PK/PD in critically ill patients: pharmacology of a β-Lactam/β-Lactamase inhibitor

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For all medicinal products mentioned, please refer to the approved Summaries of Product Characteristics

DALI study: Defining Antibiotic Levels in ICU Patients

- Prospective, multinational pharmacokinetic point-prevalence study including eight **β-lactam antibiotics**[1]
  - 248 patients treated for infection, 16% did not achieve 50% $fT_{>MIC}$ and these patients were 32% less likely to have a positive clinical outcome (odds ratio, 0.68; P=0.009)
  - Positive clinical outcome was associated with increasing **50% $fT_{>MIC}$** and **100% $fT_{>MIC}$** ratios

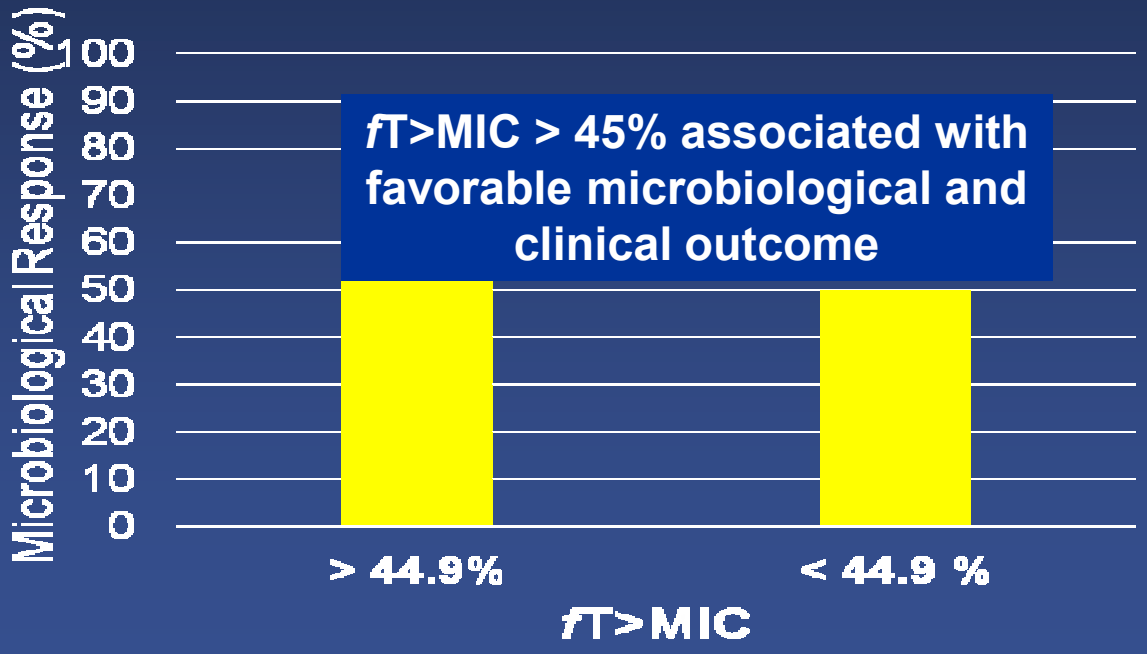
$fAUC_{0-24}$, free drug area under the concentration-time curve from 0–24 h; $fT_{>MIC}$, free antibiotic concentrations above the minimum inhibitory concentration; ICU, intensive care unit; MIC, minimum inhibitory concentration; PK, pharmacokinetic.

1. Roberts JA, et al. Clin Infect Dis 2014;58:1072–83

Clinical Pharmacodynamics of Antipseudomonal Cephalosporins

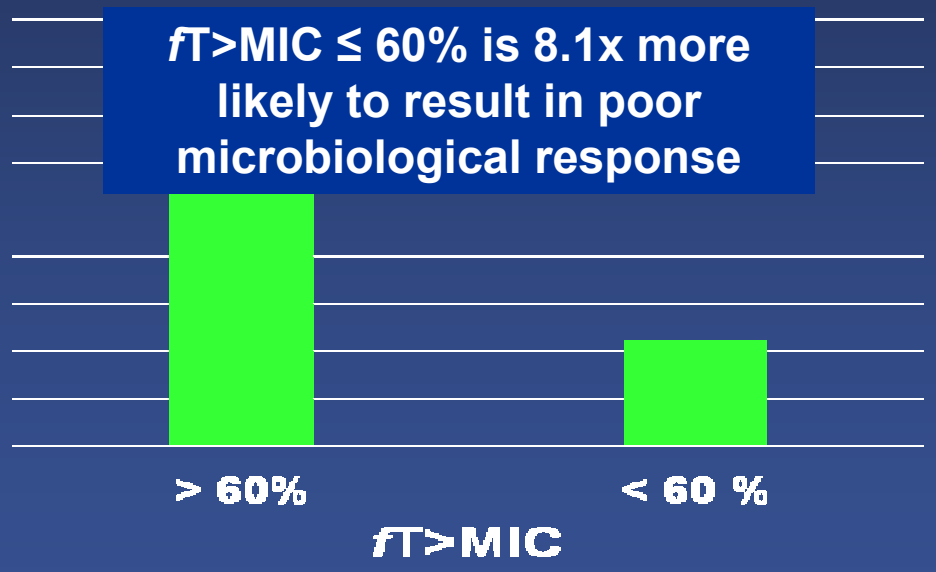
Ceftazidime[1]

