Welcome to the Jungle:
Update on New GNR Agents

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@mmPharmD

Beth Israel Lahey Health

Beth Israel Deaconess Medical Center

Disclosures

- Advisory boards: Qpex, Spero, Tetraphase
- Research funding: Merck
- Speaker’s bureau: Tetraphase, Cepheid
- Off-label uses will be discussed

Objectives

1. Identify (recognize) common mechanisms of resistance associated with Gram-negative bacteria
2. Evaluate (assess) the literature for newly approved agents in the treatment of resistant Gram-negative infections
3. Design (create) an effective treatment regimen for a resistant Gram-negative infection patient case

Each year in the US …

>2.8 million
antibiotic-resistant infections

>35,000
deaths

Prolonged & costlier treatments

Extended hospitalizations

Additional doctor visits

Greater disability & death

>$20 billion
excess direct healthcare costs

>$35 billion
lost productivity

2019 Report: https://www.cdc.gov/drugresistance/biggest-threats.html

Implicated Gram-Negatives

Urgent Threats

Carbapenem-resistant *Acinetobacter* (CRAb) • *Candida auris* • *Clostridioides difficile* • **Carbapenem-resistant Enterobacterales** • Drug-resistant *Neisseria gonorrhoeae*

Serious Threats

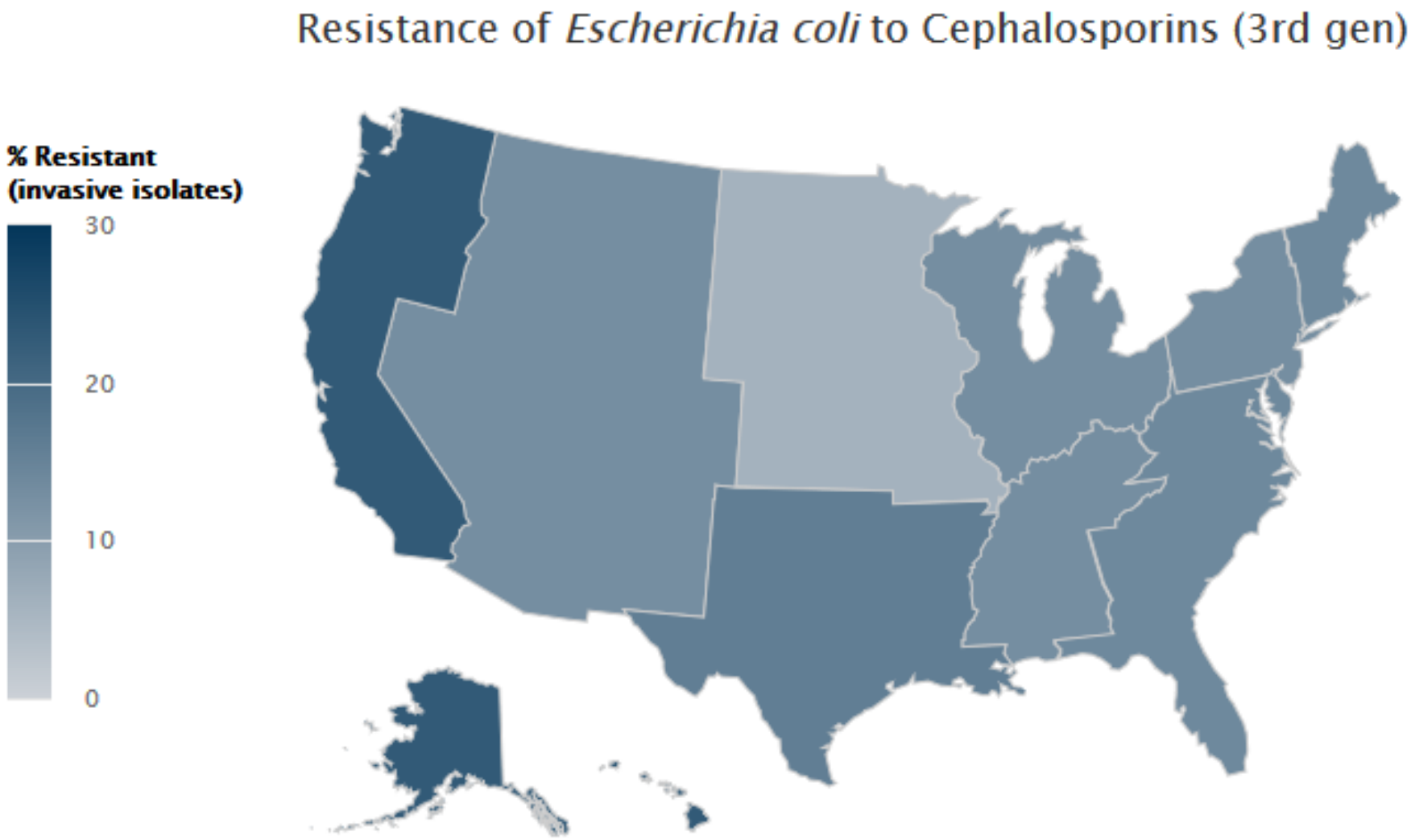
Drug-resistant *Campylobacter* • Drug-resistant *Candida* • **ESBL Enterobacterales** • Vancomycin-resistant *Enterococcus* • **MDR-*Pseudomonas*** • Drug-resistant nontyphoidal *Salmonella* • Drug-resistant *Salmonella* serotype Typhi • Drug-resistant *Shigella* • MRSA • Drug-resistant *Streptococcus pneumoniae* • Drug-resistant TB

Concerning Threats

Erythromycin-resistant group A *Streptococcus* • Clindamycin-resistant group B *Streptococcus*

