Evidenced Based Review of Pharmacology of Ceftazidime-Avibactam Combination

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Disclosures

I am a consultant, speakers bureau member or have received research funding from:

Achaogen, Bayer, Cepheid, Merck,

Medicine Co., Pfizer, Shionogi

Advisory Member: Clinical Laboratory Standards Institute (CLSI)

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World Health Organization: WHO's Driving the Cure

- **Published its first ever list of antibiotic-resistant "priority pathogens"**
- **Guide and promote research and development (R&D) of new antibiotics**

Priority 1: CRITICAL

***Enterobacteriaceae*, carbapenem-resistant, ESBL-producing**

***Pseudomonas aeruginosa*, carbapenem-resistant**

***Acinetobacter baumannii*, carbapenem-resistant**

Priority 2: HIGH

Enterococcus faecium, vancomycin-resistant

Staphylococcus aureus, MRSA, vancomycin-intermediate and resistant

Helicobacter pylori, clarithromycin-resistant

Campylobacter spp., fluoroquinolone-resistant

Salmonellae, fluoroquinolone-resistant

Neisseria gonorrhoeae, cephalosporin-resistant, FQ-resistant

Priority 3: MEDIUM

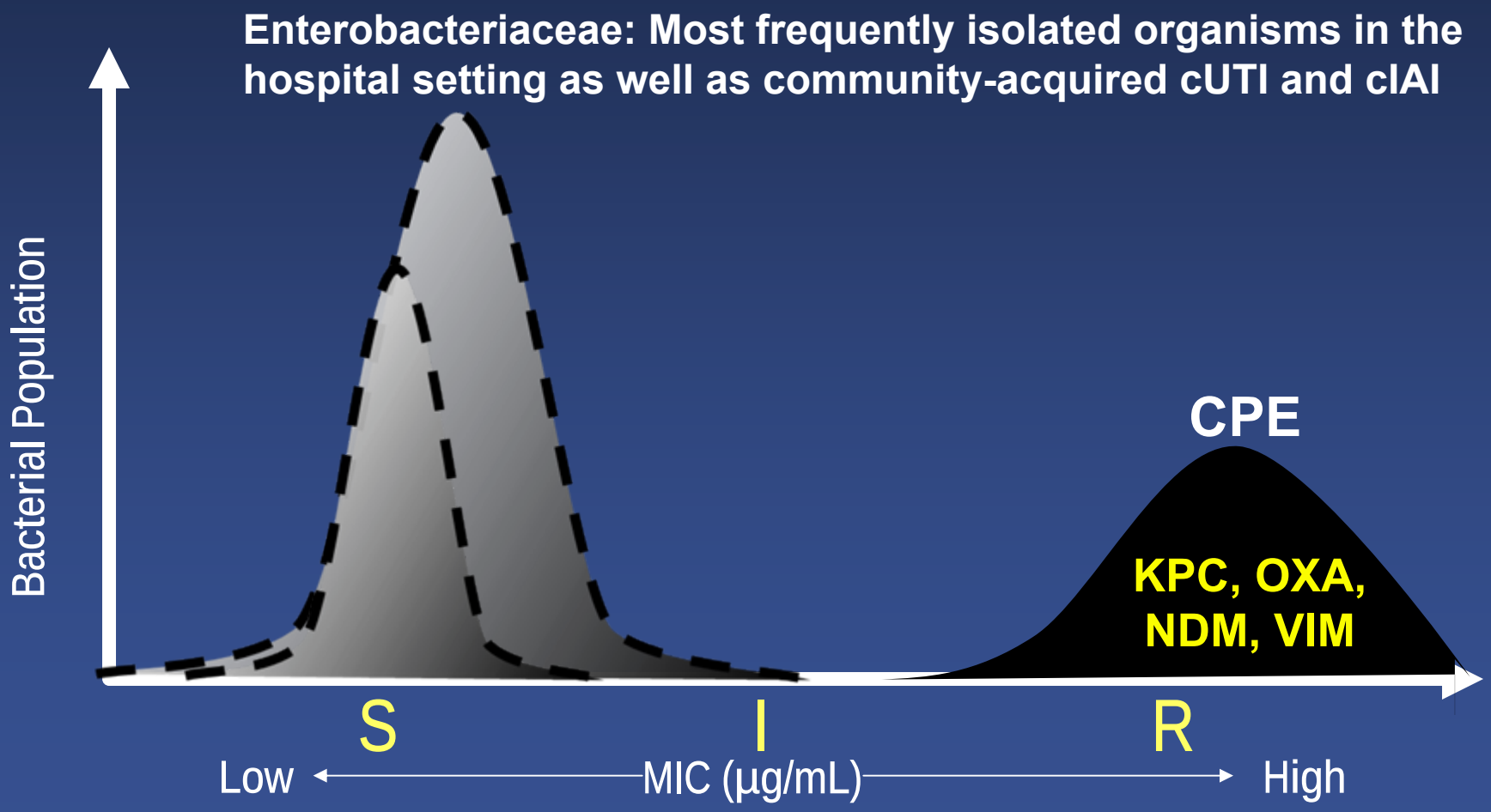
Streptococcus pneumoniae, penicillin-non-susceptible

Haemophilus influenzae, ampicillin-resistant

Shigella spp., fluoroquinolone-resistant

Prioritization of pathogens to guide discovery, research and development of new antibiotics for drug resistant bacterial infections, including tuberculosis. Sept 2017; WHO/EMP/IAU/2017.12

