Ceftolozane/tazobactam (Zerbaxa™, Merck) **September 2015**
Inpatient – Non-Formulary

Criteria for Formulary Consideration of Ceftolozane/tazobactam

Efficacy
Ceftolozane/tazobactam was approved by the Food and Drug Administration (FDA) on December 19, 2014 for the treatment of complicated intra-abdominal infection (cIAI), in combination with metronidazole, and for the treatment of complicated urinary tract infections (cUTI), including pyelonephritis. Two randomized, phase III trials provide support for these indications. A study for the treatment of nosocomial pneumonia is underway with expected completion in 2018.

Ceftolozane/tazobactam plus metronidazole was noninferior to meropenem for the treatment of cIAI for the primary endpoint of clinical cure rate at the test-of-cure visit (TOC) in the micobiological intent-to-treat (MITT) population. Eradication of *Eschericia coli*, *Klebsiella pneumoniae*, and *Pseudomonas aeruginosa* were comparable to meropenem. In the phase III trial comparing ceftolozane/tazobactam with levofloxacin for the treatment of cUTI, ceftolozane/tazobactam demonstrated statistical superiority. The primary endpoint in this study was noninferiority for composite cure which includes both microbiological eradication and clinical cure rate at the TOC visit.

Ceftolozane/tazobactam's spectrum of activity includes gram-negative bacteria such as *E. coli* and *K. pneumoniae*, including extended-spectrum beta-lactamase (ESBL)-producing strains. This novel cephalosporin also demonstrates potent activity against *P. aeruginosa*, including multidrug-resistant strains. Spectrum gaps do include *Klebsiella pneumoniae* carbapenemase (KPC) and metallo-beta-lactamase producing bacteria. In addition, ceftolozane/tazobactam does not provide activity against gram-positive bacteria such as *Staphylococcus aureus* and *Enterococcus* spp.

Safety
Clinical trials demonstrated that ceftolozane/tazobactam is well-tolerated with most adverse events (>90%) classified as mild in severity. Adverse events were not dose related, and no dose-limiting toxicities were identified. Adverse event rates in phase III clinical trials were not notably different than the comparator agents, meropenem and levofloxacin. The most common adverse events in phase III trials included nausea, diarrhea, headache, fever, insomnia, vomiting, and hypokalemia. Serious adverse events observed in clinical trials included *Clostridium difficile* infection. No deaths occurring during these trials were considered to be related to treatment with ceftolozane/tazobactam. The approved labeling contains warnings and precautions for decreased efficacy in patients with baseline creatinine clearance (CrCl) of 30 to ≤50 mL/min, hypersensitivity reactions, *Clostridium difficile*-associated diarrhea (CDAD), and the development of drug-resistant bacteria.

Uniqueness
Increasing morbidity and mortality associated with antimicrobial-resistant gram-negative bacteria calls for the development of unique antimicrobials that are effective against resistant pathogens. Ceftolozane is a novel cephalosporin with antipseudomonal activity. It has been combined with a familiar beta-lactamase inhibitor for extended spectrum coverage of drug-resistant bacteria. Ceftolozane/tazobactam offers broad spectrum of activity against difficult-to-treat gram-negative bacteria such as ESBL-producing *Enterobacteriaceae* and drug-resistant *P. aeruginosa.* In addition, high levels of AmpC expression do not significantly affect ceftolozane activity as compared to agents like cefepime or piperacillin/tazobactam. Ceftolozane/tazobactam is well-tolerated and requires minimal monitoring.

Cost

Product	Cost per Vial	Dosage	Cost per Day
Zerbaxa™ 1.5 g single-dose vial NDC 67919-030-01	$83	1.5 g IV every 8 hours	$249

Recommendation
Add to inpatient formulary with use restricted to ID services.

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Introduction[1-5]

There are limited treatment options for infections due to multidrug-resistant gram-negative pathogens such as ESBL-producing *Enterobacteriaceae* and *P. aeruginosa*, including cUTIs and cIAIs.

Appropriate management of cIAIs involves source control by way of operative or percutaneous interventions. Antibiotic treatment mainly consists of carbapenems, piperacillin/tazobactam, third or fourth generation cephalosporins plus metronidazole, or aminoglycosides. Patients who receive inadequate empiric antibiotic treatment are at a higher risk of treatment failure, sepsis, increased costs, and death. Inappropriate antibiotic treatment is becoming a pressing issue with increasingly more drug-resistant isolates.

Complicated urinary-tract infections may affect the lower urinary tract or upper urinary tract (pyelonephritis). Urosepsis is associated with mortality of up to 40% among critically ill patients. Fluoroquinolones are the most commonly used antibiotic for cUTIs. Other agents include cephalosporins, aminoglycosides, and penicillins. Patients with infections caused by resistant organisms are more likely to be treated inappropriately, have longer hospitalizations, and suffer higher costs than patients infected with more susceptible bacteria.

Ceftolozane/tazobactam, a novel cephalosporin in combination with an established beta-lactamase inhibitor, is approved for the treatment of cIAIs and cUTIs caused by ESBL-producing *Enterobacteriaceae* species, drug-resistant *P. aeruginosa,* and some *Streptococcus* species. An ongoing study is evaluating the safety and effectiveness of ceftolozane/tazobactam for treatment of nosocomial pneumonia in addition to the above indications.

Pharmacokinetics[6-8]

Table 1. Pharmacokinetic Properties of Ceftolozane and Tazobactam at Steady State

	C_{max} (mg/L)	$AUC_{0\text{-}tau}$* (mg·h/L)	Protein Binding (%)	V_d (L)	$T_{½}$ (h)	CL (L/h)	Excretion (%)
Ceftolozane 1 g q8h	74.4	182	16-21	13.5	3.12	3.41-6.69	Urine, >95%
Tazobactam 500 mg q8h	18	25	30	18.2	1.03		Urine, >80%

C_{max}: maximum observed concentration, $AUC_{0\text{-}tau}$: area under concentration curve over dosing interval, *f*$AUC_{0\text{-}tau}$: free area under concentration curve over dosing interval, V_d: volume of distribution, $T_{½}$: elimination half-life, CL: clearance

Pharmacodynamics[9-14]

Like other cephalosporins, time above MIC (T>MIC) for 40-50% of the dosing interval is the pharmacodynamic parameter that best predicts efficacy for ceftolozane and ceftolozane/tazobactam. In murine thigh infection models, ceftolozane/tazobactam has anticipated %*f*T>MIC of ≥37.5% resulting in 1-3 log reductions in bacterial density for non-ESBL-producing organisms with MICs ≤ 16 mg/L. Among ESBL-producing isolates, ceftolozane/tazobactam showed increased efficacy and a significant decrease in bacterial density of 1.2-1.5-log units over 24 hours compared to piperacillin/tazobactam.