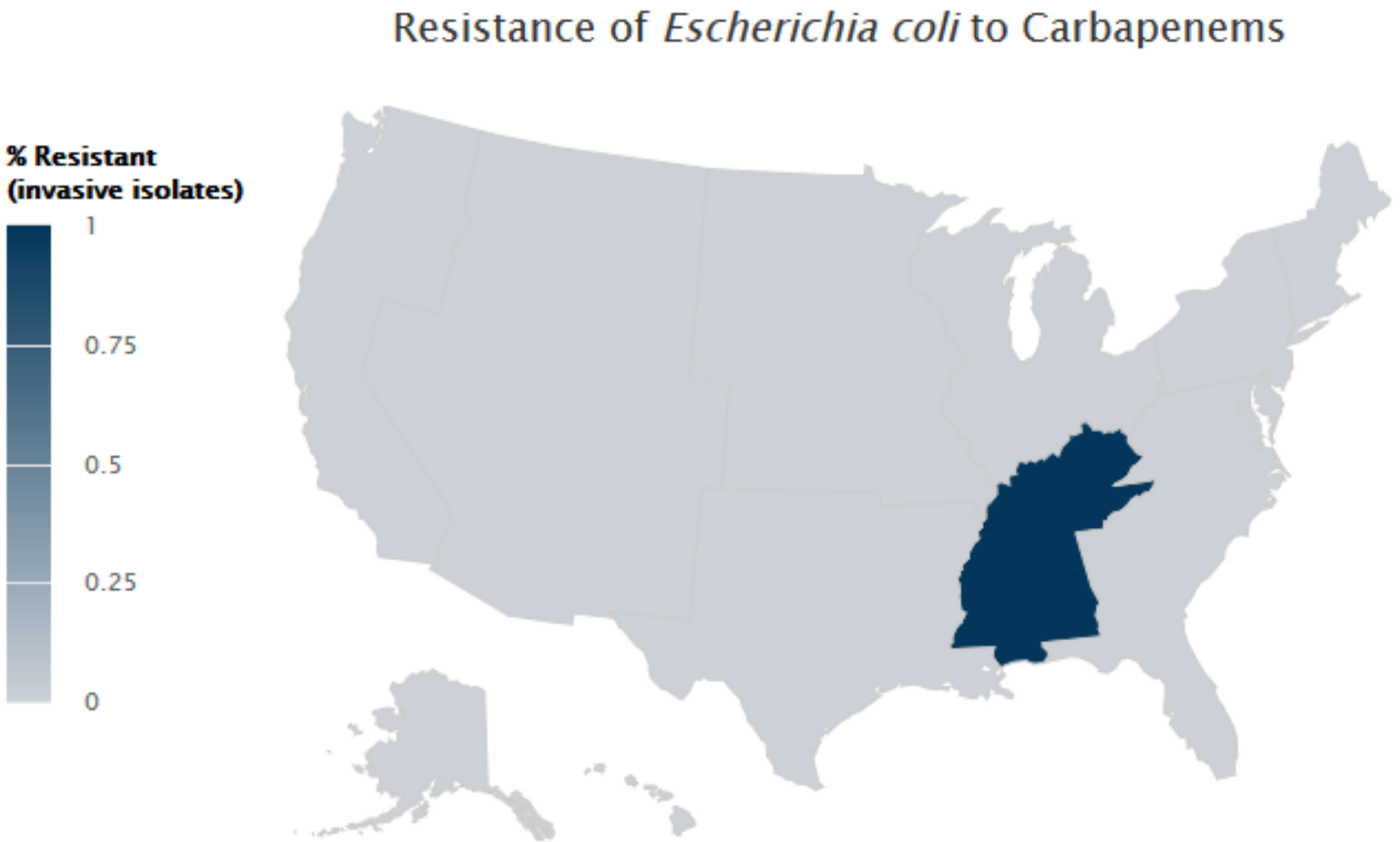
2019 Report: https://www.cdc.gov/drugresistance/biggest-threats.html

3GCR *E. coli*



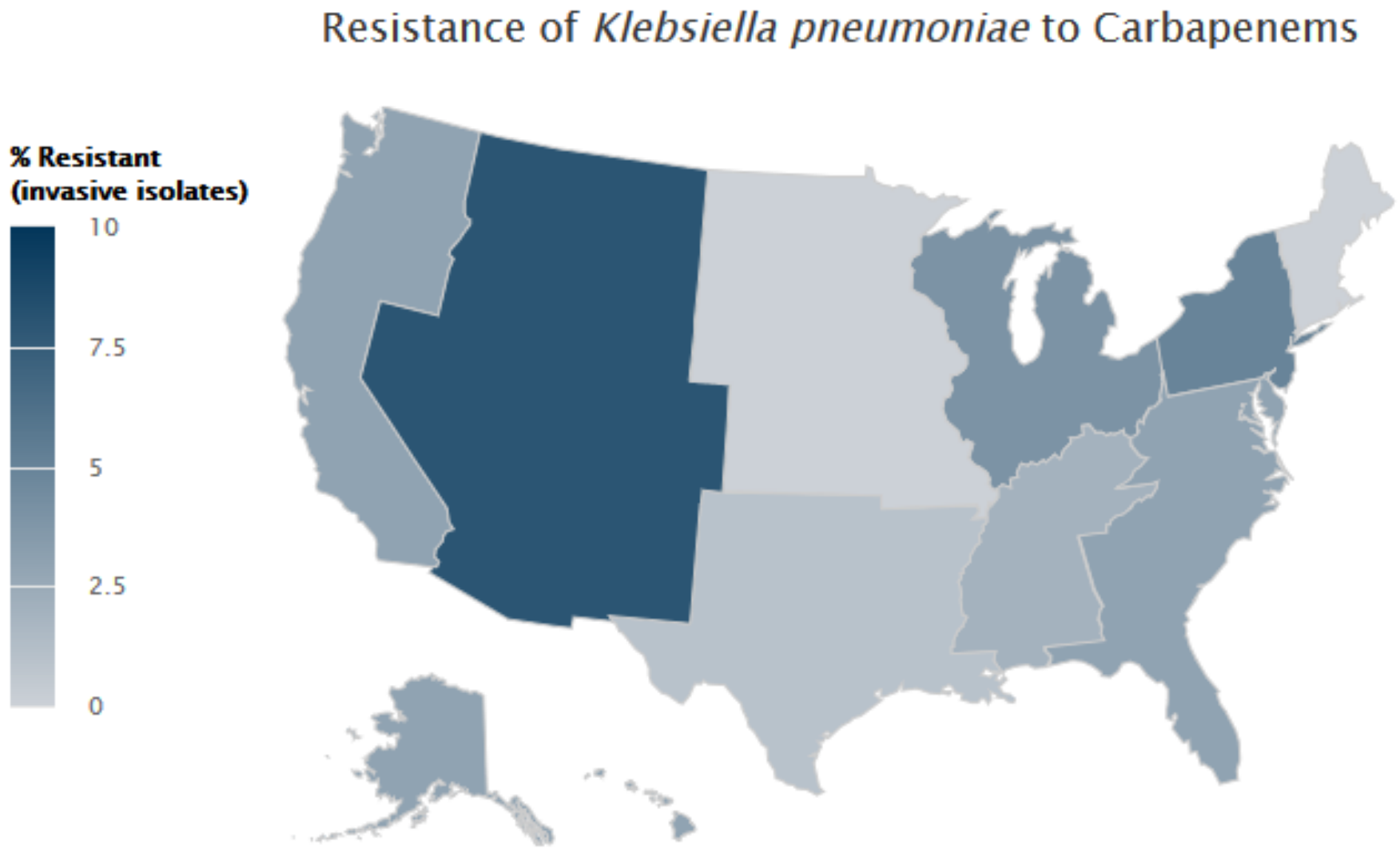
CDDEP Resistance Map. https://resistancemap.cddep.org/CountryPageSub.php?country=United+States. Accessed 11/24/19