154 patients with GNB nosocomial pneumonia treated with ceftazidime (32% VAP)



Cefepime[2]

56 patients infected with *P. aeruginosa* from non-urinary source (66% respiratory infections)



[1]Muller et al. J Antimicrob Chemother 2013; 68(4):900-6.
[2]Crandon et al. Antimicrob Agents Chemother 2010; 54(3):1111-16.

Clinical Pharmacodynamics of Antipseudomonal Cephalosporins in VAP: Predictors of Microbiological Success

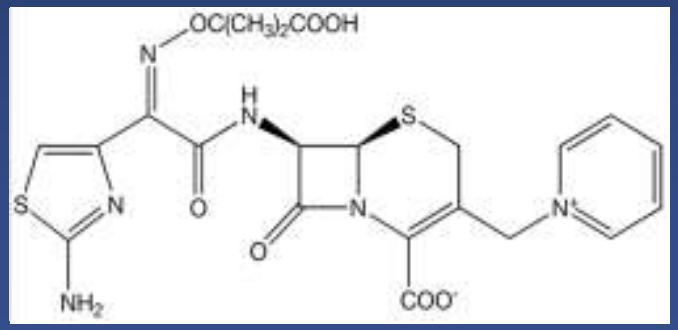
Model parameters	Odds ratio (95% CI)	P value
%$fT_{>MIC}$>53%	**10.3 (1.15–92.28)**	**0.04**
APACHE II score	1.01 (0.93–1.09)	0.85
Combination therapy	0.74 (0.25–2.19)	0.59

APACHE, Acute Physiology and Chronic Health Evaluation; CI, confidence interval; $fT_{>MIC}$, percentage of a 24-h time period that the unbound drug concentration exceeds the MIC; MIC, minimum inhibitor concentration; VAP, ventilator-associated pneumonia.
Adapted from: MacVane SH, et al. Antimicrob Agents Chemother 2014;58:1359–64.

Ceftazidime–avibactam

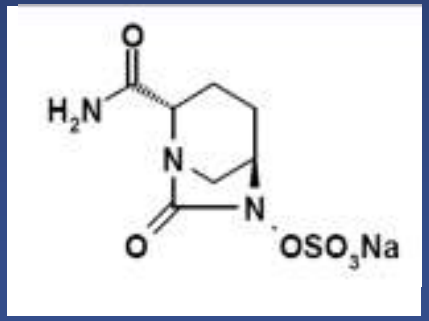
Ceftazidime

- Extended-spectrum cephalosporin with activity against Enterobacteriaceae and *P. aeruginosa*[1]
- Binds PBPs, leading to bacterial cell lysis[1]



Avibactam

- Non-β-lactam/β-lactamase inhibitor with a unique mode of action[2]
- High binding affinity for Class A, C and some Class D β-lactamases (ESBLs, KPCs, OXA-48 and AmpC), some of which are resistant to current agents (e.g. KPCs)[3]



Ceftazidime–avibactam is the first BL/BLI to retain activity against KPC-producing isolates, along with ESBLs, AmpC and OXA-48[4–6]

BL/BLI, β-lactam/β-lactamase inhibitor; ESBL, extended-spectrum beta-lactamases; KPC, *Klebsiella pneumoniae* carbapenemase; OXA, oxacillinase; PBP, penicillin binding proteins.

1. Hayes MV, Orr DC. J Antimicrob Chemother 1983;12:119–26; 2. Ehmann DE, et al. Proc Natl Acad Sci 2012;29:11663–8; 3. Aktaş Z, et al. Int J Antimicrob Agents 2012;39:86–9; 4. Lagace-Wiens P, et al. Core Evid 2014;9:13–25; 5. Crandon JL, et al. Antimicrob Agents Chemother 2012;56:6137–46; 6. Liscio JL, et al. Int J Antimicrob Agents 2015;46:266–71.

Avibactam: a broader spectrum of β-lactamase inhibition[1–6]

		Clavulanic acid	Tazobactam	Avibactam
Class A	TEM, SHV	✓	✓	✓
	CTX-M	✗	✓	✓
	KPC	✗	✗	✓
Class B	IMP, VIM, NDM-1	✗	✗	✗
Class C	AmpC	✗	✗	✓
	ACC-1, CMY-1, FOX	✗	✗	✓
Class D	OXA-48	✗	✗	✓

CTX-M, cefotaxime-β-lactamase; KPC, *Klebsiella pneumoniae* carbapenemase; NDM, New Delhi metallo-β-lactamase; TEM, temoneira; SHV, sulfhydryl variable; VIM, Verona integron-encoded metallo-β-lactamase; OXA, oxacillinase.