In another infection murine thigh model for ceftolozane/tazobactam against Enterobacteriaceae and *P. aeruginosa*, the T>MIC detected was much less compared to that for other cephalosporins. Mean T>MIC for stasis and 1-log kill was 26% and 32% for non-ESBL-producing Enterobacteriaceae, 31% and 35% for ESBL-producing Enterobacteriaceae, and 25% and 32% for *P. aeruginosa*.

Monte Carlo simulations have demonstrated high probability of target attainment using 40-50% T>MIC with current dosing and susceptibility breakpoints. A 1.5 g dose of ceftolozane/tazobactam given every 8 hours achieved 50% T>MIC for an MIC of 8 mg/L in 90% of subjects (Table 2). In Monte Carlo simulations in subjects with varying renal function, a 50% dose reduction was suggested to achieve the desired target attainment of 40% T>MIC (Table 3). In a simulated ventilator-associated pneumonia population, a dose of ceftolozane 2 g/tazobactam 1 g every 8 hours achieved target attainment of 40% T>MIC in plasma and epithelial lining fluid in >90% of simulations for gram-negative pathogens including *P. aeruginosa* (MIC range 0.12 to >32 mg/L), *E. coli* (MIC range ≤0.06 to 4 mg/L), and *K. pneumoniae* (MIC range 0.12 to >32 mg/L).

Table 2. Probability of Target For Three Dosing Regimens Using Monte Carlo Simulation

MIC	*1500 mg every 8 hours (60 minute infusion)*			*1500 mg every 8 hours (3 hour infusion)*			*3000 mg every 8 hours (60 minute infusion)*		
(mg/L)	*30% T>MIC*	*40% T>MIC*	*50% T>MIC*	*30% T>MIC*	*40% T>MIC*	*50% T>MIC*	*30% T>MIC*	*40% T>MIC*	*50% T>MIC*
0.5	100	100	100	100	100	100	100	100	100
1	100	100	100	100	100	100	100	100	100
2	100	100	100	100	100	100	100	100	100
4	100	100	99.7	100	100	100	100	100	100
8	100	98.2	89.8	100	100	99.4	100	100	99.4
6	96.1	74.9	44.9	97.9	91	70.3	100	98.8	90.7

Table 3. Probability of Target Attainment Based on Monte Carlo Simulation in Patients with Varying Renal Function

Ceftolozane/tazobactam Dose	*MIC (mg/L)*	*Renal Function*	*Probability of Target Attainment for 40% T>MIC*
1000 mg/500 mg every 8 hours	8	Normal	87.6%
1000 mg/500 mg every 8 hours	8	Mild impairment	100%
500 mg/250 mg every 8 hours	8	Moderate impairment	100%

The PBP profile of ceftolozane has been compared to ceftazidime, a PBP3 inhibitor, and imipenem, a PBP2 inhibitor. Ceftolozane showed greater than 2-fold higher potency for PBPs 1b, 1c, 2, and 3 compared to ceftazidime. Compared to imipenem, it showed higher affinity for PBP1b but lower affinity for PBP1c. Ceftolozane alone has low affinity for PBP4 and demonstrates weak induction of AmpC expression.

Pharmacology and Microbiology[2-5]

Ceftolozane is a cephalosporin antibiotic. It has bactericidal action due to inhibition of cell wall biosynthesis and is mediated through binding to penicillin-binding proteins (PBPs). Ceftolozane inhibits PBPs of *P. aeruginosa* (PBP1b, PBP1c, PBP3) and *E. coli* (PBP3). Tazobactam is an irreversible inhibitor of certain penicillinases and cephalosporinases and can bind covalently to some chromosomal and plasmid-mediated beta-lactamases. Tazobactam has little clinically relevant in vitro activity against bacteria due to reduced affinity for PBPs. Susceptibility interpretative criteria, *in vitro* activity against specific bacteria, and *in vitro* activity against specific β-lactamases are highlighted in Tables 4-6, respectively.

Table 4. Susceptibility Interpretive Criteria for Ceftolozane/Tazobactam

Pathogen	*Minimum Inhibitory Concentration (mg/L)*			*Disk Diffusion Zone Diameter (mm)*		
	S	*I*	*R*	*S*	*I*	*R*
Enterobacteriaceae	≤2/4	4/4	≥8/4	---	---	---
Pseudomonas aeruginosa	≤4/4	8/4	≥16/4			
Streptococcus anginosus *Streptococcus constellatus* *Streptococcus salivarius*	≤8/4	16/4	≥32/4	---	---	---
Bacteroides fragilis	≤8/4	16/4	≥32/4	---	---	---