Carbapenem Resistant *E. coli*



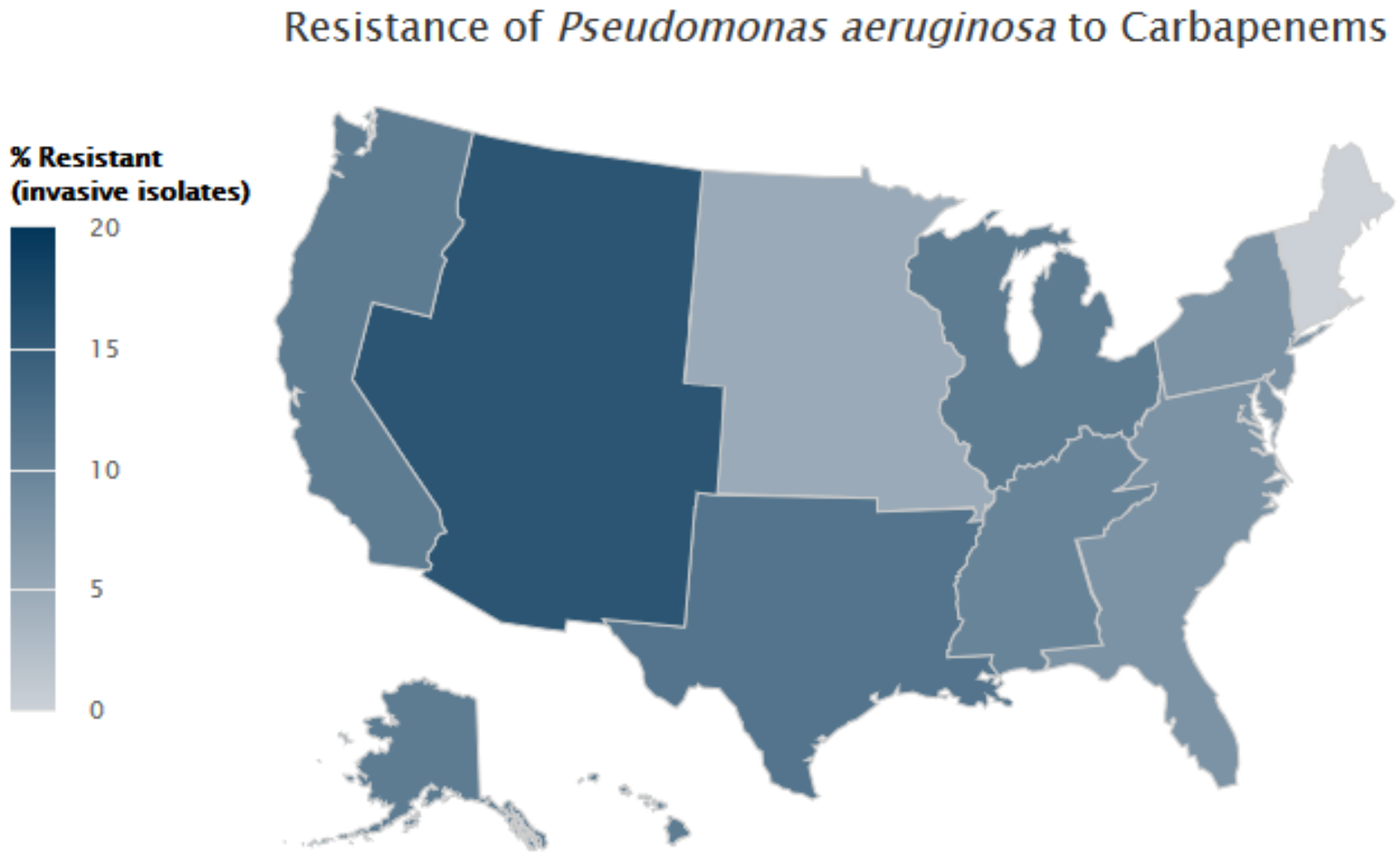
CDDEP Resistance Map. https://resistancemap.cddep.org/CountryPageSub.php?country=United+States. Accessed 11/24/19

Carbapenem Resistant *K. pneumoniae*



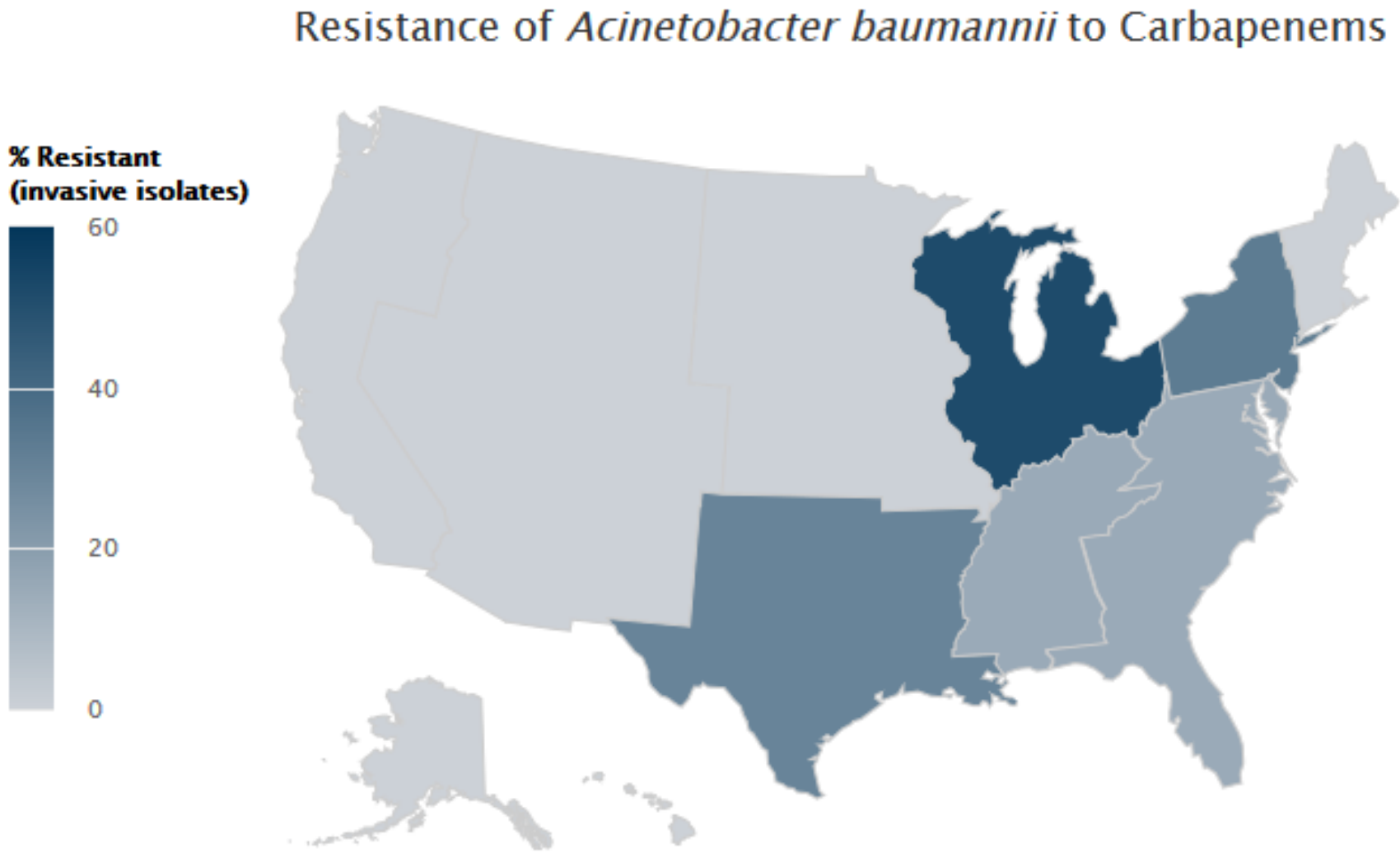
CDDEP Resistance Map. https://resistancemap.cddep.org/CountryPageSub.php?country=United+States. Accessed 11/24/19