Adapted from: 1. Zhanel GG, et al. Drugs 2013;73:159–77; 2. Stachyra T, et al. Antimicrob Agents Chemother 2010;54:5132–8; 3. Lagacé-Wiens P, et al. Core Evid 2014;9:13–25; 4. Amoxicillin–clavulanic acid Summary of Product Characteristics, 2018; 5. Piperacillin–tazobactam Summary of Product Characteristics, 2017; 6. Zavicefta® (ceftazidime–avibactam) Summary of Product Characteristics, April 2019.

Ceftazidime–avibactam: PK properties

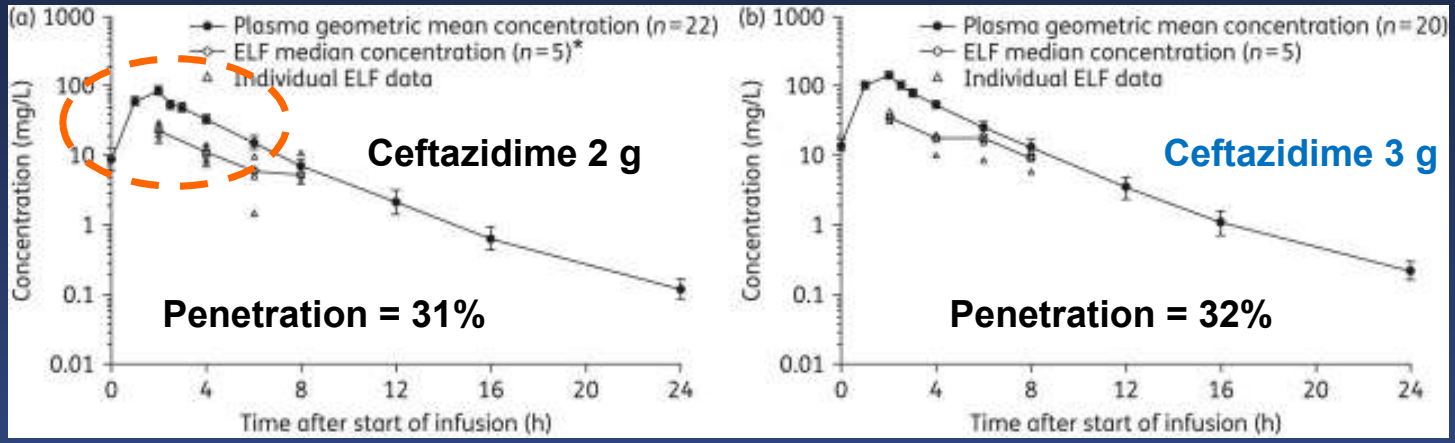
- **Studied in Phase I trials**
- **Healthy males, females, older age, renal impairment**

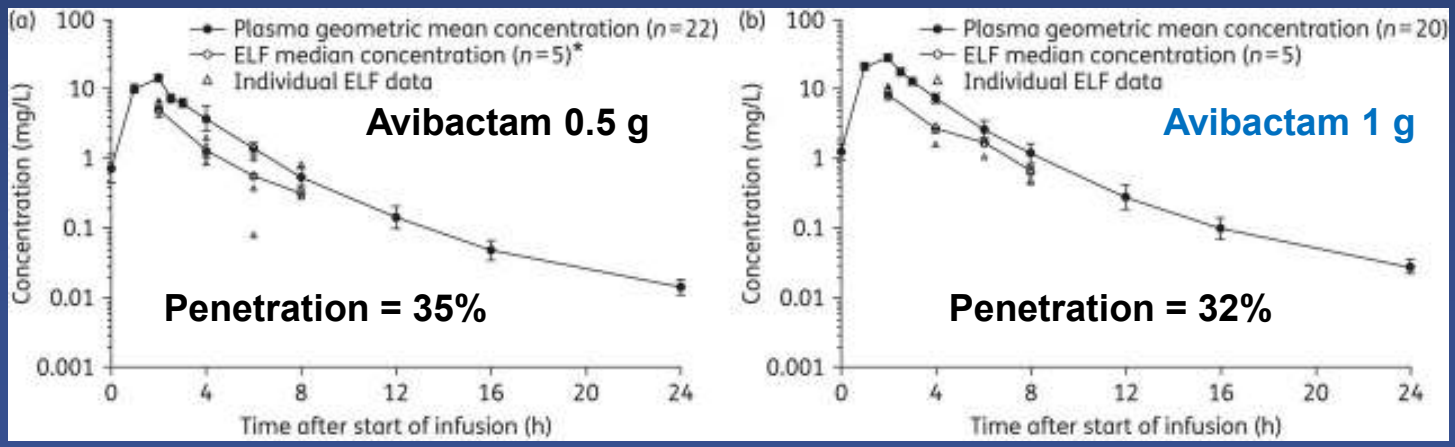
→ PK very much alike: similar half-life and PB
→ Allows dosing in fixed combination ratio: 4:1