Table 5. *In Vitro* Activity of Ceftolozane/Tazobactam Against Select Bacteria

Organism	**Ceftolozane**		**Ceftolozane/tazobactam**	
	MIC_{50}/MIC_{90}	**MIC Range**	**MIC_{50}/MIC_{90}**	**MIC Range**
Gram-negative aerobes				
Acinetobacter spp.	8/>32	≤0.12-≥32	8/>32	≤0.12-≥32
Acinetobacter baumannii	NA	NA	0.5/2	≤0.12-16
Burkholderia cepacia	4/32	≤0.25->256	NA	NA
Citrobacter spp.	0.5/16	≤0.12-≥32	0.25/8	≤0.12-≥32
Ceftazidime-resistant	32/>32	1->32	16/>16	0.25->16
Enterobacter spp.	0.5/16	NA	0.25/8	≤0.12-≥32
Ceftazidime-resistant/non-susceptible	>32/>32	4->32	0.25/8	≤0.03-≥32
Enterobacter cloacae	0.25/32	≤0.12-≥32	0.25/8	≤0.12-≥32
Escherichia coli	0.12/0.5	0.12/>64	0.12/0.5	≤0.12->32
Ceftazidime-resistant	>32/>32	1->32	1/16	≤0.12->32
ESBL-producing	64/>64	0.25->64	0.5/4	≤0.12->16
Haemophilus influenzae	0.12/0.25	≤0.12-1	≤0.12/0.25	≤0.12-1
Klebsiella spp.	0.25/>32	NA	0.25/4	0.12->32
ESBL-producing	>32/>32	NA	2/>32	0.12->32
Klebsiella oxytoca	NA	NA	≤0.12/0.5	≤0.12-2
Klebsiella pneumoniae	0.25/16	≤0.12->64	0.25/8	≤0.12-≥32
Ceftazidime-resistant	>32/>32	4->32	4/>16	≤0.12->16
ESBL-producing	32/>64	2->64	0.5/64	≤0.12->64
KPC-producing	>32/>32	32->32	>16/>16	16->16
Proteus spp., indole-positive	NA	NA	0.25/1	0.12-≥32
Ceftazidime-resistant	>32/>32	4->32	2/>16	0.25->16
Proteus mirabilis	0.25/0.5	≤0.12-16	0.25/0.5	≤0.12-16
ESBL-producing	8/>32	≤0.25->32	1/8	0.25->16
Serratia spp.	0.5/1	NA	0.5/1	0.12-≥32
Serratia marcescens	0.5/1	0.25-≥32	0.5/1	≤0.12-≥32
Stenotrophomonas maltophilia	NA	NA	16/>64	0.5->64
Pseudomonas aeruginosa	0.5/2	≤0.12-≥128	0.5/2	≤0.12->128
Amikacin-resistant	1/32	≤0.5->32	2/NA	≤0.25->16
Aztreonam-resistant/non-susceptible	1/4	≤0.12->32	NA	NA
Cefepime-resistant/non-susceptible	1/4	≤0.12-≥128	4/NA	2-≥16
Ceftazidime-resistant/non-susceptible	2/16	≤0.12-≥128	4/16	0.25->64
Ciprofloxacin-resistant	1/4	0.12-≥128	1/4	≤0.25->16
Gentamicin-resistant	1/4	≤0.12-≥128	1/4	≤0.25->16
Imipenem-resistant/non-susceptible	1/4	≤0.12-≥128	1/8	0.25->64
Levofloxacin-resistant/non-susceptible	1/4	0.25->32	NA	NA
Meropenem-resistant/non-susceptible	1/8	≤0.12-≥128	1/8	0.25->32
Piperacillin/tazobactam-resistant/non-susceptible	2/4	≤0.12-≥128	2/4	0.5->64
Tobramycin-resistant	2/64	≤0.12-≥128	2/64	0.5->64
Ceftazidime and imipenem non-susceptible	4/16	0.5/>128	2/16	0.5->128
Ceftazidime and meropenem non-susceptible	NA	NA	4/≥32	1-≥32
Multidrug-resistant	2/16	0.12-≥128	1/2	0.5->64
Gram-positive aerobes				
Enterococcus faecalis	64/>64	NA	NA	NA
Enterococcus faecium	64/>64	NA	NA	NA
Staphylococcus aureus	32/32	16-64	32/64	4-128
Streptococcus agalactiae	0.5/0.5	≤0.12-0.25	0.5/0.5	≤0.12-0.5
Streptococcus anginosus	NA	NA	1/2	≤0.03-4
Streptococcusconstellatus	NA	NA	0.5/2	≤0.03-4
Streptococcus pneumoniae	≤0.12/4	≤0.12-16	≤0.12/8	≤0.12-16

Streptococcus pyogenes	≤0.12/≤0.12	≤0.12-0.25	≤0.12/≤0.12	≤0.12-2
Streptococcus salivarius	NA	NA	1/2	0.12-4
Gram-negative anaerobes				
Bacteroides caccae	64/>256	≤0.12-≥256	0.25/16	0.25-16
Bacteroides fragilis	>32/>32	≤0.12-≥256	1/4	0.25-256
Bacteroides ovatus	>256/>256	1->256	4/32	0.25->256
Bacteroides thetaiotamicron	>256/>256	0.25->256	4/32	0.25->128
Bacteroides uniformis	64/≥256	NA	2/16	NA
Bacteroides vulgatus	128/>256	0.25->256	4/32	0.25->256
Other *Bacteroides* spp.	8/>256	0.25->256	0.25/8	<0.12-128
Fusobacterium spp.	≤0.12/16	≤0.12-16	≤0.12/0.25	≤0.12-≥256
Parabacteroides distasonis	>256/>256	8->256	16/32	≤0.12-16
Prevotella spp.	16/≥256	≤0.12-≥256	≤0.12/1	≤0.12-4
Gram-positive anaerobes				
Anaerobic gram-positive cocci	4/16	≤0.12->256	2/8	≤0.12-64
Clostridium spp.	>256/>256	0.5->256	16/>256	≤0.12->256
Clostridium difficile	>256/>256	32->256	>256/>256	0.25->256
Clostridium perfringens	1/64	0.5-64	0.25/32	≤0.12-32
Propionibacterium spp.	0.5/NA	≤0.12-16	≤0.12/NA	≤0.12

Table 6. *In Vitro* Activity of Ceftolozane/tazobactam Against Select β-Lactamases