Reduced Potency of β-Lactams in the Face of Carbapenemase-Producing Enterobacteriaceae (CPE)



Avery LM & Nicolau DP. *Expert Opinion on Investigational Drugs; In Press*

β-Lactam Antimicrobials: The Backbone of Therapy

- **Penicillins, Cephalosporins, Carbapenems**
  - **Reconstitute potency with β-Lactamase inhibitor**
- **Most frequently used agents in hospital**
- **Used to treat wide range of severity of illness: Sepsis → Urinary tract infections**
- **Considerations for use:**
  - ***In vitro potency*** **→ *Gram+, Gram- and anaerobic***
  - ***Clinical efficacy*** **→ *Sepsis, Pneumonia, Urinary, …***
  - ***Safety profile*** **→ *Well established***
  - ***Flexibility in dosing*** **→ Dose, Interval, Duration of Infusion**

Monogue ML, Kuti JL, Nicolau DP. *Expert Review of Clinical Pharmacology* 2016;9(3):459-476.

Novel β-lactam / β-lactamase Inhibitors for Carbapenemase-Producing Enterobacteriaceae

- **β-lactam plus Novel Inhibitor**
  - **Ceftazidime - Avibactam [KPC, OXA]**
  - **Aztreonam - Avibactam [MBL]**
  - **Imipenem - Relebactam [KPC]**
  - **Meropenem - Vaborbactam [KPC]**
  - **Cefepime - VNRX-5113 [KPC, OXA, MBL]**
  - **Cefepime - Zidebactam [KPC, OXA, MBL]**
  - **Meropenem – Nacubactam [KPC, OXA, MBL]**

KPC: *K. pneumoniae* carbapenemase; OXA: oxacillinase; MBL: metallo-β-lactamase
Except Ceftazidime-Avibactam, referenced combinations are not licensed by EMA [status: Phase II or III, preregistration]

Avery LM & Nicolau DP. *Expert Opinion on Investigational Drugs; In Press*

Avibactam: broader spectrum of activity than currently available β-lactamase inhibitors

		Clavulanic acid	Tazobactam	Avibactam
Class A	TEM, SHV	✓	✓	✓
	CTX-M	✗	✓	✓
	PER, VEB, GES	✗	✓	✓
	KPC	✗	✗	✓
Class B	IMP, VIM, NDM1	✗	✗	✗
Class C	Chromosomal Enterobacteriaceae AmpC	✗	✗	✓
	Chromosomal *Pseudomonas* AmpC	✗	✗	✓
	Plasmid-encoded ACC, DHA, CMY, FOX, LAT, MOX, MIR, ACT	✗	✗	✓
Class D	OXA-1, -31, -10, -13	Variable OXA-1, -10	Variable	Variable OXA-1, -31
	Carbapenemase-type OXA-23, -40, -48, -58	Variable	Variable OXA-23, -48	Variable OXA-48

PP-ZVA-GLB-0061
Date of preparation: April 2017

Stachyra T, et al. *AAC*. 2010;54:5132–8;
Lagacé-Wiens P, et al. *Core Evid*. 2014;9:13.

Avibactam: A broader spectrum of β-lactamase inhibition

	IC50 (nM) for inhibition of β-lactamase activity		
	Avibactam	Clavulanic acid	Tazobactam
Class A			
TEM-1	8	130	40
TEM-1	8	58	32
SHV-4	1.5	5	120
SHV-4	3	4	55
KPC-2	38	6,500	80,000
KPC-2	170	>100,000	50,000
CTX-M-15	5	12	6
CTX-M-15	5	12	6
Class C			
AmpC	128	>100,000	4,600

Avibactam potency is 10 to >100 times that of currently available therapeutic inhibitors

TEM: temoneira; SHV: sulfhydryl variable; KPC: *K. pneumoniae* carbapenemase; CTX-M: cefotaxime-β-lactamase

Zhanel GG, et al. *Drugs* 2013;73:159–177.

New β-Lactamase Inhibitors: a Therapeutic Renaissance in an MDR World

Very potent vs. serine beta-lactamases

Sarah M. Drawz,[a] Krisztina M. Papp-Wallace,[b,c] Robert A. Bonomo[b,c,d,e]

Department of Laboratory Medicine and Pathology, University of Minnesota, Minneapolis, Minnesota, USA[a]; Research Service, Louis Stokes Cleveland Department of Veterans Affairs, Cleveland, Ohio, USA[b]; Departments of Medicine,[c] Pharmacology,[d] and Molecular Biology and Microbiology,[e] Case Western Reserve University, Cleveland, Ohio, USA

TABLE 1 MICs of β-lactam and β-lactam-avibactam combinations against select pathogens[a]