		Ceftazidime	Avibactam
Distribution	Protein binding	15%	8.2%
	Vd,ss	18 L	22 L
Elimination	Hepatic metabolism	No	No
	Renal clearance	83%, via GFR	>97%, via GFR + tubular secretion
	$t_{1/2}$	2.7 h (after MD)	2.7 h (after MD)
Type of PK	Dose linearity	Yes	Yes
	Accumulation after MD?	No	No
Lung penetration		~30%	~30%

GFR, glomerular filtration rate; MD, multiple dosing; PB, protein binding; PK, phamacokinetic; $t_{1/2}$, terminal half-life; Vd,ss, volume of distribution at steady state.
Adapted from: Zasowski EJ, et al. Pharmacotherapy 2015;35:755–70; Zavicefta European Public Assessment Report. Available at: www.ema.europa.eu/en/medicines/human/EPAR/zavicefta. Accessed: March 2019; Zavicefta® (ceftazidime–avibactam) Summary of Product Characteristics, Apr 2019.

Bronchopulmonary penetration of ceftazidime–avibactam in healthy subjects





ELF, epithelial lining fluid.

Nicolau DP, et al. J Antimicrob Chemother 2015;70:2862–9.

Indications, Posology and Method of Administration

Recommended intravenous dose for patients with estimated CrCL ≥51 mL/min*

Indications	Dose ceftazidime–avibactam	Frequency	Infusion time	Duration of treatment
Complicated IAI†‡	2 g/0.5 g	8 hours	2 hours	5–14 days
Complicated UTI, including pyelonephritis‡	2 g/0.5 g	8 hours	2 hours	5–10 days§
Hospital-acquired pneumonia, including VAP‡	2 g/0.5 g	8 hours	2 hours	7–14 days
Infections due to aerobic Gram-negative organisms in patients with limited treatment options†‡	2 g/0.5 g	8 hours	2 hours	Guided by the severity of the infection, the pathogen(s) and the patient's clinical and bacteriological progress¶

*CrCL estimated using the Cockcroft-Gault formula.
†To be used in combination with metronidazole when anaerobic pathogens are known or suspected to be contributing to the infectious process.
‡To be used in combination with an antibacterial agent active against Gram-positive pathogens when these are known or suspected to be contributing to the infectious process.
§The total duration shown may include intravenous ceftazidime–avibactam followed by appropriate oral therapy.
¶There is very limited experience with the use of ceftazidime–avibactam for more than 14 days.
CrCL, creatinine clearance; IAI, intra-abdominal infection; UTI, urinary tract infection; VAP, ventilator-associated pneumonia.
Zavicefta® (ceftazidime–avibactam) Summary of Product Characteristics, Zavicefta Apr 2019.

Special populations

Elderly and hepatic impairment

- No dosage adjustment is considered necessary

Renal impairment

- In patients with mild renal impairment (CrCL ≥51–≤80 mL/min) no dose adjustment is necessary
- Dose recommendations are based on PK modelling
- Following each haemodialysis, the dose of ceftazidime–avibactam recommended should be repeated and continued every 48 h until next haemodialysis

Recommended intravenous doses for patients with estimated CrCL ≤50 mL/min*

Estimated CrCL (mL/min)	Dose regimen†	Frequency	Infusion time
31–50	1 g/0.25 g	Every 8 hours	2 hours
16–30	0.75 g/0.1875 g	Every 12 hours	2 hours
6–15	0.75 g/0.1875 g	Every 24 hours	2 hours
ESRD, including on haemodialysis‡	0.75 g/0.1875 g	Every 48 hours	2 hours

*CrCL estimated using the Cockcroft-Gault formula.
†Dose recommendations are based on pharmacokinetic modelling.
‡Ceftazidime and avibactam are removed by haemodialysis. Dosing of ceftazidime–avibactam on haemodialysis days should occur after completion of haemodialysis.
CrCL, creatinine clearance level; ESRD, end-stage renal disease; PK, pharmacokinetics.
Zavicefta® (ceftazidime–avibactam) Summary of Product Characteristics, Apr 2019.