Organism	*β-Lactamase*	*Ceftolozane MIC*	*Ceftolozane/tazobactam MIC*
Escherichia coli			
Extended-spectrum β-lactamases	CTX-M-2	8-32	<0.25-4
	CTX-M-3	4-26	0.25
	CTX-M-14	<0.25->64	<0.25-4
	CTX-M-15	2->64	<0.25-64
	CTX-M-18	16	NA
	OXA-1	0.25-0.5	0.25
	OXA-2	0.25-4	0.25
	OXA-3	0.5	0.5
	OXA-4	0.25	0.25
	OXA-5	32	0.5
	OXA-7	2	1
	SHV-1	0.25-0.5	0.5
	SHV-2	4-32	2
	SHV-3	32	NA
	SHV-4	16-64	16
	SHV-5	2-64	<0.25-2
	SHV-12	2-16	<0.25-4
	TEM-1	0.12-0.25	0.25
	TEM-2	0.12-0.5	0.06
	TEM-3	0.5-1	0.25
	TEM-4	2	NA
	TEM-5	32	NA
	TEM-6	32-64	0.5
	TEM-7	32	NA
	TEM-8	16	NA
	TEM-9	32->128	8
	TEM-10	16-64	1-16
Carbapenemases	NMC-A	0.25	0.12
	PER-1	>128	16
Metallo-β-lactamases	IMP-1	32->128	32
Klebsiella pneumoniae			
Extended-spectrum β-lactamases	CTX-M-2	8	<0.25
	CTX-M-14	2-32	<0.25-1
	CTX-M-15	16->64	<0.25->64
	SHV-5	8->64	<0.25-64
	TEM-29	>64	32
	SHV-1, TEM-10	>64	8
	SHV-1, TEM-26	>64	16
AmpC β-lactamases	AmpC, CTX-M-3	32-64	1

FDA Approved Indications[6,15]

The FDA approved ceftolozane/tazobactam on December 19, 2014 for the treatment of patients 18 years or older with the following infections caused by designated susceptible microorganisms:

- Complicated intra-abdominal infections, in combination with metronidazole, caused by *Enterobacter cloacae, Escherichia coli, Klebsiella oxytoca, Klebsiella pneumonia, Proteus mirabilis, Pseudomonas aeruginosa, Bacteroides fragilis, Streptococcus anginosus, Streptococcus constellatus,* and *Streptococcus salivarius.*
- Complicated urinary tract infections, including pyelonephritis, caused by *Escherichia coli, Klebsiella pneumoniae, Proteus mirabilis,* and *Pseudomonas aeruginosa.*

In order to reduce the development of drug resistant bacteria and maintain the effectiveness of ceftolozane/tazobactam, it should only be used to treat infections that are proven or strongly suspected to be caused by susceptible bacteria.

Clinical Trials[16,17]

Table 7. Clinical Trials

Study Design

Lucasti C et al, 2014

Trial Design:

- Phase II, multicenter, prospective, randomized (2:1), double-blind trial
- Compared ceftolozane/tazobactam ± metronidazole and meropenem for treatment of cIAI
-
- June 2010-March 2011

Interventions:

- Ceftolozan/tazobactam 1.5 g IV every 8 hours ± metronidazole 500 mg IV every 8 hours for 4-14 days
- Meropenem 1 g IV every 8 hours + placebo IV every 8 hours
- Treatment duration: 4-7 days

Primary Outcome:

- Clinical response in the microbiological MITT (mMITT) and microbiologically evaluable (ME) populations

Secondary Outcomes:

- Clinical response in the CE population at the TOC visit
- Clinical response in mMITT and ME populations by patient subtype
- Overall microbiological success
- Clinical and microbiological success per pathogen for the ME population
- Safety

Methods

Inclusion Criteria:

- Age 18-90 years old
- Evidence of cIAI requiring surgical intervention

Exclusion Criteria:

- High risk of recurrent infections due to exogenous contamination (cIAI managed by a staged repair process)
- Systemic antibiotics used for > 24 hours in the 48 hours period prior to the first dose of study drug (unless treatment failure was documented)
- Hematocrit < 25%
- Platelets < 75,000/mm^3
- Neutrophils < 1000/mm^3
- Life-threatening disease or immunocompromising illness

Statistical Analysis:

- Inferential statistical analyses not conducted
- Two-sided 95% CI calculated using the Copper-Pearson method for clinical and microbiological response rate

Results

Primary and Secondary Outcomes:

	Ceftolozane/tazobactam n (%)	Meropenem n (%)	% Difference (95% CI)
mMITT population	n=61	n=25	
Clinical cure	51 (83.6)	24 (96.0)	-12.4 (-34.9 to 11.1)
Clinical failure	6 (9.8)	1 (4.0)	
Indeterminate	4 (6.6)	0 (0.0)	
ME population	n=53	n=24	
Clinical cure	47 (88.7)	23 (95.8)	-7.1 (-30.7 to 16.9)
Clinical failure	6 (11.3)	1 (4.2)	
Microbiologic success	48 (90.6)	23 (95.8)	
CE population	n=70	n=35	
Clinical cure	64 (91.4)	33 (94.3)	-2.9 (-23.5 to 18.0)
Clinical failure	6 (8.6)	2 (5.7)	

Per-Pathogen Microbiological Success at TOC (ME Population):

	Ceftolozane/tazobactam (n=53)	Meropenem (n=24)
Gram-negatives		
E. coli	34/38 (89.5)	18/19 (94.7)
K. pneumoniae	8/8 (100.0)	0
P. aeruginosa	4/4 (100.0)	3/3 (100.0)
P. mirabilis	3/3 (100.0)	0
A. baumannii	1/1 (100.0)	1/1 (100.0)
Other	4/5 (80.0)	3/3 (100.0)
Gram-positives		
Streptococcus spp.	8/8 (100.0)	4/4 (100.0)
E. faecium	5/5 (100.0)	2/2 (100.0)
E. faecalis	5/5 (100.0)	1/1 (100.0)
G. morbillorum	1/1 (100.0)	1/1 (100.0)
G. bergeri	0	1/1 (100.0)
Other	0	1/1 (100.0)
Anaerobes		
Bacteroides (non-*fragilis*)	2/2 (100.0)	4/4 (100.0)
B. fragilis	6/7 (85.7)	1/1 (100.0)
F. nucleatum	1/1 (100.0)	0
P. buccae	1/2 (50.0)	0
B. adolescentis	1/1 (100.0)	0
E. lenta	0	1/1 (100.0)
P. acnes	1/1 (100.0)	0

Adverse Events Occurring in ≥5% of Patients (MITT Population):