Carbapenem Resistant *Pseudomonas*



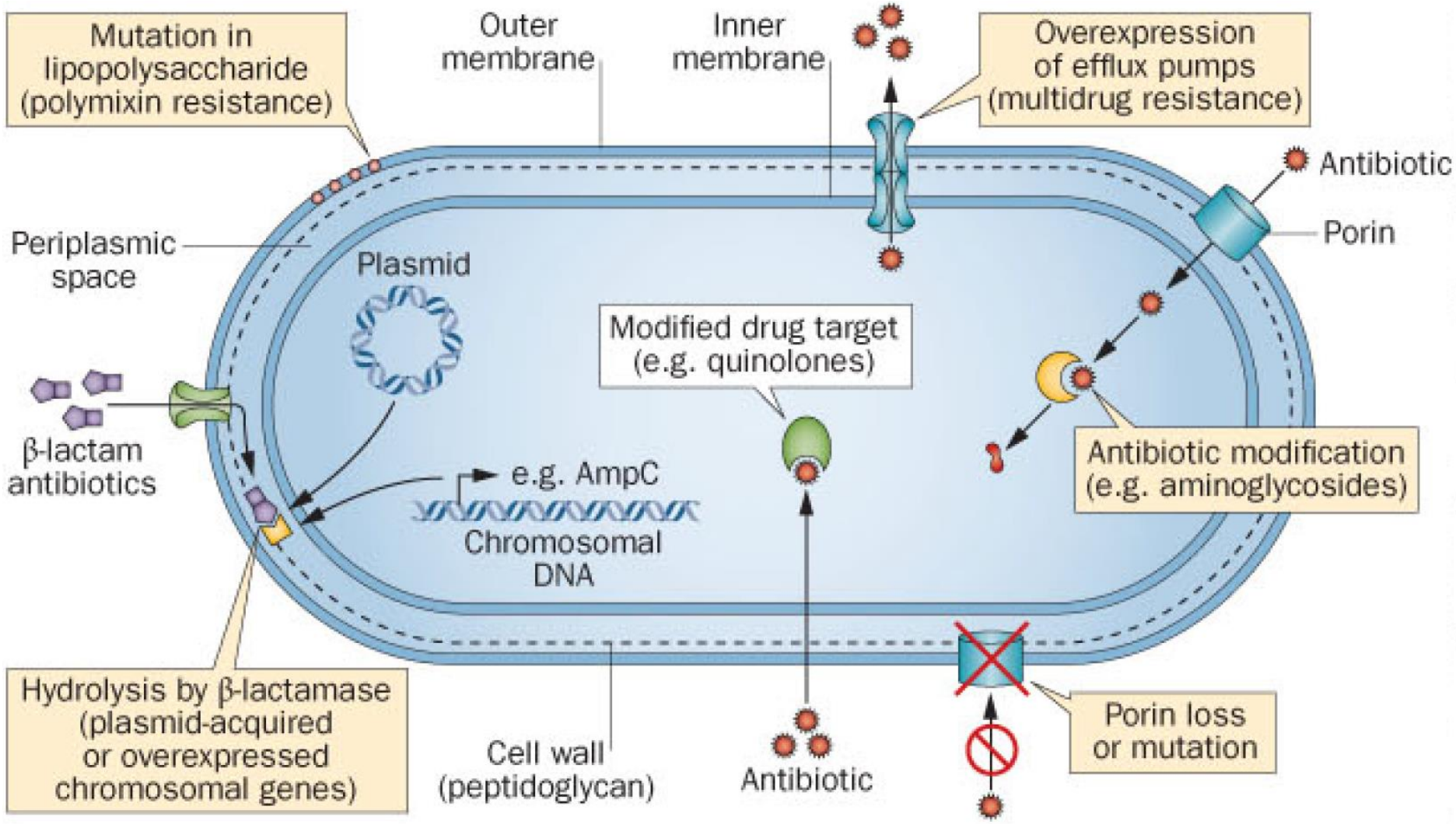
CDDEP Resistance Map. https://resistancemap.cddep.org/CountryPageSub.php?country=United+States. Accessed 11/24/19

Carbapenem Resistant *Acinetobacter*



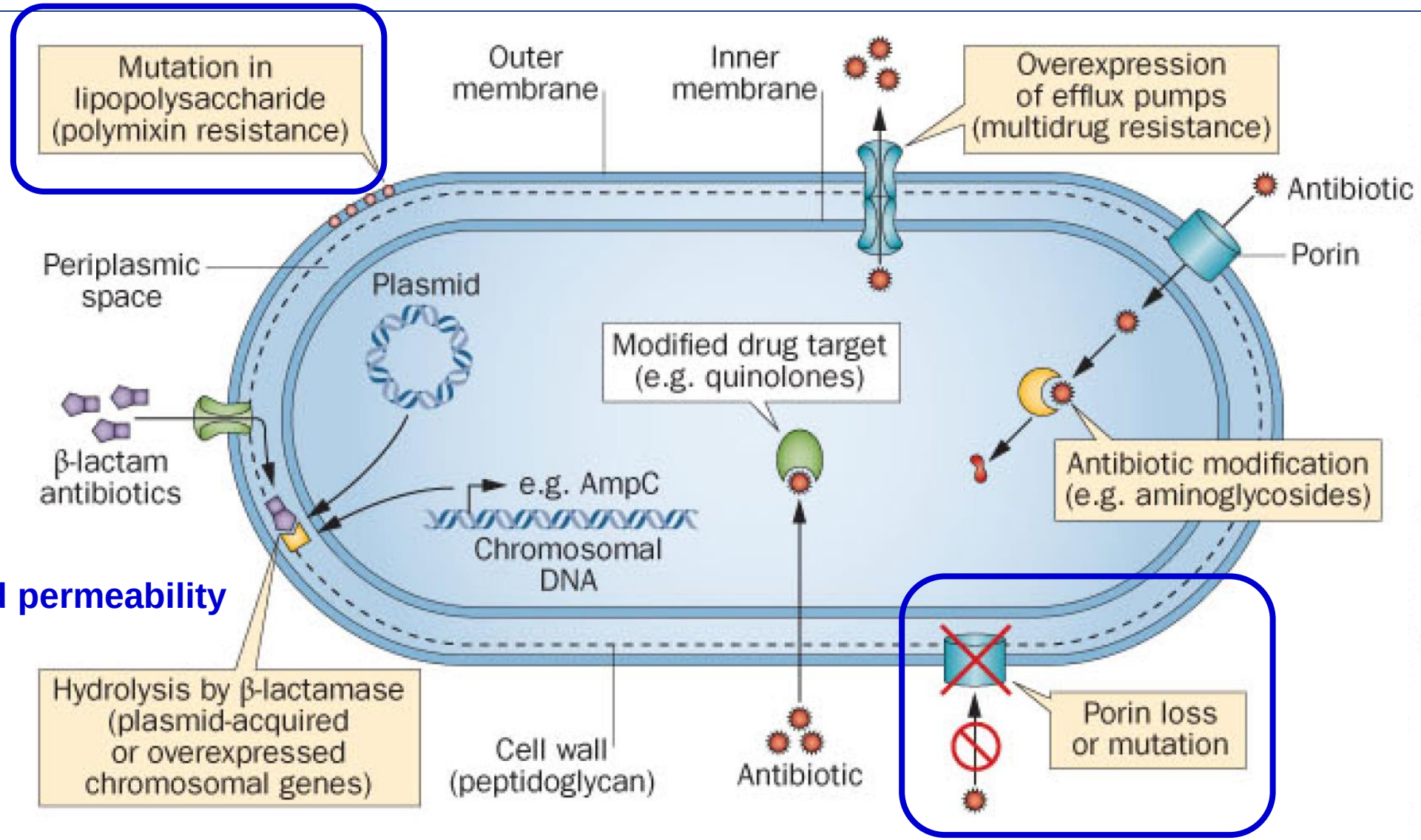
CDDEP Resistance Map. https://resistancemap.cddep.org/CountryPageSub.php?country=United+States. Accessed 11/24/19