Pharmacodynamics: ceftazidime–avibactam

- Ceftazidime target[1]
  - Previously established for Enterobacteriaceae and *P. aeruginosa* in murine neutropenic thigh infection model
  - 50% $fT_{>MIC}$ associated with efficacy
- Avibactam target[2]
  - Determined using *in vitro* hollow fibre and *in vivo* animal models of infection (murine neutropenic thigh and lung infection models)
  - %$fT_{>CT}$ of 1 mg/L associated with efficacy
- Joint PK/PD target used in target attainment simulations[3]
  - 50% $fT_{>MIC}$ for ceftazidime and 50% $fT_{>CT}$ of 1 mg/L for avibactam

$fT_{>MIC}$, percentage of a 24-h time period that the unbound drug concentration exceeds the MIC; MIC, minimum inhibitory concentration; PK/PD, pharmacokinetic/pharmacodynamic.

1. Coleman K, et al. Antimicrob Agents Chemother 2014:58:3366–72; 2. Berkhout J, et al. Antimicrob Agents Chemother 2015;60:368–75; 3. Nichols WW, et al. Antimicrob Agents Chemother 2018;62. pii:e02446–17.

Dose selection and validation for ceftazidime–avibactam in adults with cIAI, cUTI and nosocomial pneumonia

- Population PK models for ceftazidime and avibactam were used in PTA simulations using joint PD targets for ceftazidime and avibactam
- The joint PTA analyses supported a ceftazidime–avibactam dosage regimen of 2,000 mg + 500 mg every 8 h by 2-h intravenous infusion for patients with CrCL >50 mL/min across all approved indications and modified dosage regimens for patients with CrCL ≤50 mL/min
- Subgroup simulations for individual Phase III patients showed that the dosage regimen was robust, with high target attainment (>95%) against MICs ≤8 mg/L achieved regardless of older age, obesity, augmented renal clearance or severity of infection

cIAI, complicated intra-abdominal infection; CrCL, creatinine clearance; cUTI, complicated urinary tract infection; MIC, minimum inhibitory concentration; PD, pharmacodynamic; PK, pharmacokinetic; PTA, probability of target attainment.

Das S, et al. Antimicrob Agents Chemother 2019 Mar 27;63(4). pii: e02187-18

Exposures for ceftazidime and avibactam

- >90% joint PTA at an MIC of 8 mg/L was predicted in each indication for patients with normal renal function (CrCL >80 mL/min) receiving the standard dosage regimen

Steady-state exposures for ceftazidime and avibactam (geometric mean [CV%]) and joint PTA at an MIC of 8 mg/L summarised by indication (n=5,000 simulated patients per cohort)

	Ceftazidime		Avibactam		
	$C_{max,ss}$ (mg/mL)	$AUC_{ss,0-24}$ (mg.h/mL)	$C_{max,ss}$ (mg/mL)	$AUC_{ss,0-24}$ (mg.h/mL)	Joint PTA, %
cIAI	61.1 (44)	683 (45)	11.5 (83)	121 (72)	94.9
cUTI	73.0 (47)	880 (49)	11.2 (87)	126 (82)	95.2
NP	65.4 (53)	805 (55)	12.8 (94)	147 (89)	98.3
VAP	55.1 (59)	719 (64)	10.7 (85)	129 (79)	96.1
Non-VAP	75.7 (43)	894 (48)	14.7 (92)	164 (93)	100.0

The final population PK models included PK data from 1,975 subjects for ceftazidime and 2,249 subjects for avibactam. Simulations were conducted for 5,000 patients with normal renal function (CrCL >80 mL/min) in each indication, receiving ceftazidime–avibactam 2,000 + 500 mg, q8h as a 2-h infusion. AUC and C_{max} values are based on total plasma concentrations for ceftazidime and avibactam.