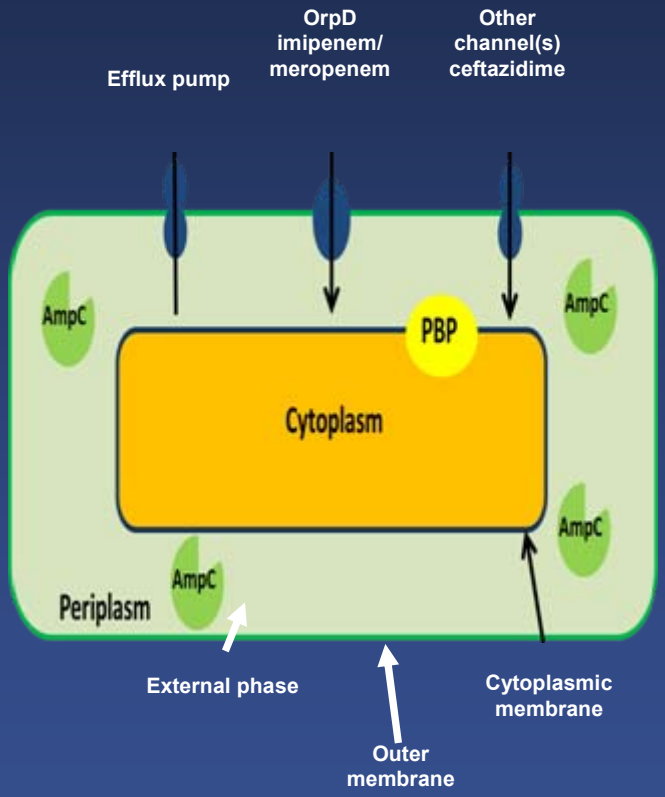
	MIC (μg/ml)[b]					
Pathogen	CAZ	CAZ-AVI	CPT	CPT-AVI	ATM	ATM-AVI
K. pneumoniae with OXA-48	256/512	0.25/0.5				
K. pneumoniae with CTX-M-15	8/64	0.06/0.25				
K. pneumoniae with KPC-2	≥512/≥512	0.25/1			≥512/≥512	≤0.06/≤0.06
E. coli with ESBL	16/64	0.12/0.25				
E. coli with AmpC	16/64	0.12/0.5				
E. coli with OXA-48	4	<0.008				
E. coli with IMP-1	256	64				
Enterobacteriaceae with multiple β-lactamases, including KPC-2			>64/>64	0.5/2		
Enterobacteriaceae with multiple β-lactamases, including AmpC			256/>256	0.5/2		
Enterobacteriaceae with VIM	64–512	64–512			0.25–256	0.12–0.5
P. aeruginosa	8/64	4/8	>64/>64	16/>32	16/32	8/32
P. aeruginosa with ESBL PER-1	128/128	4/16				
A. baumannii			>64/>64	32/>32		
A. baumannii with PER-1, OXA-51, and OXA-58	128/≥512	32/256				
S. aureus			1/2	1/2		

[a] Data were adapted from references 15, 16, 19, 20, 21, and 24. Avibactam was added at 4 μg/ml. Abbreviations: CAZ, ceftazidime; AVI, avibactam; CPT, ceftaroline; ATM, aztreonam.

[b] Numbers separated by a forward slash indicate MIC_{50}/MIC_{90} values. Empty cells indicate that values were not reported.

Activity against *P. aeruginosa* resistant to carbapenems through derepressed AmpC and OprD deletion

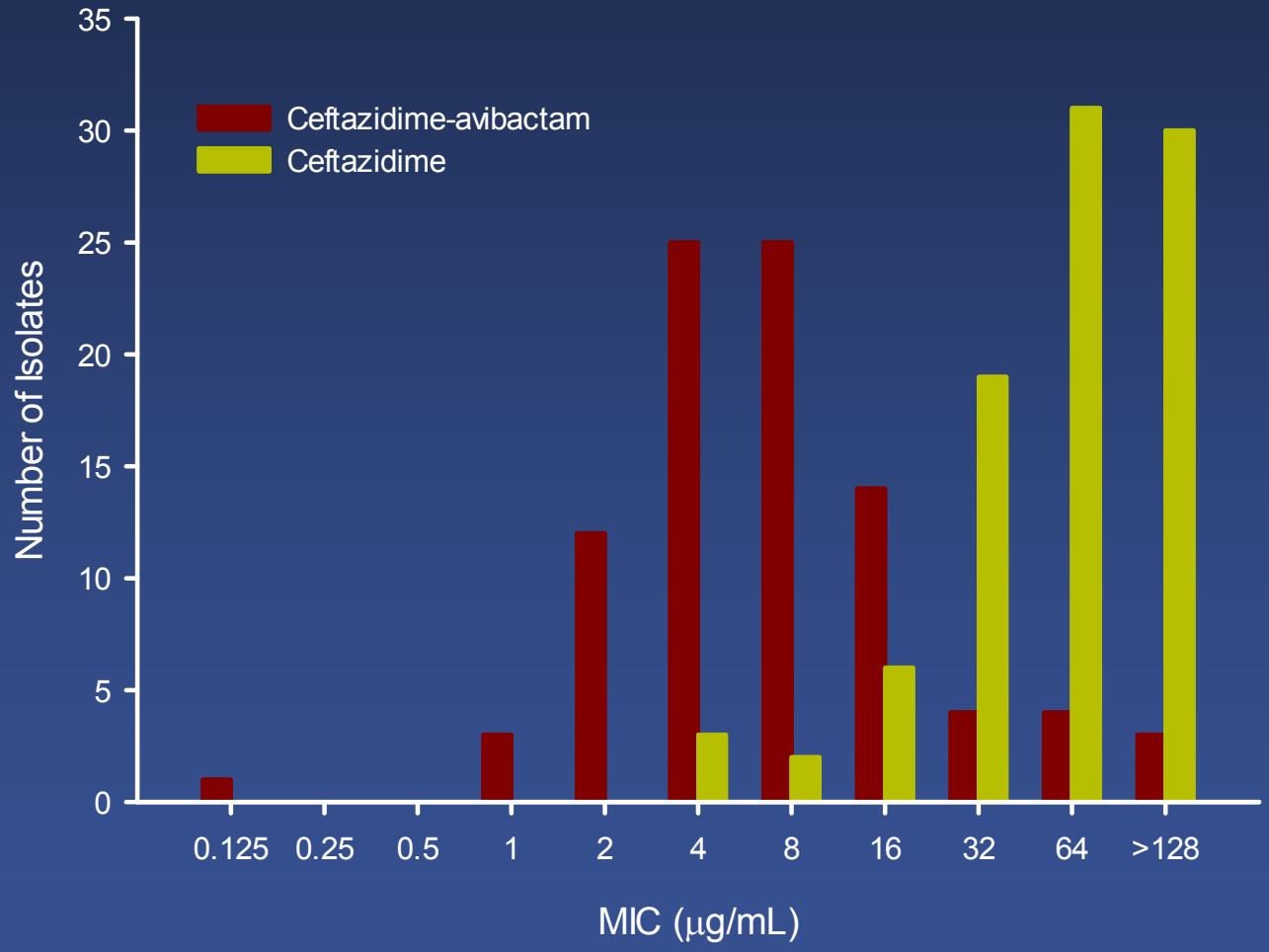
Strain[1]	AmpC	OprD	MIC (mg/L)		
			CAZ	CAZ – AVI	MEM
1405-def	Basal	Basal	4	2	0.25
1405-con	Up-regulated	Basal	128	8	0.5
1405-con D2-	Up-regulated	Deleted	128	8	16