	Ceftolozane/tazobactam (n=82)	Meropenem (n=39)
Nausea	5 (6.1)	4 (10.3)
Vomiting	4 (4.9)	3 (7.7)
Diarrhea	4 (4.9)	3 (7.7)
Pyrexia	12 (14.7)	4 (10.3)
Hypertension	4 (4.9)	2 (5.1)
Phlebitis	2 (2.4)	2 (5.1)
Hypomagnesemia	2 (2.4)	2 (5.1)
Wound dehiscence	0 (0.0)	2 (5.1)
Anemia	5 (6.1)	1 (2.6)
GGT increased	1 (1.2)	2 (5.1)
ALT increased	0 (0.0)	3 (7.7)
AST increased	0 (0.0)	2 (5.1)

Conclusions/Comments

Author's Conclusion:

- Ceftolozane/tazobactam in combination with metronidazole was well tolerated and resulted in clinical and microbiological success rates supportive of further clinical trials

Comments:

- Ceftolozane/tazobactam administered in combination with metronidazole at the discretion of the prescribing physician
- Similar incidence and distribution of baseline infecting pathogens between groups
- Small sample size
- Not designed or powered to statistically compare efficacy between groups
- Suggests that ceftolozane/tazobatam is effective for cIAIs

Study Design	*Methods*	*Results*	*Conclusions/Comments*

Solomkin J et al, 2015

Trial Design:
- Two identical phase III multicenter, prospective, randomized (1:1), double-blind, non-inferiority trials
- Compared ceftolozane/tazobactam + metronidazole and meropenem for treatment of cIAI
- December 2011-September 2013

Interventions:
- Ceftolozan/tazobactam 1.5 g IV every 8 hours + metronidazole 500 mg IV every 8 hours for 4-14 days
- Meropenem 1 g IV every 8 hours + placebo IV every 8 hours
- Treatment duration: 4-14 days

Primary Outcome:
- Clinical cure rates at TOC in the microbiological MITT (mMITT) population

Secondary Outcomes:
- Clinical cure rates at TOC in the microbiologically evaluable (ME) population
- Microbiological outcomes
- Safety

Inclusion Criteria:
- Age ≥18 years
- Clinical evidence of cIAI
- Operative/percutaneous drainage of infectious focus planned or performed within 24 hours confirming presence of cIAI

Exclusion Criteria:
- cIAI managed by staged abdominal repair in which the fascia was not closed
- Low likelihood of adequate source control at surgery
- CrCl <30 ml/min
- Use of systemic antimicrobial therapy for IAI for > 24 hours prior to first dose of study drug unless this treatment failed

Statistical Analysis:
- Planned pooled sample size to ensure minimum 90% power to demonstrate non-inferiority at a 10% non-inferiority margin at a 1-sided significance level of 0.025
- Assumed 80% of patients would meet criteria to be included in mMITT population and clinical cure rate in both arms would be 75%
- Non-inferiority hypothesis tested through 2-sided 95% CI approach
- Weighted difference in cure rates calculated using stratified Newcombe CI with minimum risk weights
- Non-inferiority claimed if the lower bound of the 95% CI for the difference was above -10%
- Other endpoints were analyzed using a 95% CI calculated by the Wilson score methodology

Primary and Secondary Outcomes:

	Ceftolozane/tazobactam + metronidazole n (%)	Meropenem + placebo n (%)	% Difference (95% CI)
MITT population	n=389	n=417	
Cure	323 (83.0)	364 (87.3)	-4.2 (-8.9 to 5.4)
Failure	32 (8.2)	34 (8.2)	
Indeterminate	34 (8.7)	19 (4.6)	
ME population	n=275	n=321	
Cure	259 (94.2)	304 (94.7)	-1.0 (-4.5 to 2.6)
Failure	16 (5.8)	17 (5.3)	

Per-Pathogen Clinical Cure of ESBL-Producing Enterobactericeae at TOC (ME Population):

	Ceftolozane/tazobactam + metronidazole n (%)	Meropenem + placebo n (%)
Enterobacteriaceae ESBL+	23/24 (95.8)	23/26 (88.5)
Enterobacteriaceae, CTX-M-14/15	13/13 (100.0)	8/11 (72.7)
E. coli, ESBL+	14/14 (100.0)	18/20 (90.0)
E. coli, CTX-M-14/15	9/9 (100.0)	7/9 (77.8)
K. pneumoniae, ESBL+	7/8 (87.5)	3/4 (75.0)
K. pneumoniae, CTX-M-14/15	5/5 (100.0)	0/1 (0.0)

Per-Pathogen Clinical Cure at TOC (ME Population):

	Ceftolozane/tazobactam + metronidazole (n=307)	Meropenem + placebo n (%) (n=345)
Gram-negatives		
Enterobacteriaceae	227/241 (94.2)	255/272 (93.8)
E. cloacae	19/22 (86.4)	22/22 (100.0)
E. coli	197/208 (94.7)	216/231 (93.5)
K. oxytoca	12/12 (100.0)	21/22 (95.5)
K. pneumoniae	28/30 (93.3)	22/25 (88.8)
P. mirabilis	10/11 (90.9)	9/10 (90.0)
P. aeruginosa	26/26 (100.0)	27/29 (93.1)
Gram-positives		
E. faecalis	31/37 (83.8)	37/40 (92.5)
E. faecium	23/25 (92.0)	38/41 (92.7)
S. aureus	13/13 (100.0)	12/12 (100.0)
S. anginosus	25/30 (83.3)	23/23 (100.0)
S. constellatus	17/18 (94.4)	20/23 (87.0)
S. salivarius	9/10 (90.0)	8/8 (100.0)
Anaerobes		
B. fragilis	39/41 (95.1)	56/57 (98.2)
B. ovatus	36/37 (97.3)	42/42 (100.0)
B. thetaiotaomicron	20/20 (100.0)	40/43 (93.0)
B. vulgatus	12/13 (92.3)	21/22 (95.5)

Adverse Events Occuring in ≥2% of Patients in Either Treatment Group:

	Ceftolozane/tazobactam + metronidazole (n=482)	Meropenem + placebo (n=497)
Any adverse event	212 (44.0)	212 (42.7)
Nausea	38 (7.9)	29 (5.8)
Diarrhea	30 (6.2)	25 (5.0)
Vomiting	16 (3.3)	20 (4.0)
Pyrexia	25 (5.2)	20 (4.0)
Hypokalemia	14 (2.9)	8 (1.6)
Insomnia	17 (3.5)	11 (2.2)
Headache	12 (2.5)	9 (1.8)

Author's Conclusion:
- Treatment with ceftolozane/tazobacam plus metronidazole was noninferior to meropenem in adult patients with cIAI, including infections caused by MDR pathogens

Comments:
- Only 7.2% of Enterobacteriaceae isolates were ESBL-producing and only 5.7% of Pseudomonas isolates were classified as multidrug-resistant
- Patients with ESRD were excluded and only 4.5% of patients had moderate renal impairment at baseline
- In subgroup analyses, clinical cure rates in both treatment groups were generally lower in high-risk patient populations including elderly patients, and patients with higher APACHE II scores, moderate renal impairment, or small bowel and colon infections

Anemia, postoperative	10 (2.1)	8 (1.6)
Hypertension	9 (1.9)	10 (2.0)

Drug-related Adverse Events Leading to Discontinuation:

- Ceftolozane/tazobactam + metronidazole: n=3 (0.6%)
- Meropenem + placebo: n=4 (0.8%)

Serious Adverse Events:

- Ceftolozane/tazobactam + metronidazole: n=39 (8.1%)
- Meropenem + placebo: n=36 (7.2%)

Deaths:

- Ceftolozane/tazobactam + metronidazole: n=11 (2.3%)
- Meropenem + placebo: n=8 (1.6%)
- None of the deaths considered to be related to the study treatment

Study Design

Wagenlehner FM et al, 2015

Trial Design

- Two identical phase III multicenter, prospective, randomized (1:1), double-blind, non-inferiority trials
- Compared ceftolozane/tazobactam and levofloxacin for treatment of cUTI, including pyelonephritis
- July 2011-September 2013

Interventions:

- Ceftolozane/tazobactam 1.5 g IV every 8 hours
- Levofloxacin 750 mg IV daily
- Treatment duration: 7 days

Primary Outcome

- Composite cure rate at test-of-cure visit in the microbiological MITT (mMITT) population

Secondary Outcome

- Composite cure rate at test-of-cure visit in the per-protocol population
- Clinical cure, microbiological eradication, and composite cure in subgroups
- Safety

Methods

Inclusion Criteria:

- ≥18 years
- Pyuria
- Diagnosis of pyelonephritis or complicated lower-urinary-tract infection
- Admitted for intravenous antibiotic therapy
- Pretreatment urine culture specimen obtained within 36 hours of initiating study

Exclusion Criteria:

- Concomitant infections requiring treatment with non-study antibacterial agents with gram-negative activity
- Infection at baseline that would require more than 7 days of treatment
- Severe renal failure

Statistical Analysis:

- Pooled sample size of 800 patients in the mMITT population with assumed composite cure rate of 74% for at least 90% power to show non-inferiority at a margin of 10%
- Prespecified statistical criteria for primary and secondary outcome was two-sided 95% CI around the treatment difference with stratification by Newcombe minimum-risk rates
- Superiority shown if treatment difference was positive and lower bound of the 95% CI of this difference was positive
- Other secondary outcomes analyzed with 95% CI calculated by Wilson score method

Results

Primary and Secondary Efficacy Results:

	Ceftolozane/tazobactam n (%)	Levofloxacin n (%)	% Difference (95% CI)
mMITT population			
Composite cure	306/398 (76.9)	275/402 (68.4)	8.5 (2.3 to 14.6)
Micro.eradication	320/398 (80.4)	290/402 (72.1)	8.3 (2.4 to 14.1)
Clinical cure	366/398 (92.0)	356/402 (88.6)	3.4 (-0.7 to 7.6)
Per-protocol population			
Composite cure	284/341 (83.3)	266/353 (75.4)	8.0 (2.0 to 14.0)
Micro. eradication	294/341 (86.2)	274/353 (77.6)	8.6 (2.9 to 14.3)
Clinical cure	327/341 (95.9)	329/353 (93.2)	2.7 (-0.8 to 6.2)

Composite Cure at TOC Visit by Subgroup in the mMITT Population:

	Ceftolozane/tazobactam n (%)	Levofloxacin n (%)
Diagnosis		
Pyelonephritis	259/328 (79.0)	240/328 (73.2)
Other cUTI	47/70 (67.1)	35/74 (47.3)
Age		
< 65 years	236/298 (79.2)	222/303 (73.3)
≥ 65 years	70/100 (70.0)	53/99 (53.5)
Bacteremia at baseline		
Yes	23/29 (79.3)	19/33 (57.6)
No	283/369 (76.7)	256/369 (69.4)
Baseline pathogen		
Resistant to levofloxacin	60/100 (60.0)	44/112 (39.3)
Susceptible to levofloxacin	231/272 (84.9)	210/259 (81.1)
ESBL-positive	38/61 (62.3)	20/57 (35.1)

Microbiologic Eradication at TOC by Pathogen in the Per-Protocol Population:

	Ceftolozane/tazobactam n (%)	Levofloxacin n (%)	% Difference (95% CI)
Gram-negatives			
All	287/323 (88.9)	263/340 (77.4)	11.5 (5.8 to 17.1)
Enterobacteriaeceae	281/316 (88.9)	263/340 (77.4)	10.9 (5.2 to 16.6)
E. coli	237/262 (90.5)	226/284 (79.6)	10.9 (4.9 to 16.8)
ESBL-producers	27/36 (75.0)	18/36 (50.0)	NA
CTX-M-14/15	20/27 (74.1)	13/25 (52.0)	NA
K. pneumoniae	21/25 (84.0)	14/23 (60.9)	23.1 (-2.1 to 45.4)
ESBL-producers	7/10 (70.0)	2/7 (28.6)	NA
CTX-M-15	5/8 (62.5)	1/4 (25.0)	NA
P. mirabilis	10/10 (100.0)	8/11 (72.7)	27.3 (-5.6 to 56.6)
E. cloacae	2/6 (33.3)	6/7 (85.7)	-52.4 (-78.8 to -0.3)
P. aeruginosa	6/7 (85.7)	7/12 (58.3)	27.4 (-15.9 to 56.3)
Gram-positives			
All	8/21 (38.1)	16/20 (80.0)	-41.9 (-63 to -11.8)
E. faecalis	5/16 (31.3)	12/16 (75.0)	-43.8 (-66.4 to -9.2)
E. faecium	1/2 (50.0)	3/3 (100.0)	-50 (-90.6 to 19.3)
S. aureus	3/4 (75.0)	1/1 (100.0)	-25 (-69.9 to 56.9)