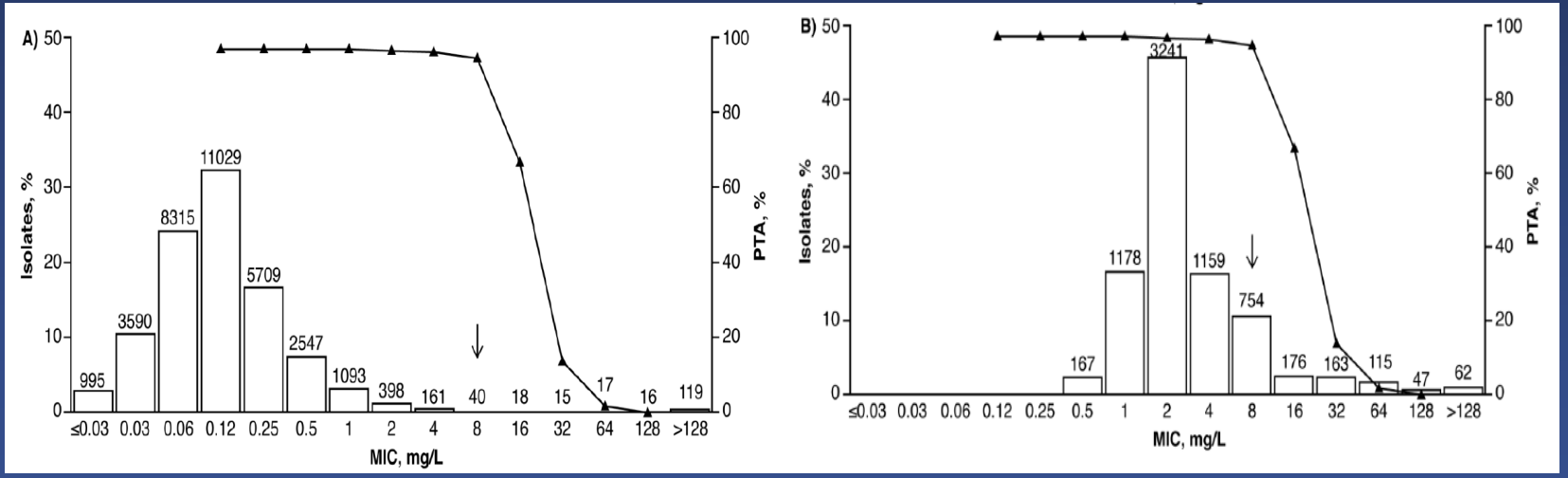
$AUC_{ss,0-24,}$ area under the curve over 24 h at steady state; cIAI, complicated intra-abdominal infection; $C_{max,ss}$, maximum concentration at steady state; CrCL, creatinine clearance; cUTI, complicated urinary tract infection; CV, coefficient of variation; MIC, minimum inhibitory concentration; NP, nosocomial pneumonia; PK, pharmacokinetic; PTA, probability of target attainment; q8h, every 8 h; VAP, ventilator-associated pneumonia.

Adapted from: Das S, et al. Antimicrob Agents Chemother 2019 Mar 27;63(4). pii: e02187-18

Ceftazidime–avibactam pharmacodynamic profiling Enterobacteriaceae and *P. aeruginosa*

Joint PTA for patients with cIAI receiving ceftazidime–avibactam 2,000 + 500 mg q8h plotted as a function of ceftazidime–avibactam MIC overlaying the ceftazidime–avibactam MIC distributions against Enterobacteriaceae (n=34,062) and *P. aeruginosa* (n=7,062) from the INFORM global surveillance study (2012–2014)

Enterobacteriaceae | **Pseudomonas aeruginosa**



Defined as simultaneous attainment of 50% $fT_{>MIC}$ of ceftazidime–avibactam for ceftazidime and 50% $fT_{>CT}$ of 1 mg/L for avibactam, with both targets having to be achieved for a simulated patient to be categorised as achieving the joint target. Joint PTA calculated using iteration 4 of the population PK models. Ceftazidime–avibactam MIC distributions were obtained from the INFORM 2012–2014 global surveillance study. Values above the bars are the numbers of isolates tested at each MIC. The arrows show the position of the approved ceftazidime–avibactam susceptible clinical breakpoint of MIC ≤8 mg/L.

cIAI, complicated intra-abdominal infection; $fT_{>MIC}$, percentage of a 24-h time period that the unbound drug concentration exceeds the MIC; MIC, minimum inhibitory concentration; PTA, probability of target attainment.

Das S, et al. Antimicrob Agents Chemother 2019 Mar 27;63(4). pii: e02187-18

Ceftazidime–avibactam in ICU patients

- Ceftazidime–avibactam, infused over 2 h, in 10 ICU patients
- Two patients with ARC, 6 patients with normal RF, two patients with moderate RI

TABLE 2. BASELINE CHARACTERISTICS OF STUDY PARTICIPANTS (n = 10)

Characteristic	*Mean (range)*
Age (y)	55 (37– 86)
Weight (kg)	75 (50–131)
BMI (kg/m^2)	25 (17– 39)
APACHE II (score)	21 (11– 33)
Creatinine clearance (mL/min)	103 (47–190)

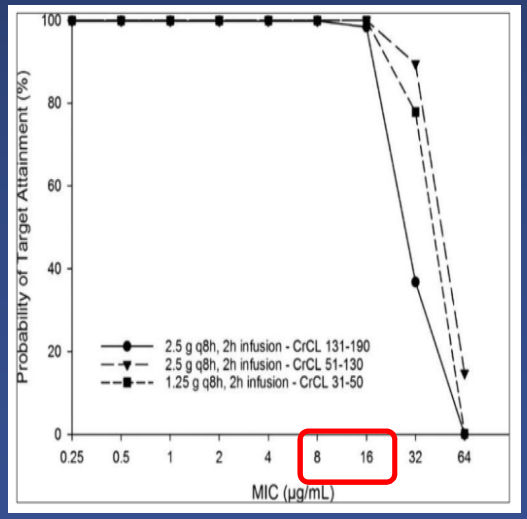
BMI = body mass index; APACHE = Acute Physiology and Chronic Health Evaluation.