Mushtaq S, et al. *JAC.* 2010;65:2376.

Ceftazidime-Avibactam *In Vitro* Activity against *P. aeruginosa*

- **91 clinical, non-urine *P. aeruginosa***



Crandon *et al*. Antimicrob Agents Chemother 2012;56:6137-46

Ceftazidime – Avibactam

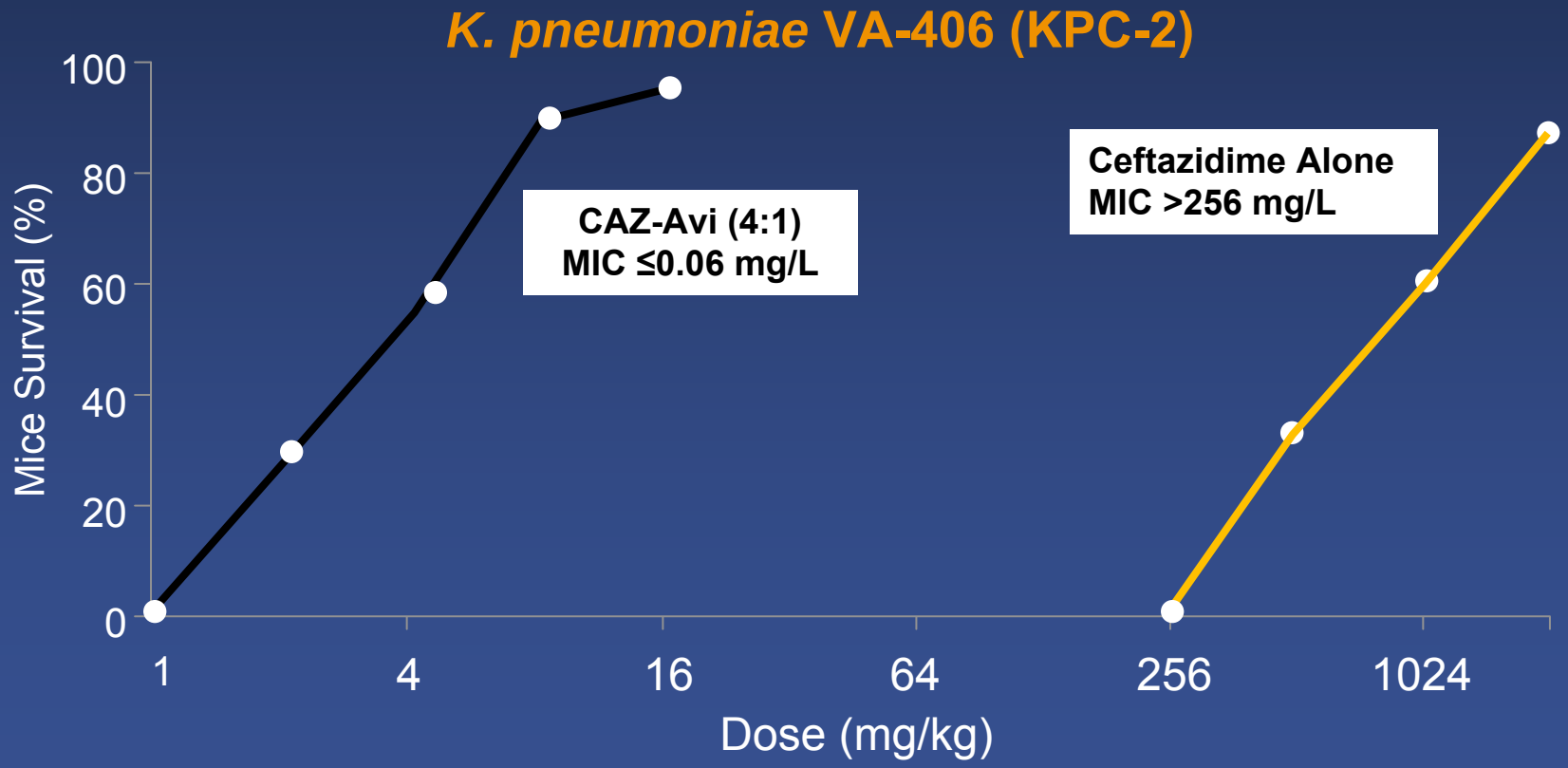
Indications

- Complicated intra-abdominal infections plus metronidazole
- Complicated urinary tract infection including pyelonephritis
- Hospital-acquired pneumonia (HAP), including ventilator associated pneumonia (VAP)
- Infections due to aerobic Gram-negative organisms in adult patients with limited treatment options