Mechanisms of GNR Resistance



Zowawi HM. *Nat Rev Urol* 2015;12:570-84

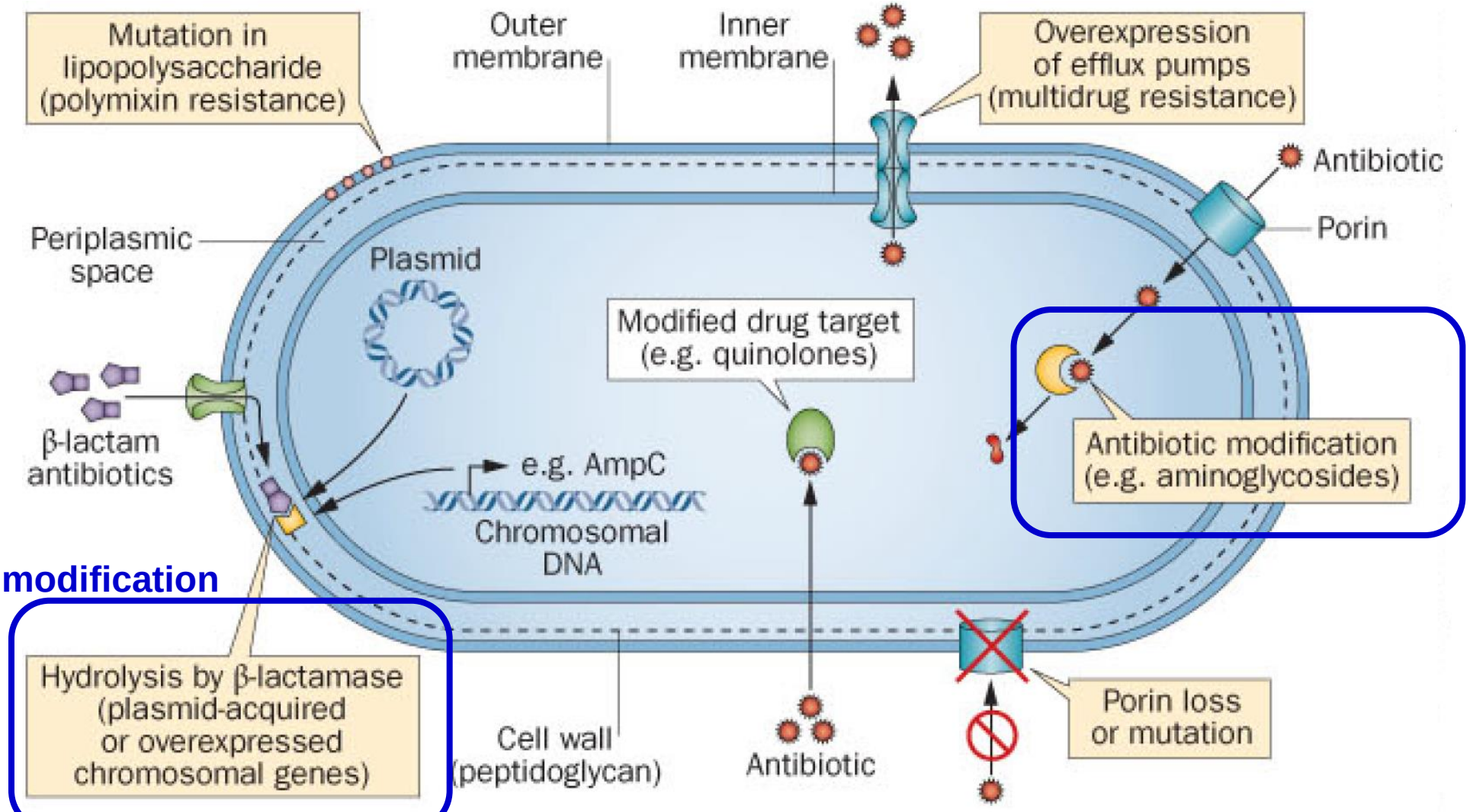
Mechanisms of GNR Resistance



1. Decreased permeability

Zowawi HM. *Nat Rev Urol* 2015;12:570-84

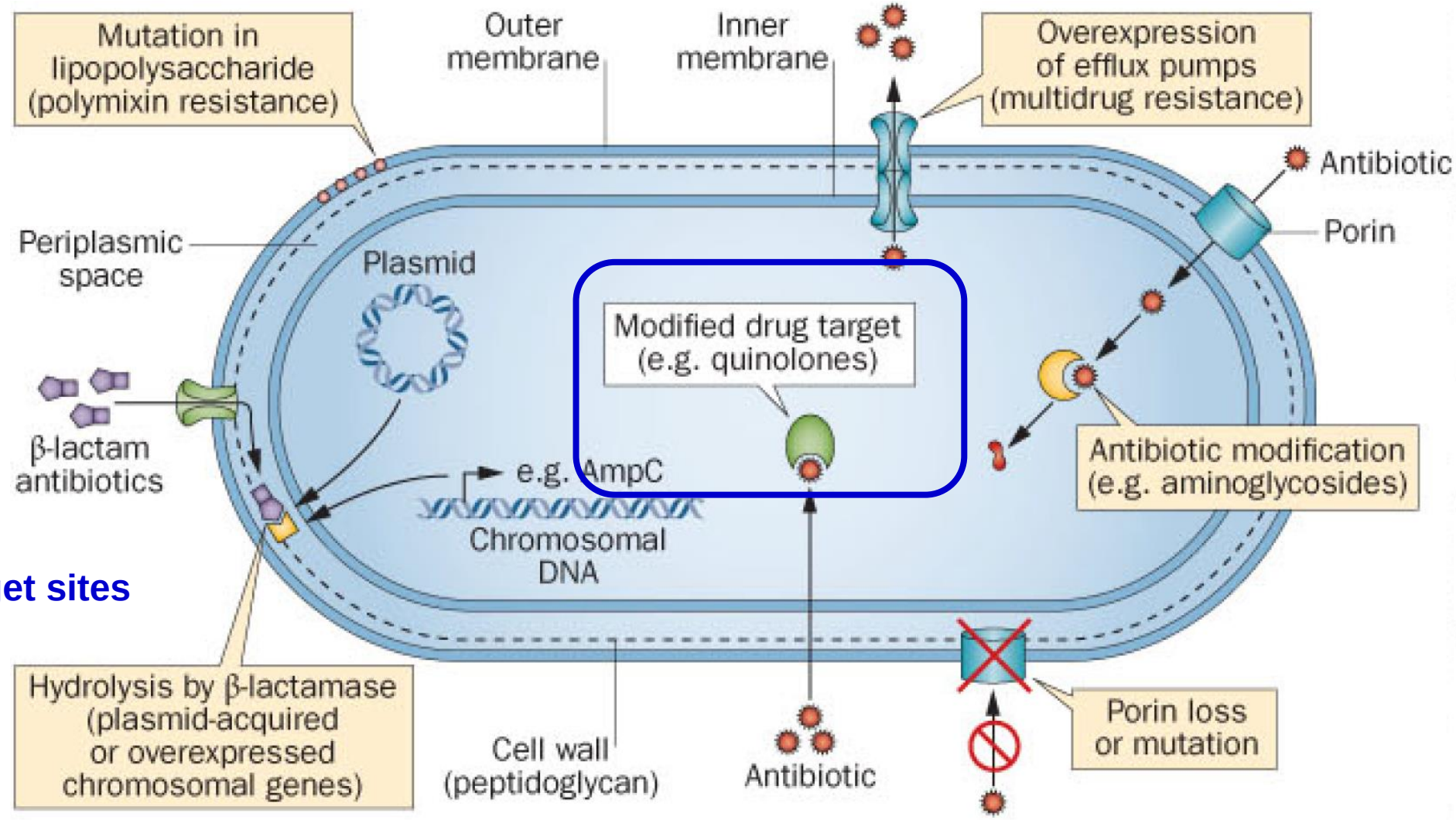
Mechanisms of GNR Resistance



2. Enzymatic modification

Zowawi HM. *Nat Rev Urol* 2015;12:570-84