TABLE 3. POPULATION PHARMACOKINETIC PARAMETERS FOR CEFTAZIDIME AND AVIBACTAM IN ADULT INTENSIVE CARE UNIT PATIENTS

Pharmacokinetic parameter	*Mean (SD)*
Ceftazidime	
Model derived parameters	
V_d	34.78 (10.49)
CL_i	1.15 (0.63)
CL_s	0.043 (0.016)
Calculated parameters	
CL	6.14 (3.80)
$t_{1/2}$	4.84 (2.15)
Avibactam	
Model derived parameters	
V_d	50.81 (14.32)
CL_i	0.89 (0.58)
CL_s	0.10 (0.03)
Calculated parameters	
CL	11.09 (6.78)
$t_{1/2}$	4.09 (2.13)

V_d = volume of distribution; CL_i = clearance intercept term; CL_s = clearance slope term; CL = total body clearance, where $CL = CL_i + (CL_s * CrCL)$; $t_{1/2}$ = half-life.

Higher Vd and Longer $t_{1/2}$



ARC, augmented renal clearance; CL, clearance; ICU, intensive care unit; MIC, minimum inhibitory concentration; PTA, probability of target attainment; RF, renal function; RI, renal impairment; $t_{1/2}$, half-life; Vd, volume of distribution.

Adapted from: Stein GE, et al. Surg Infect 2019;20:55–61.

Is it Time to Put the Polymyxins Back on the Shelf?

- **Ceftazidime–avibactam**
  - Prospective, multicenter, observational study vs **colistin-based regimens**
    - » **Improved efficacy**
    - » **Reduced toxicity**

1. Van Duin D, et al. *Clin Infect Dis* 2018;66(2):163–71

Clinical Outcomes and Emergence of Ceftazidime–Avibactam Resistance in Patients Treated for CRE Infection

- 37 CRE patients were treated with ceftazidime–avibactam
- Clinical success and survival rates at 30 days were 59% (22/37) and 76% (28/37), respectively
- In 23% (5/22) of clinical successes, CRE infections recurred within 90 days
- Microbiologic failure rate was 27% (10/37)
- Ceftazidime–avibactam resistance was detected in 30% (3/10) of microbiologic failures

Pfizer has data on combination therapy of Zavicefta along with metronidazole, aminoglycosides, vancomycin and linezolid based only on Phase III trials and *in vitro* studies. Beyond this, Pfizer has no data to recommend combination therapy.
CRE, carbapenem-resistant Enterobacteriaceae.
Shields RK, et al. Clin Infect Dis 2016;63:1615–8.

When "S" ≠ success ?

- **Discordant therapy (i.e., inadequate therapy and low exposures due to insufficient dose and/or regimen)**
  - **Increased body weight**
  - **↑ Vd (sepsis/septic shock)**
  - **Renal function**
    - **Reduced**
    - **Augmented**
  - **High MIC organisms/mutational variants**
    - **Mutations in plasmid-borne *bla*$_{KPC-3}$** [Shields RK, et al. AAC 2017]
  - **Therapeutic interventions (i.e., CRRT*, ECMO)**

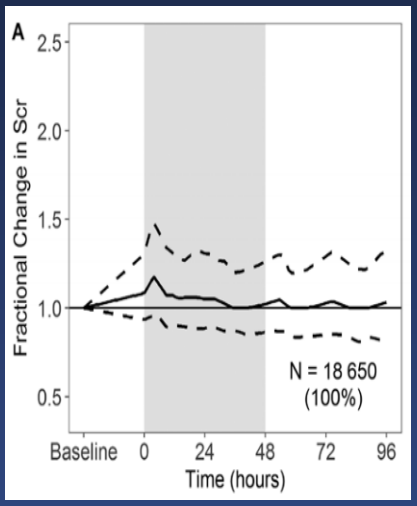
*Pneumonia and renal replacement therapy are risk factors for ceftazidime–avibactam treatment failures & resistance among patients with carbapenem-resistant Enterobacteriaceae infections.
CRRT, continuous renal replacement therapies; ECMO, extracorporeal membrane oxygenation; KPC, *Klebsiella pneumoniae* carbapenemase; MIC, minimum inhibitory concentration; Vd, volume of distribution.

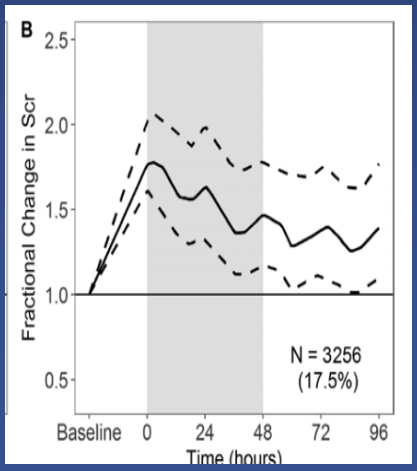
Shields RK, et al. Antimicrob Agents Chemother 2017;61:e02097-16; David Nicolau, personal communication.