Zavicefta, Summary of Product Characteristics, EMA, July 2017

Ceftazidime – Avibactam: Activity against Ceftazidime–Non Susceptible Isolates in Animal Infection Model

Activity of Ceftazidime – Avibactam and Ceftazidime against *K. pneumoniae* KPC-2 Induced Septicemia in Mice

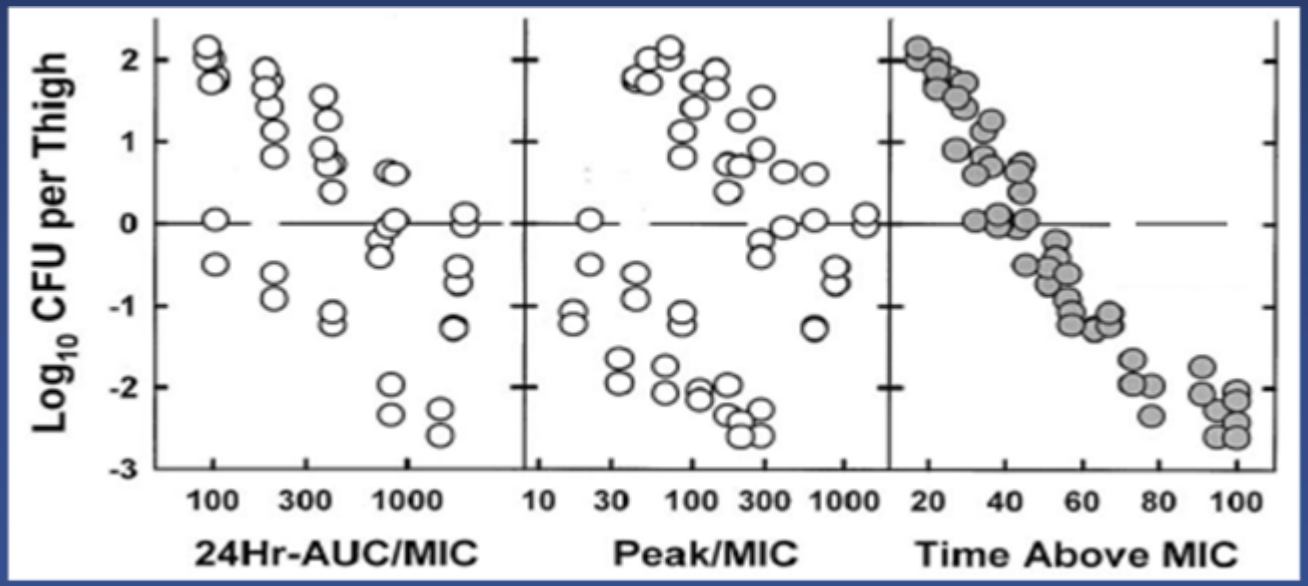


Ceftazidime-Avibactam FDA Briefing Document. December 5, 2014. Cerexa, Inc., a subsidiary of Actavis plc.

Pharmacodynamics: Ceftazidime

- %*f*T>MIC is well-established as the PK/PD index associated with efficacy of ceftazidime
  - ~50% *f*T>MIC associated with efficacy based on both nonclinical[1] and clinical data[2]

PK/PD of ceftazidime vs. *P. aeruginosa* in a neutropenic mouse thigh infection model



1. Craig, Infect Dis Clin N Am 2003
2. Mueller et al., J Antimicrob Chemother 2013; MacVane et al., Antimicrob Agents Chemother 2014

Pharmacodynamics: CAZ-AVI

- **Ceftazidime target**
  - **Previously established for Enterobacteriaceae and *P. aeruginosa* in murine neutropenic thigh infection model**
  - **50% *f*T>MIC associated with efficacy**
- **Avibactam target**
  - **Determined using *in vitro* hollow fiber and *in vivo* animal models of infection (murine neutropenic thigh and lung infection models)**
  - **%*f*T>C_T of 1 mg/L associated with efficacy**
- **Joint PK/PD target used in target attainment simulations:**
  - **50% *f*T>MIC for ceftazidime and 50% *f*T>C_T of 1 mg/L for avibactam**

Coleman et al., Antimicrob Agents Chemother 2014
Berkhout et al., Antimicrob Agents Chemother 2015

Posology and Method of Administration

Type of infection	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

IAI, invasive intra-abdominal infection; UTI, urinary tract infection; VAP, ventilator-associated pneumonia.
Zavicefta SmPC. 2017.