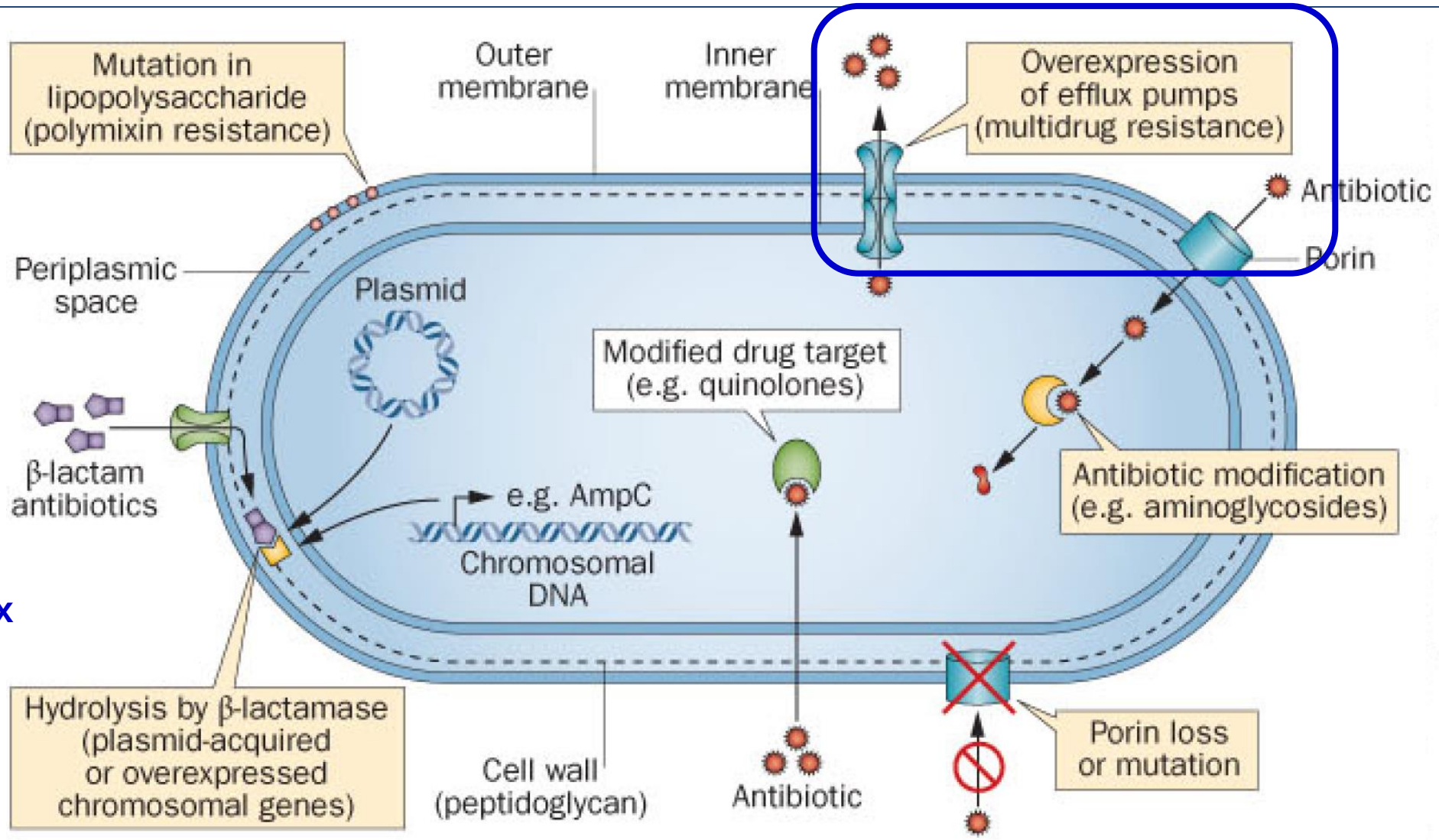
Mechanisms of GNR Resistance



3. Altered target sites

Zowawi HM. *Nat Rev Urol* 2015;12:570-84

Mechanisms of GNR Resistance



4. Active efflux

Zowawi HM. *Nat Rev Urol* 2015;12:570-84

Question

Which of the following currently available antibiotics could be a treatment option for a metallo-β-lactamase infection?