Adverse Events Occurring in ≥2% of Patients in the MITT Population:

	Ceftolozane/tazobactam (n=533)	Levofloxacin (n=535)
Any adverse event	185 (34.7)	184 (34.4)
Headache	31 (5.8)	26 (4.9)
Constipation	21 (3.9)	17 (3.2)
Nausea	15 (2.8)	9 (1.7)
Diarrhea	10 (1.9)	23 (4.3)
Upper abdominal pain	7 (1.3)	6 (1.1)
Vomiting	6 (1.1)	6 (1.1)
Hypertension	16 (3.0)	7 (1.3)

Conclusions/Comments

Author's Conclusion:

- Ceftoloxane/tazobactam was superior to levofloxacin for composite cure rates
- Ceftolozane/tazobactam demonstrated greater eradication rates compared to levofloxacin among patients with *Enterobacteriaceae* spp., including ESBL-producing strains

Comments:

- Included more seriously ill patients, as required IV therapy for treatment
- Patients with severe renal failure excluded because dosing recommendations for this group were not available yet
- Used high dose levofloxacin beyond the labeled duration (7 days as opposed to 5 days)
- Most patients had pyelonephritis (82%)
- Low incidence of *P. aeruginosa* (2.9%), limiting statistical conclusions related to this pathogen
- Safety profile consistent with that of other cephalosporins

Pyrexia	8 (1.5)	4 (0.7)		
Urinary tract infection	9 (1.7)	9 (1.7)		
Insomnia	7 (1.3)	14 (2.6)		
Dizziness	6 (1.1)	1 (0.2)		
Myalgia	6 (1.1)	4 (0.7)		
Arthralgia	1 (0.2)	6 (1.1)		
Increased alanine aminotransferase	9 (1.7)	5 (0.9)		
Increased aspartate aminotransferase	9 (1.7)	5 (0.9)		

Drug-related Adverse Events Leading to Discontinuation

- Incidence <2% in both treatment groups

Serious Adverse Events

- Ceftolozane/tazobactam: n=15 (2.8%)
- Levofloxacin: n=18 (3.4%)

Death

- Ceftolozane/tazobactam: n=1
- Not considered to be related to the study treatment

Warnings, Precautions, and Adverse Effects[6,16,17]

Table 8. Warnings and Precautions	
Warning/Precaution	*Description*
Decreased efficacy in patients with baseline CrCl of 30 to ≤50 mL/min	In a subgroup analysis of a phase III cIAI trial, clinical cure rates were lower in patients with baseline CrCl of 30 to ≤50 mL/min compared to those with CrCl > 50 mL/min. This was more marked in the ceftolozane/tazobactam plus metronidazole arm compared to the meropenem arm. A similar trend was also seen in the cUTI trial. Monitor CrCl at least daily in patients with changing renal function and adjust the dosage accordingly.
Hypersensitivity reactions	Serious and occasionally fatal hypersensitivity reactions and anaphylaxis have been reported in patients receiving beta-lactam antibiotics. Inquire about previous hypersensitivity reactions to other cephalosporins, penicillins, or other beta-lactams. Cross-sensitivity has been established.
Clostridium difficile-associated diarrhea (CDAD)	CDAD has been reported for nearly all systemic bacterial agents, including ceftolozane/tazobactam, and may range in severity from mild diarrhea to fatal colitis. CDAD must be considered in all patients who present with diarrhea following antibiotic treatment. If confirmed, discontinue antibacterials not directed against *C. difficile*, if possible.
Development of drug-resistant bacteria	Prescribing of ceftolozane/tazobactam in the absence of a proven or strongly suspected bacterial infection is unlikely to provide benefit and risks the development of drug-resistant bacteria.
Increased mortality	In phase 2 and 3 cIAI trials, there was an increased mortality associated with patients in the ceftolozane/tazobactam + metronidazole arm (2.5%, 14/564) compared to the meropenem arm (1.5%, 8/536). Causes of death included worsening and/or complications of infection, surgery, and underlying conditions.
Pregnancy category B	No adequate and well-controlled studies in pregnant women.

Table 9. Adverse Effects Occurring in ≥1% of Patients Receiving Ceftolozane/tazobactam in Phase III Clinical Trials		
	Phase III cIAI Trial (n=482)	*Phase III cUTI Trial (n=533)*
Gastrointestinal Disorders		
Vomiting	3.3%	1.1%
Nausea	7.9%	2.8%
Diarrhea	6.2%	1.9%
Constipation	1.9%	3.9%
Abdominal pain	1.2%	0.8%
Central Nervous System		
Headache	2.5%	5.8%
Insomnia	3.5%	1.3%
Dizziness	0.8%	1.1%
Fever	5.6%	1.7%
Psychiatric		
Anxiety	1.9%	0.2%
Cardiovascular		
Hypotension	1.7%	0.4%
Atrial fibrillation	1.2%	0.2%
Dermatologic		
Skin rash	1.7%	0.9%
Endocrine		
Hypokalemia	3.3%	0.8%
Hematologic		
Anemia	1.5%	0.4%
Thrombocytosis	1.9%	0.4%
Laboratory		
Increased alanine aminotransferase	1.5%	1.7%
Increased aspartate aminotransferase	1%	1.7%

Interactions[6]

Ceftolozane and tazobactam do not inhibit or show potential for induction of the cytochrome P450 enzyme system and there is limited potential for significant drug-drug interactions. Tazobactam is a known substrate for OAT1 and OAT3. Coadministration with probenicid, an OAT1/OAT3 inhibitor, has been shown to prolong the half-life of tazobactam by 71%. Coaadministration of ceftolozane/tazobactam with drugs that inhibit OAT1 and/or OAT3 may increase tazobactam plasma concentrations.