Special populations

Elderly , Hepatic impairment

No dosage adjustment is considered necessary

Renal impairment

In patients with mild renal impairment (estimated creatinine clearance CrCL 51–≤ 80 mL/min) no dose adjustment is necessary

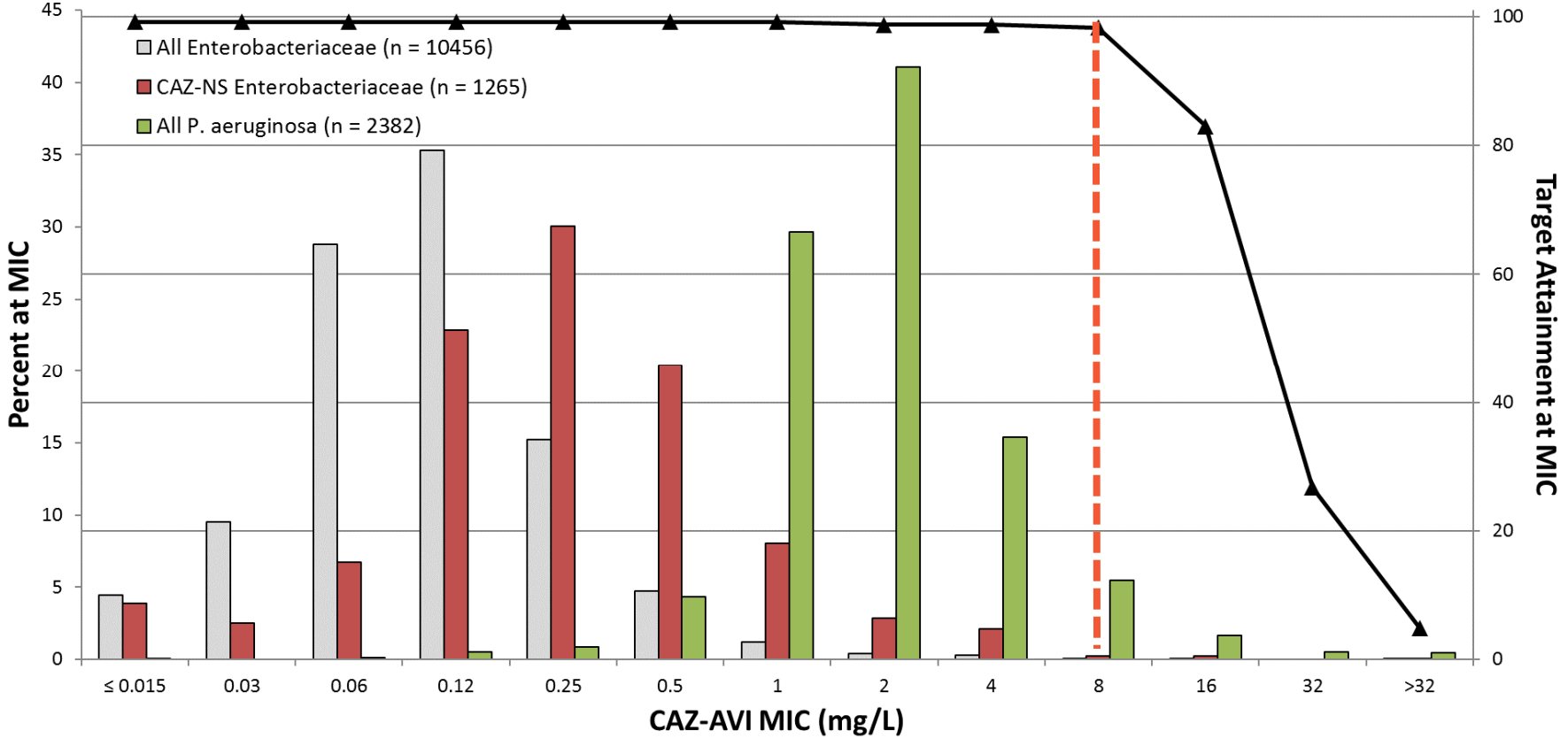
Dose recommendations are based on PK modelling

Following each haemodialysis, the dose of ceftazidime–avibactam recommended should be repeated and continued every 48 hours until next haemodialysis

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, creatinine clearance level; ESRD, end stage renal disease; PK, pharmacokinetics.
Zavicefta SmPC. 2017.

