected to alter elimination	Not expected to alter elimination	Unknown

Abbreviations: cIAI, complicated intra-abdominal infections; cUTI, complicated urinary tract infections including pyelonephritis; CrCl, creatinine clearance

Incidence of adverse effects varied based off the indication studied. Generally, cefiderocol and β-lactam/β-lactamase inhibitors have similar adverse effects compared to other carbapenems and cephalosporins. The most common side effects include nausea, vomiting, diarrhea, constipation, headache, electrolyte disturbances, and skin rash (<10%). The table below represents adverse reactions occurring ≥10%. At HAP/VAP dosing, ceftolozane/tazobactam is associated with renal failure syndrome occurring ≤9%. For plazomicin, the most common adverse reaction was decreased renal function, which occurred ≤4%.

Adverse Effect	Cefiderocol	Ceftazidime/ avibactam	Ceftolozane/ tazobactam	Imipenem/ cilastatin/ relebactam	Meropenem/ vaborbactam	Plazomicin
Elevations in liver function tests			X (HAP/VAP dosing)	X		
+ Direct Coombs test		X	X			
Anemia				X		

Interactions[19–24]

	Cefiderocol	Ceftazidime/ avibactam	Ceftolozane /tazobactam	Imipenem/ cilastatin/ relebactam	Meropenem/ vaborbactam	Plazomicin
↑ nephrotoxicity or ototoxicity						
aminoglycosides	+	+	+			
others						Amphotericin B, arbekacin, ataluren, vancomycin, tacrolimus, methoxyflurane, mannitol, loop diuretics, foscarnet, cyclosporine, oxatomide, cisplatin, colistimethate, cephalosporins, carboplatin
↑ effect of						
Vitamin K antagonists	+	+	+			
Others						+ Tenofovir, NMB, mecamylamine, bisphosphonate, botulinum toxin containing products
↓ effect of						
lactobacillus/estriol	+	+	+	+	+	+
BCG	+	+	+	+	+	+
sodium picosulfate	+	+	+	+	+	+
vaccines	+	+	+	+	+	+
valproate products	-	-	-	+	+	-
cyclosporine	-	-	-	+	-	-
aminoglycosides	-	+	+	+	-	-
						distigmine
↑ serum conc of focus agent						
Probenecid	+	+	+	+	+	
Others		Nitisinone, pretomanid, teriflunomide		ganciclovir/valganciclovir, cyclosporine		NSAIDS (decrease excretion)
↓ serum conc of focus agent						
Others		chloramphenicol				penicillins
Other interactions						
Other						capreomycin
Lab interactions						
False + dipstick tests (urine protein, glucose, ketones, occult blood)	+					

Abbreviations: NMB, neuromuscular blockers, Vaccines: Cholera, Typhoid, BCG

Dosage and Administration [13–24]

	Cefiderocol	Ceftazidime/ avibactam	Ceftolozane/ tazobactam		Imipenem/ cilastatin/ relebactam	Meropenem/ vaborbactam	Plazomicin
Indication (Adult)							
cUTI	2g q8h	2.5 g q8h	1.5g q8h		1.25g q6h	4g q8h	15 mg/kg once daily
HABP/VABP	-	2.5 g q8h	3g q8h		1.25g q6h	-	-
cIAI	2g q8h	2.5 g q8h	1.5g q8h		1.25g q6h	-	-
Infusion duration	3 h	2 h	1 h		30 min	3 h	30 min
Renal Adjustment (CrCl ml/min)			Usual dose= 1.5g q8h	Usual dose=3g q8h			
≥ 120	2g q6h	-	-	-	-	-	-
60 - ≤120	2g q8h	-	-	-	-	-	-
60-89	-	-	-	-	1g q6h	-	-
31 – 50	-	1.25g q8h	-	-	-	1.25g q8h	-
30-50	-	-	750mg q8h	1.5g q8h	-	-	-
30-59	-	-	-	-	750mg q6h	-	-
30 - ≤60	1.5g q8h	-	-	-	-	-	10mg/kg q24h
15-29	-	-	375mg q8h	750 mg q8h	500 mg q6h	-	-
16-30	-	0.94g q12h	-	-	-	0.94g q12h	-
15 - ≤30	1g q8h	-	-	-	-	-	10mg/kg q48h
≤15	750mg q12h	-	Not studied		Do not use	0.94g q24h	Not studied
6-15	-	0.94 g q24h	-	-	-	-	-
≤5	-	0.94g q48h	-	-	-	-	-
Hemodialysis	750 mg q12h	0.94g q24-48h	Refer to labeling		500mg q6h	0.94g q24-48h	-

The above medications are administered intravenously. Ceftazidime/avibactam has approved indications for pediatric patients ≥3 months old. Refer to packaging labeling for specific dosing. None of the above medications have dosage adjustments indicated for geriatric patients. Plazomicin should be dosed based off total body weight. For patients with TBW greater than IBW by 25% or more, use adjusted body weight.

Monitoring Parameters [19–24]

For cefiderocol and the β-lactam/β-lactamase drugs, observe for signs and symptoms of anaphylaxis during the first dose. Renal function (serum creatinine) and creatinine clearance should be obtained at baseline in all patients and at least daily in patients with changing renal function. For plazomicin, patients with CrCl >15 ml/min to <90 ml/min, a plasma trough concentration should be measured 30 minutes prior to second dose. If trough concentration is >3 mcg/mL, dosing interval should be extended by 1.5-fold. Additionally, monitor for symptoms of ototoxicity or neuromuscular blockade.

How Supplied/Cost

	Cefiderocol	Ceftazidime /avibactam	Ceftolozane/ tazobactam†	Imipenem/ cilastatin/ relebactam	Meropenem/ vaborbactam	Plazomicin*
Dosing						
Dose (grams)	2	2.5	3	1.25	4	1.2
Frequency (hour)	8	8	8	6	8	24
Infusion duration (hours)	3	4	1	0.5	3	0.5
Inpatient Cost						
Cost/Dose	460	430	300	330	396	910
Cost/Day	1370	1290	900	1320	1190	910
Cost/Course (7 day)	9560	9030	6310	9240	8330	6370
Products						
Supplied as	1 GM PWVL	2-0.5GM PWVL	1-0.5 GM PWVL	1.25 GM PWVL	2 GM PWVL	500 mg/10 mL

Average Wholesale Price (AWP) per Lexicomp, 08/20/2021

†Ceftolozane/tazobactam is currently unavailable

*Dose based on 80kg (15mg/kg)

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