A. Omadacycline + fosfomycin

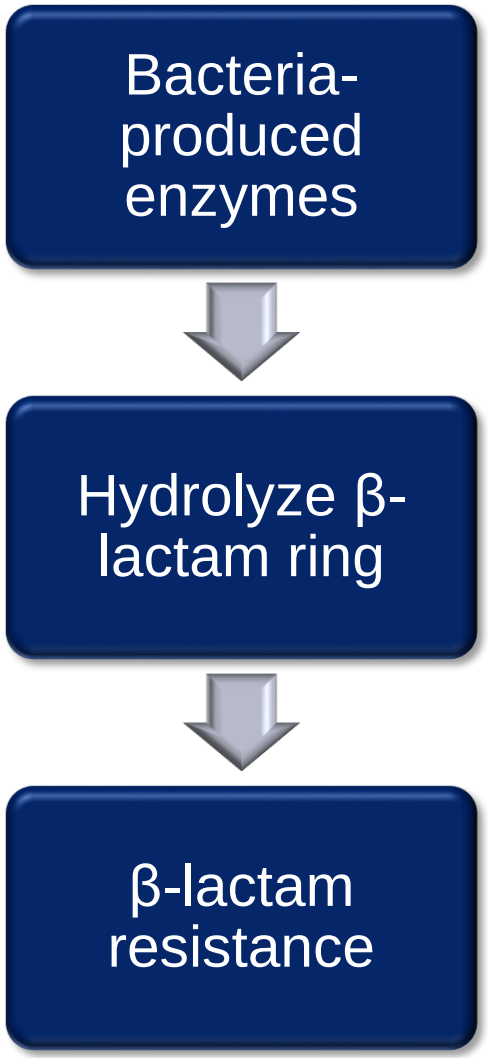
B. Delafloxacin + meropenem/vaborbactam

C. Aztreonam + ceftazidime/avibactam

D. Ceftolozane/tazobactam + eravacycline

Slide courtesy of Rachel Britt, PharmD

β-Lactamases



- Different β-lactamases = different drug resistance patterns
- Two main β-lactamase classification systems
  - Ambler
  - Bush-Jacoby-Medeiros
- Four Ambler classes
  - A – Serine ESBLs, carbapenemases
  - B – MBLs
  - C – AmpC
  - D – OXA enzymes1

ESBL: extended spectrum β-lactamase , MBL: metallo-β-Lactamase

Ghafourian S, et al. Curr Issues Mol Biol. 2015;17:11-22; Liscio JL, et al. Int J Antimicrob Agents. 2015;46:266-71

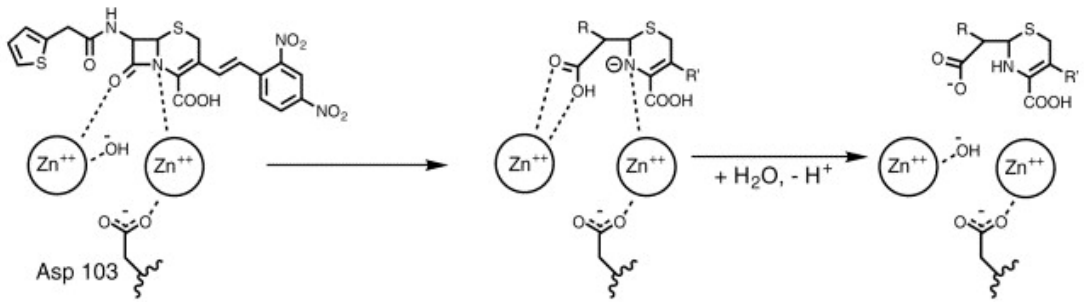
Slide courtesy of Rachel Britt, PharmD

Metallo-β-Lactamases (MBL)

- Hydrolyze β-lactam ring through the use of zinc ions
- Different subclasses and subtypes

Verona integrin-encoded MBL (VIMs) | **Imipenemase (IMPs)** | **New Delhi MBL (NDMs)**

- Can be chromosomally-mediated or acquired
- Lead to resistance to all β-lactam antibiotics except monobactams
- Found in Gram-negative organisms, like Enterobacterales



Mojica MF, et al. Curr Drug Targets. 2016;17:1029-50; Cornaglia G, et al. Lancet Infect Dis. 2011;11:381-93; Wang Z, et al. Curr Opin Chem Biol. 1999;3(5):614-22.

β-Lactamases

Ambler Class	Enzyme Type	Examples	Antibiotic Activity (Inhibited by)
A	Narrow-spectrum	TEM-1, TEM-2, SHV-1	Avibactam, clavulanate, tazobactam, vaborbactam
A	Extended-spectrum (ESBL)	SHV, CTX, KLUG	Avibactam, clavulanate, tazobactam, vaborbactam
A	Serine carbapenemase	KPC	Avibactam, vaborbactam
B	Metallo-β-lactamase (MBL), carbapenemase	VIM, IMP, NDM	Aztreonam
C	ESBL, cephalosporinase	AmpC	Avibactam, cefepime, ceftolozane, vaborbactam
D	Carbapenemase	OXA	Avibactam

Liscio JL. *IJAA* 2015;46:266-71; Pogue JM. *CID* 2019;68:519-24

FDA Recap: Last 6 Years

Generic Name	Brand Name	Description	Indication	Approval
Ceftolozane / tazobactam	Zerbaxa	Novel **anti-Psa cephalosporin** + β-lactamase inhibitor	cUTI, cIAI, HABP/VABP	2014
Ceftazidime / avibactam	Avycaz	Anti-Psa cephalosporin + novel **diazabicyclooctane inhibitor**	cUTI, cIAI, HABP/VABP	2015
Meropenem / vaborbactam	Vabomere	Anti-Psa carbapenem + novel **boronic acid-based inhibitor**	cUTI	2017
Plazomicin	Zemdri	AG not susceptible to AG modifying enzymes	cUTI	2018
Eravacycline	Xerava	**Fluorocycline**	cIAI	2018
Imipenem – cilastatin / relebactam	Recarbrio	Anti-Psa carbapenem + novel **diazabicylooctane inhibitor**	cUTI, cIAI	2019
Cefiderocol	Fetroja	**Novel cephalosporin** using iron transport mechanisms	cUTI	2019

Psa: Pseudomonas; cUTI: complicated urinary tract infection; cIAI: complicated intra-abdominal infection; HABP: hospital acquired bacterial pneumonia; VABP: ventilator-associated bacterial pneumonia; AG: aminoglycoside; ABSSSI: acute bacterial skin and skin structure infection; CABP: community-acquired bacterial pneumonia

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B. Delafloxacin + meropenem/vaborbactam

C. Aztreonam + ceftazidime/avibactam

D. Ceftolozane/tazobactam + eravacycline

Problem Organisms

ESBL

CRE

Pseudomonas

Acinetobacter

Use Your ~~Illusion~~ I: ESBL

Antibiotics

Question

A patient with no relevant medical history presents with a wound infection, sustained from a cut 3 days ago. Blood and wound cultures grow *E. coli,* with the susceptibilities pending. The primary team wants to change from piperacillin/tazobactam to meropenem. How do you respond?