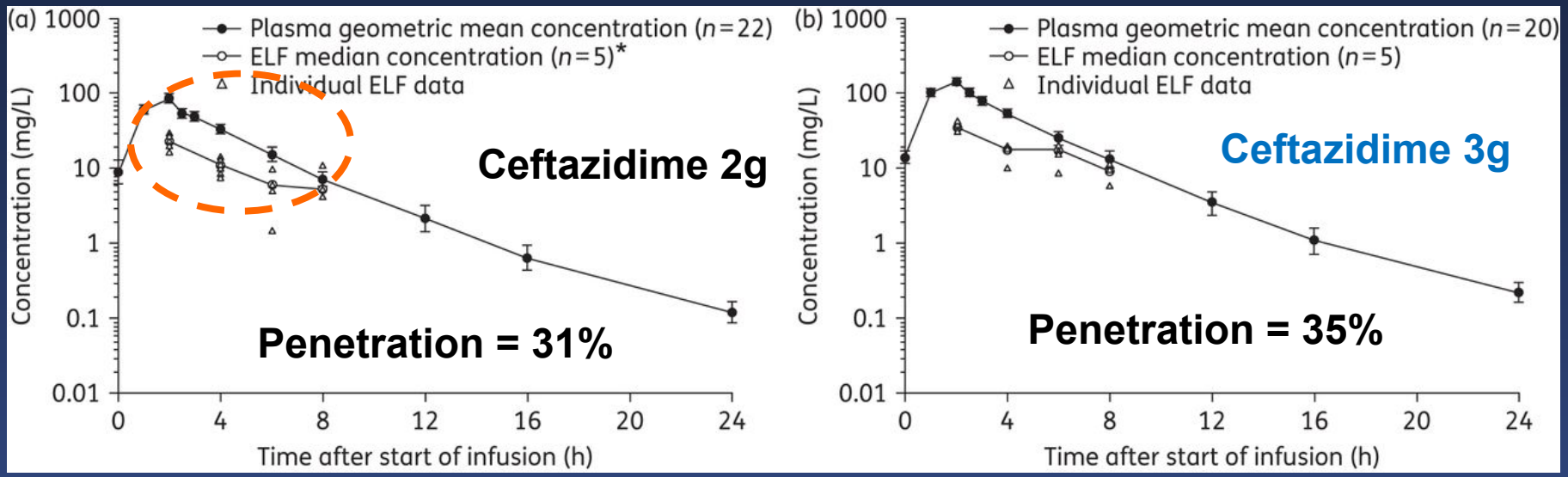
Target Attainment Simulations – cIAI, Normal Renal Function

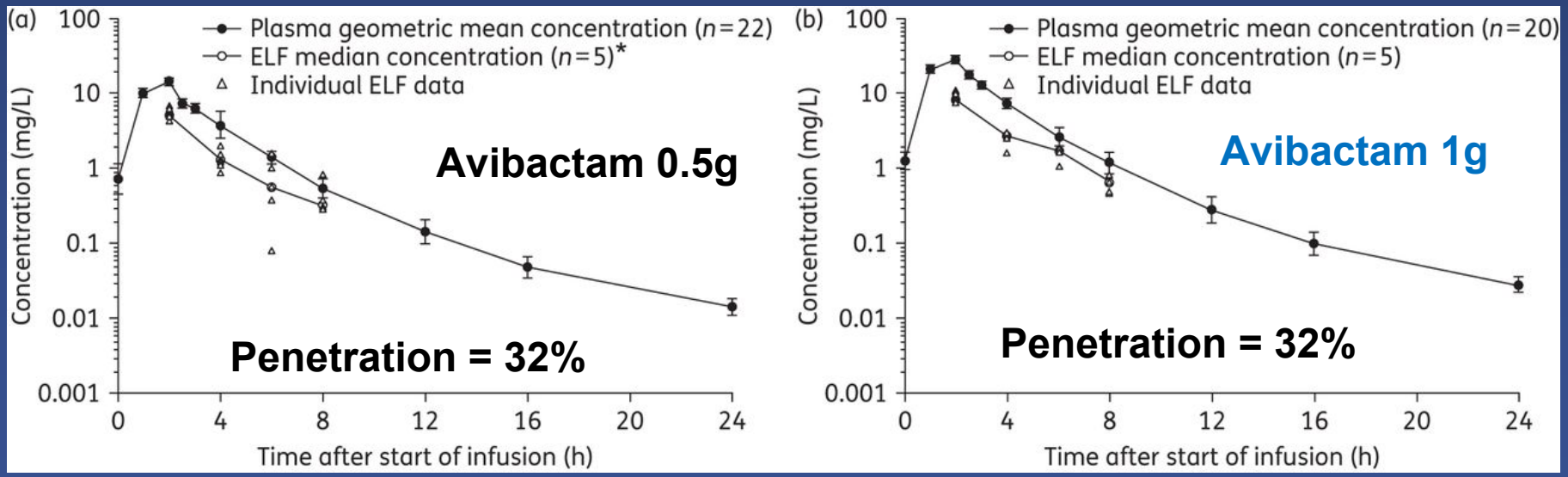


- **Supports breakpoint of 8 mg/L**

Data on file

BronchopuImonary Penetration of Ceftazidime/Avibactam Healthy Subjects





Nicolau DP, et al. J. Antimicrob. Chemother. 2015;70:2862-2869

Ceftazidime-Avibactam Versus Other Treatment Regimens against Carbapenem-Resistant *K. pneumoniae* Bacteremia

- Single-center observation, 109 patients [50% ICU]
- Ceftazidime-avibactam treatment of carbapenem-resistant *Klebsiella pneumoniae* bacteremia was associated with higher rates of clinical success ($P = 0.006$) and survival ($P = 0.01$) than other regimens.
- Across treatment groups, there were no differences in underlying diseases, severity of illness, source of bacteremia, or strain characteristics (97% produced *K. pneumoniae* carbapenemase).
- Aminoglycoside- and colistin-containing regimens were associated with increased rates of nephrotoxicity ($P = 0.002$).