Dosage and Administration[6]

Table 10. Recommended Dosage

Indication	*Dose*[a]	*Route*	*Infusion Time*	*Frequency*	*Duration*
cUTI	1.5 g	Intravenous	1 hour	Every 8 hours	7 days
cIAI[b]	1.5 g	Intravenous	1 hour	Every 8 hours	4-14 days

[a]Ceftolozane/tazobactam 1.5 g contains ceftolozane 1 g and tazobactam 500 mg
[b]Used in conjunction with metronidazole 500 mg intravenously every 8 hours

Table 11. Dosage Recommendations in Special Populations

Special Population	*Recommendation*	
Renal impairment	CrCl >50 mL/min	No dosage adjustment necessary
	CrCl 30-50 mL/min	750 mg (500 mg and 250 mg) every 8 hours
	CrCl 15-29 mL/min	375 mg (250 mg and 125 mg) every 8 hours
	CrCl <15 mL/min, not on dialysis	No dosage adjustments provided in the labeling
	End-stage renal disease on hemodialysis	Administer single loading dose of 750 mg (500 mg and 250 mg) followed by a 150 mg (100 and 50 mg) maintenance dose administered every 8 hours. On hemodialysis days, administer the dose at the earliest possible time following completion of dialysis.
Hepatic impairment	No dosage adjustment necessary	
Geriatric patients	Dosage adjustments should be based on renal function	
Pediatric patients	Safety and effectiveness has not been established in patients less than 18 years of age	
Gender	No dosage adjustment is recommended based on gender	
Race	No dose adjustment is recommended based on race	

Monitoring Parameters[6]

Monitor serum creatinine and CrCl at baseline and daily in patients with changing renal function.

How Supplied/Cost/Preparation[6,11]

Table 12. Product Supply

Product	*Cost per Vial*	*Dosage*	*Cost per Day*
Zerbaxa™ 1.5 g single-dose vial NDC 67919-030-01	$83	1.5 g IV every 8 hours	$249

Constitute the vial with 10 mL of sterile water for injection or 0.9% Sodium Chloride for Injection, USP and shake gently to dissolve. The final volume is approximately 11.4 mL. The constituted solution is not for direct injection. To prepare the required dose, withdraw the appropriate volume from the reconstituted vial. Add the withdrawn volume to an infusion bag containing 100 mL of 0.9% Sodium Chloride for Injection, USP or 5% Dextrose Injection, USP. Inspect drug products visually for particulate matter and discoloration prior to use. Ceftolozane/tazobactam infusions range from clear, colorless solutions to solutions that are clear and slightly yellow.

Compatibility of ceftolozane/tazobactam with other drugs has not been established. Ceftolozane/tazobactam should not be mixed with other drugs or physically added to solutions containing other drugs.

Upon constitution with sterile water for injection or 0.9% sodium chloride injection, reconstituted ceftolozane/tazobactam solution may be held for one hour prior to transfer and dilution in a suitable infusion bag. Following dilution of the solution with 0.9% sodium chloride or 5% dextrose, ceftolozane/tazobactam is stable for 24 hours when stored at room temperature or 7 days when stored under refrigeration at 2-8^{o}C (36-46^{o}F).

Non-Formulary Utilization Data[18]

A total of 5 patients have received non-formulary ceftolozane/tazobactam for infections due to multidrug resistant pathogens, all with consultation with an infectious diseases service, from January 2015 – September 2015.

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Appendix A: Summary of Safety Issues and Implications for Pharmacy Operations

Characteristic	Summary
Drug generic name (brand name)	Ceftolozane/tazobactam (Zerbaxa™)
Drug manufacturer	Merck
Schedule of medication	None
Anticipated use per month, anticipated patient population	<5 patients with infections due to MDR organisms with no other treatment options
Route of administration	Intravenous
Does the product package insert currently have any black box warning?	No
Contraindications or significant warnings against medication use?	Contraindicated in patients with known serious hypersensitivity to ceftolozane/tazobactam, piperacillin/tazobactam, or other members of the beta-lactam class.
Is there a Risk Evaluation and Management Strategy (REMS) program for the medication? If so, where may healthcare providers find these criteria?	No
Does the manufacturer require patients to meet specific criteria for treatment with this medication? If so, where may healthcare providers find these criteria?	No
Does the manufacturer have a restricted or special distribution program? If so, how may healthcare providers contact the program?	No
Is the medication (brand name, generic name, product packaging) similar to any other medications on the Institute for Safe Medication Practices (ISMP) Sound-Alike-Look-Alike (SALA) list? If not, is the medication expected to be added to the list?	No, not expected to be added to the list.
Recommended storage conditions for medication, and how to manage excursions outside these conditions	Store intact vials at 2°C to 8°C (36°F to 46°F); protect from light. Reconstituted solution may be held for 1 hour prior to transfer and dilution in an infusion bag. Diluted solution may be stored for 24 hours at room temperature or for 7 days at 2°C to 8°C (36°F to 46°F); do not freeze
Preparation	Constitute the vial with 10 mL sterile water for injection or NS. Gently shake to dissolve. Final volume is approximately 11.4 mL and contains ceftolozane/tazobactam 1.5g. Withdraw the appropriate volume from the reconstituted vial. Add the withdrawn volume to an infusion bag containing 100 mL of NS or D5W.
Stability	Keep intact vials at 2-8°C (36-46°F); protect from light. Keep diluted solution for 24 hours at room temperature or for 7 days at 2-8°C (36-46°F).
Are Safe Handling precautions required?	No
Does the medication require disposal in a Resource Conservation and Recovery Act (RCRA) black box?	No
Can medication doses be sent to patient care units via pneumatic tube system?	Yes
Is filtration required during preparation or administration of the IV medication?	No
Is the IV medication a vesicant or irritant?	No
Is special monitoring recommended when starting therapy with this medication (eg. Telemetry)?	No
Is there a significant risk of a hypersensitivity risk with this medication?	No

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