Renal Dosing of Antibiotics: Are We Jumping the Gun?

Ryan L. Crass,[1] Keith A. Rodvold,[2] Bruce A. Mueller,[1] Manjunath P. Pai[1]

- **Illustration of the dynamic nature of renal impairment in acutely infected patients**
  - **Retrospective study**
  - **18,500 patients included with cUTI (41%), acute bacterial pneumonia (11%), SSSI (32%) or cIAI (16%)**
  - **Total population:**
    - » **Rate of AKI on admission: 17.5%**
    - » **Kidney injury resolved in 57% of patients after 48 h**
  - **Subgroup with moderate RI (16.4%)**
    - » **Rate of AKI on admission: 38%**
    - » **Kidney injury resolved in 46% of patients after 48 h**





AKI, acute kidney injury; cIAI, complicated intra-abdominal infection; cUTI, complicated urinary tract infection; SSSI, skin and skin structure infections; RI, renal impairment.
Crass RL, et al. Clin Infect Dis 2019 Apr 24;68(9):1596-160

Renal Dosing of Antibiotics: Are We Jumping the Gun?

Ryan L. Crass,[1] Keith A. Rodvold,[2] Bruce A. Mueller,[1] Manjunath P. Pai[1]

- **Conclusions:**
  - **Adequate antibiotic exposure is very important in the first 48 h – the authors call this 'THE CRITICAL PERIOD'**
  - **For antibiotics with a wide safety margin (e.g., β-lactams) dose adjustments should be deferred until 48 h after initiation when the trajectory of the patient's renal function is better known**
  - **If renal impairment persists: dose adjustment should be carried out on Day 3 to minimise toxicity**

Crass RL, et al. Clin Infect Dis 2019 Apr 24;68(9):1596-160.

Ceftazidime–avibactam: dosing recommendations

- Dosing regimen – model based and validated across many patient populations[1,2]
  - Based on >90% PTA (>50% $fT_{>MIC}$ (8 mg/L) for CAZ and >50% $fT_{>Ct}$ (1 mg/L) for AVI
  - Validated across the target indications, including critically ill patients with ARC
- Standard dosing is 2.5 g q8h – important to infuse this over 2 h[1]
- Adequate (sufficient) dosing in patients with renal insufficiency is important[3]

ARC, augmented renal clearance; AVI, avibactam; CAZ, ceftazidime; Ct, threshold concentration; CVVH, continuous venovenous haemofiltration; ECMO, extracorporeal membrane oxygenation; MIC, minimum inhibitory concentration; PTA, probability of target attainment.

1. Das S, et al. Antimicrob Agents Chemother 2019; DOI: 10.1128/AAC.02187-18. Epub ahead of print; 2. Stein GE, et al. Surg Infect 2019;20:55–61;
3. Crass RL, et al. Clin Infect Dis 2019 Apr 24;68(9):1596-160

Ceftazidime-Avibactam: Important Safety Information (SmPC Apr2019)

Contraindications: Hypersensitivity to the active substances or to any of the excipients, Hypersensitivity to any cephalosporin antibacterial agent, Severe hypersensitivity (e.g. anaphylactic reaction, severe skin reaction) to any other type of β-lactam antibacterial agent (e.g. penicillins, monobactams or carbapenems)

Warnings: Ceftazidime and avibactam are eliminated via the kidneys, therefore, the dose should be reduced according to the degree of renal impairment. Neurological sequelae, including tremor, myoclonus, non-convulsive status epilepticus, convulsion, encephalopathy and coma, have occasionally been reported with ceftazidime when the dose has not been reduced in patients with renal impairment . In patients with renal impairment, close monitoring of estimated creatinine clearance is advised. In some patients, the creatinine clearance estimated from serum creatinine can change quickly, especially early in the course of treatment for the infection. Concurrent treatment with high doses of cephalosporins and nephrotoxic medicinal products such as aminoglycosides or potent diuretics (e.g. furosemide) may adversely affect renal function. *Clostridium difficile*-associated diarrhoea (CDAD) has been reported for nearly all systemic antibacterial drugs, including Ceftazidime-avibactam may range in severity from mild diarrhoea to fatal colitis. Treatment with antibacterial drugs alters the normal flora of the colon and may permit overgrowth of *C. difficile.* If CDAD is suspected or confirmed, antibacterial drugs not directed against *C. difficile* may need to be discontinued. Manage fluid and electrolyte levels as appropriate, supplement protein intake, monitor antibacterial treatment of *C. difficile*, and institute surgical evaluation as clinically indicated. Ceftazidime-avibactam use may cause development of a positive direct antiglobulin test (DAGT, or Coombs test), which may interfere with the cross-matching of blood and/or may cause drug induced immune haemolytic anaemia.