Shields RK et al Antimicrob Agents Chemother 2017 Jul 25;61(8) / AAC.00883-17

Clinical Outcomes, Drug Toxicity, and Emergence of Ceftazidime-Avibactam Resistance Among Patients Treated for Carbapenem-Resistant Enterobacteriaceae Infections

Shields RK et al Clin Infect Dis 2016;63(12):1615-1618

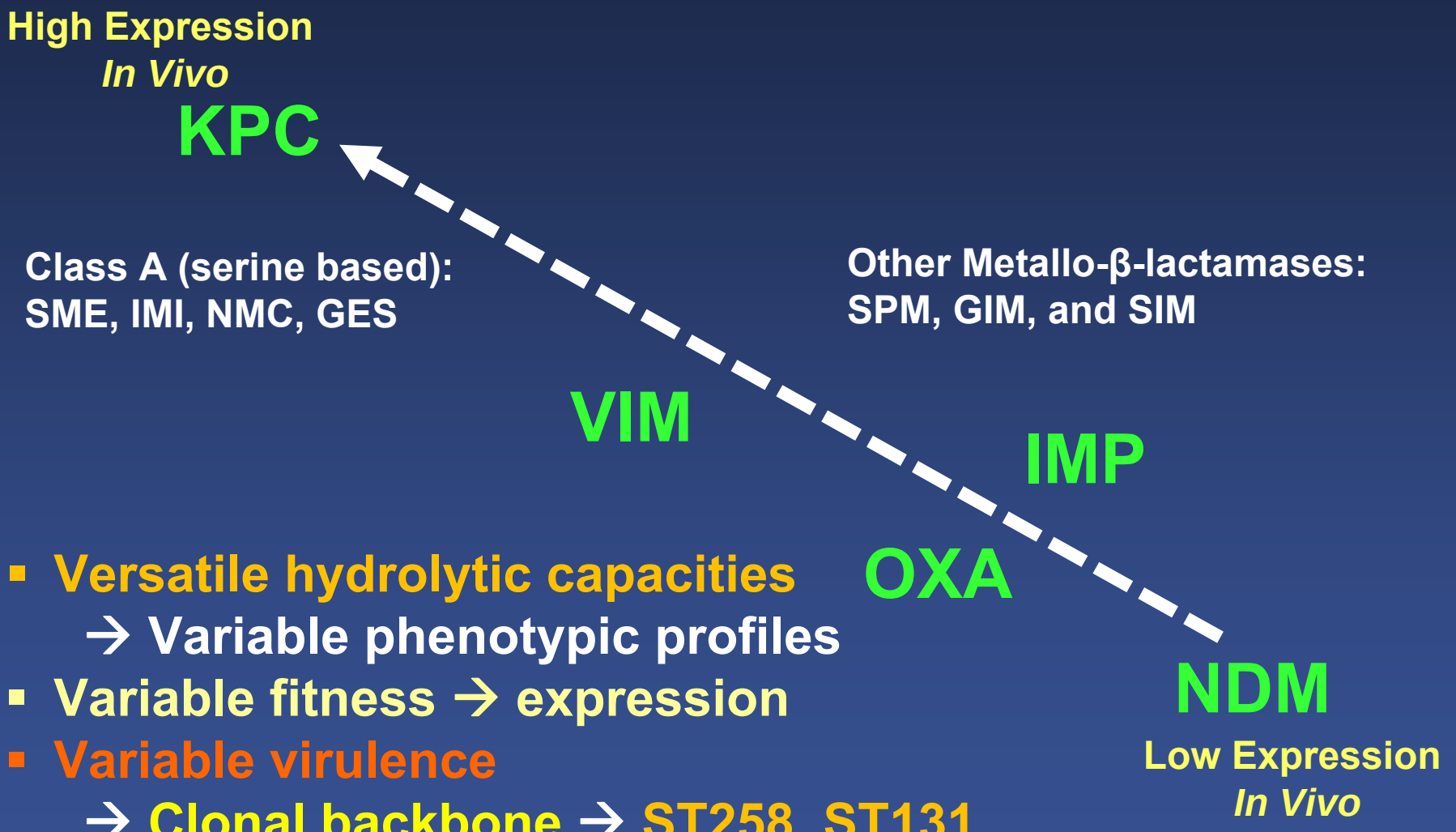
- 37 CRE patients were treated with ceftazidime-avibactam
- Clinical success and survival rates at 30 days were 59% (22/37) and 76% (28/37), respectively
- In 23% (5/22) of clinical successes, CRE infections recurred within 90 days
- Microbiologic failure rate was 27% (10/37)
- Ceftazidime-avibactam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

When "S" ≠ Success ?

- Discordant therapy (i.e., inadequate therapy low exposures due to insufficient dose and / or regimen)
  - » Increased body weight
  - » ↑ volume of distribution (sepsis / septic shock)
  - » Renal function
    - Reduced
    - Augmented
  - » Therapeutic interventions (i.e., CRRT, ECMO)

DP Nicolau: Personal Communication

Evolving *In Vivo* Understanding of Carbapenemases



- Versatile hydrolytic capacities
  → Variable phenotypic profiles
- Variable fitness → expression
- Variable virulence
  → Clonal backbone → ST258, ST131

DP Nicolau: Personal Communication

Optimal Regimen for Carbapenemase-Producing Enterobacteriaceae

- **Effectiveness v. Toxicity of Colistin – Meropenem – Tigecycline?**
  - » Van Duin D et al. Clin Infect Dis 2017 ePub 4 Sept
- **New CRE βL/βLI → *Ceftazidime-Avibactam***
  - » **Microbiologic potency → KPC & OXA**
  - » **Safety profile → Well tolerated**
  - » **Monotherapy → Renal v. Extra-Renal**
  - » **Combination therapy → ??**
  - » **Colistin / Polymixin**
  - » **Tigecycline**
  - » **Fosfomycin**
  - » **Carbapenems**
  - » **Gentamicin → Amikacin → Plazomicin**

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