Stony Brook Medicine
Antimicrobial Stewardship Program

Drug Name	**Ceftazidime/Avibactam**
Brand Name(s)	Avycaz®
Drug Class	Beta lactam (Cephalosporin) with non-beta lactam beta lactamase inhibitor
Restriction level	**ID consult required**

Accepted Indications	- Management of infections due to multidrug resistant, carbapenem resistant *Enterobacteriaceae* (KPC producing).
	  o Complicated intraabdominal infection (cIAI) with metronidazole
	  o Complicated urinary tract infection (cUTI)
	  o Nosocomial/healthcare associated pneumonia

Unacceptable Uses	- Empiric treatment of cIAI or cUTI
Side Effects	- Caution if history of hypersensitivity/anaphylactic reaction to other beta lactam antibiotics - Nausea - Headache - Diarrhea
Pregnancy Class	B
Dosing	2.5g (Ceftazidime 2g/avibactam 0.5g) IV over 2 hours q8h Renal dosing: - CrCl 30-50 mL/min: 1.25g IV q8h - CrCl 10-29 mL/min: 0.94g IV q12h - CrCl <10 mL/min: 0.94g IV q48h - ESRD on HD: 0.94g IV q48h, administer after HD on dialysis days
Lab monitoring	Susceptibility testing must be requested from the Microbiology lab Chem8 *at least* weekly

Questions to ask prior to approval:

- Does the patient have an active, culture proven infection or a high suspicion (i.e. recent prior culture positive) of an infection with multi-drug, carbapenem resistant *E.coli, Klebsiella,* or *Enterobacter*?
- Are there other acceptable alternative agents (i.e. aminoglycosides in women with UTI and stable renal function)?
- Does the case match one of the Accepted Indications?

Answer of “no” to any of the above questions should prompt evaluation for an alternative therapy.

Formal consultation with Infectious Diseases required.

Susceptibility testing must be requested from the microbiology lab.

Background:

Ceftazidime-avibactam is a cephalosporin β-lactam and β-lactamase inhibitor combination approved in the United States for the treatment of complicated urinary tract and intraabdominal infections in combination with metronidazole. Ceftazidime is a bactericidal agent as a result of the inhibition of bacterial cell wall synthesis mediated by penicillin-binding proteins (PBPs). It is active against gram negative bacteria, including Pseudomonas aeruginosa. It has limited activity against Acinetobacter and against gram-positive and anaerobic organisms.

This formulation combines ceftazidime with a novel beta lactamase inhibitor, avibactam, to restore activity against some β-lactam resistant gram negative bacteria. Avibactam is a non-β-lactam β-lactamase inhibitor that exhibits activity against Ambler class A β-lactamases, including extended spectrum beta-lactamases (ESBLs) and serine based carbapenemases (KPCs) and class C β-lactamases (i.e. AmpC enzymes). It has no activity against Class B β-lactamases (metallo- β-proteinases, most commonly NDMs) and limited activity against Class D β-lactamases (OXA enzymes).

Ceftazidime-avibactam has been assessed in prospective, randomized, double-blinded clinical trials in the treatment of complicated intraabdominal infections (combined with metronidazole) and complicated urinary tract infections. In the phase 2 trials, ceftazidime-avibactam was compared to a carbapenem (meropenem for cIAI, imipenem-cilastatin for cUTI) and found to be noninferior. A phase 3 trial for cIAI showed similar results to the phase 2 study. In a phase 3, pathogen directed, clinical trial, ceftazidime-avibactam was noninferior to best available therapy. Clinical conditions studied here were cUTIs and cIAIs with ceftazidime-resistant *Enterobacteriaceae* and *Pseudomonas aeruginosa*. Phase 3 trials for cUTI have been completed; however, the data has not been presented. Phase 3 trials for nosocomial pneumonia are in progress.

Of note, while this antibiotic is generally reserved for the treatment of carbapenem-resistant *Enterobacteriaceae* infections, there is limited published experience with ceftazidime-avibactam.

Serious side effects were not common and not significantly different compared to comparator agents in the published clinical trials. Most common adverse effects were abdominal pain, vomiting, nausea, and constipation. The most common laboratory events involved increases in alkaline phosphatase, ALT, and AST levels.

No significant drug-drug interactions were noted in the clinical studies. There is a potential for probenecid to decrease the elimination of avibactam. While this has not been studied, co-administration of ceftazidime-avibactam with probenecid is not recommended.

In vitro activity of ceftazidime-avibactam against gram-negative isolates.[5]					
Isolate	No.	MIC $_{50}$, µg/mL	MIC $_{90}$, µg/mL	Range	% Susceptible
Enterobacteriaceae	20,709	0.12	0.25	≤0.03 to >32	99.9
Escherichia coli	6486	0.06	0.12	≤0.03 to 4	100
-ESBL	776	0.12	0.25	≤0.03 to 4	100
Klebsiella pneumoniae	4421	0.12	0.25	≤0.03 to >32	99.9
-ESBL	721	0.25	1	≤0.03 to >32	99.6
-Meropenem-NS	276	0.5	2	≤0.03 to >32	98.9
Klebsiella oxytoca	1159	0.06	0.25	≤0.03 to 4	100
-ESBL	119	0.25	1	≤0.03 to 4	100
Proteus mirabilis	1626	≤0.03	0.06	≤0.03 to >32	99.9
-ESBL	80	0.06	0.12	≤0.03 to >32	98.8
Enterobacter cloacae	2261	0.12	0.5	≤0.03 to 32	>99.9
-Ceftazidime-NS	473	0.5	1	≤0.03 to 32	99.8
Enterobacter aerogenes	831	0.12	0.25	≤0.03 to 16	99.9
-Ceftazidime-NS	165	0.25	0.5	≤0.03 to 16	99.4
Morganella morganii	776	0.06	0.12	≤0.03 to 8	100
Citrobacter koseri	503	0.06	0.12	≤0.03 to 2	100
Citrobacter freundii	547	0.12	0.5	≤0.03 to 16	99.8
Serratia marcescens	1260	0.12	0.5	≤0.03 to 16	99.8
Proteus vulgaris	301	0.06	0.06	≤0.03 to 0.5	100
***Providencia* species**	538	0.12	0.5	≤0.03 to 16	99.6
Pseudomonas aeruginosa	3902	2	4	≤0.03 to >32	96.9
-MDR	580	4	16	0.25 to >32	81.0
-XDR	338	8	32	0.5 to >32	73.7
Haemophilus influenzae	1494	≤0.015	0.03	≤0.03 to 0.12	100
***Acinetobacter* species**	468	16	>32	0.25 to >32	33.1
-KPC producers (2013)	120	1	4	≤0.03 to >32	97.5
-CTX-M-15–like (2013)	284	0.25	1	≤0.03 to 4	100
-CTX-M-14–like (2013)	107	0.25	0.5	≤0.003 to 0.5	100

Note: above may not reflect data from Stony Brook University Hospital.

References:

1. Gilber D *et al., Sanford Guide to Antimicrobial Therapy*
2. Cosgrove SE *et al. John Hopkins Antibiotic Guidelines*
3. Avycaz®. Allergan, Plc, Dublin, Ireland; 2015. http://www.allergan.com/assets/pdf/avycaz_pi
4. Mazuski JE *et al. Clin Infect Dis* 2016; 62(11): 1380-1389
5. Carmeli Y *et al. Lancet Infect Dis* 2016; 16(6): 661-673
6. Sharma R *et al. Clin Ther* 2016; 38(3): 431-444