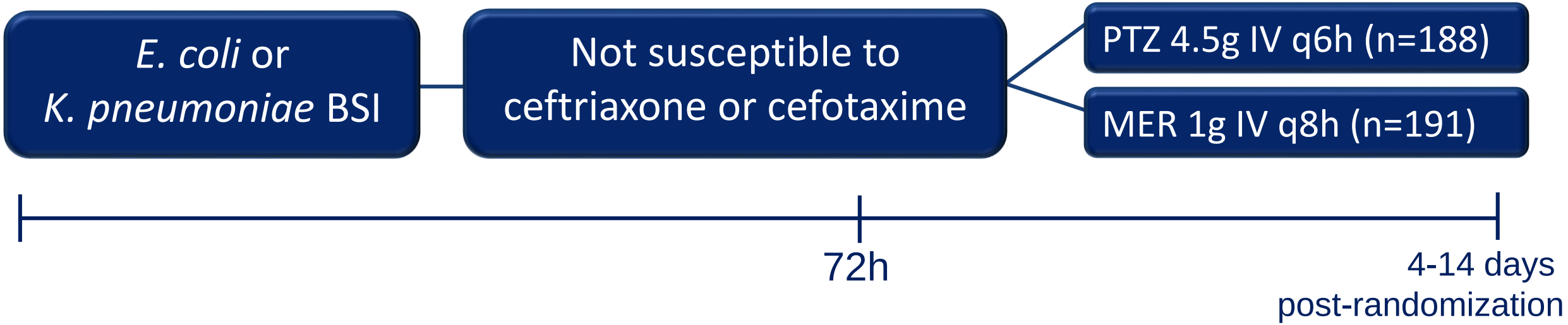
A. Change to meropenem because the Merino trial proved that meropenem is better than piperacillin/tazobactam.

B. Change to cefazolin because this patient is from the community.

C. Continue the piperacillin/tazobactam because the Merino trial studied definitive treatment rather than empiric treatment.

D. Change to oral therapy because this is an uncomplicated infection.

Preference for ESBL



Harris PNA. JAMA 2018;320:984-94

PTZ MER

Preference for ESBL

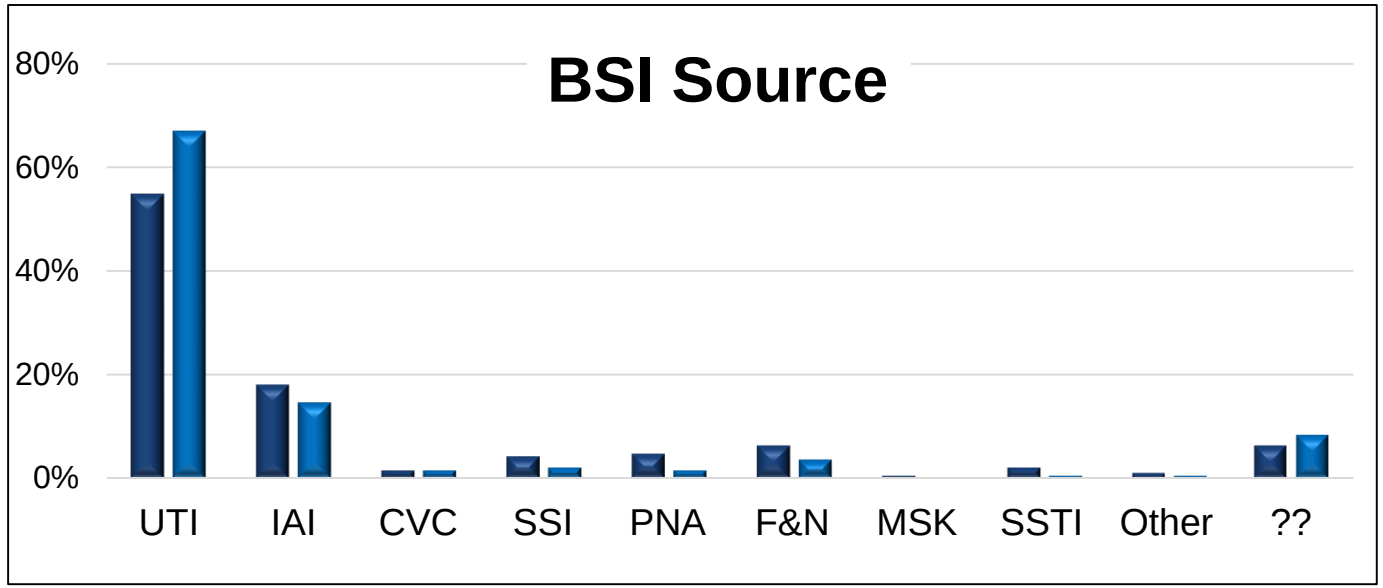
E. coli or *K. pneumoniae* BSI

Not susceptible to ceftriaxone or cefotaxime

- PTZ 4.5g IV q6h (n=188)
- MER 1g IV q8h (n=191)

72h

4-14 days post-randomization



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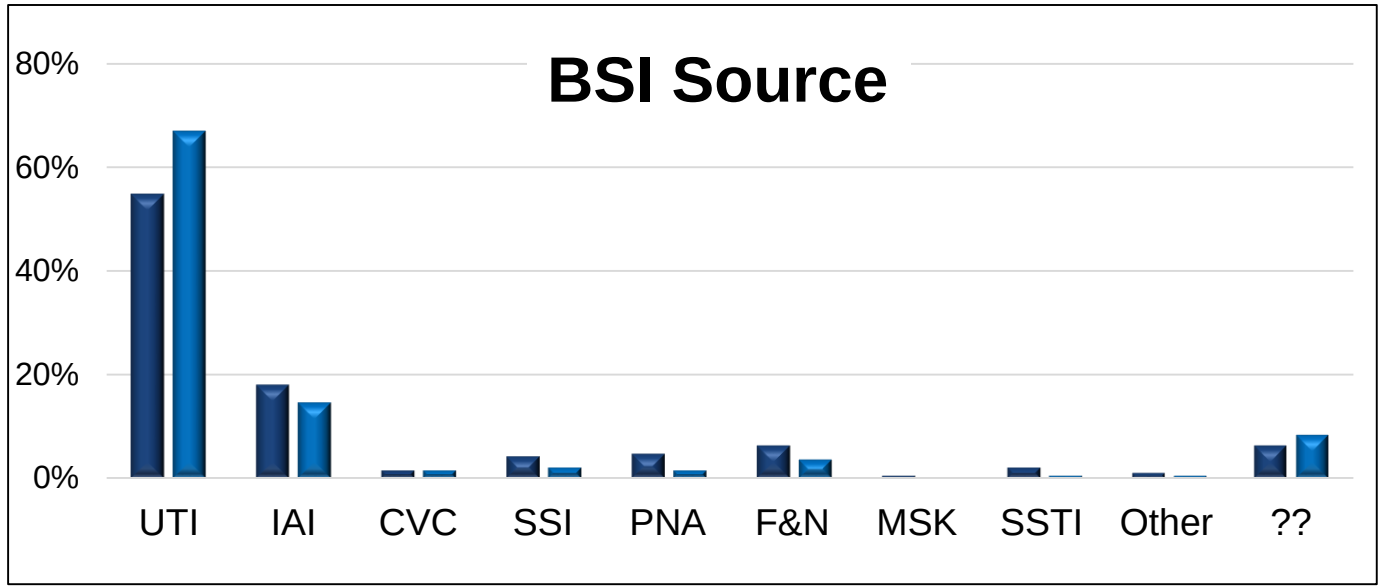

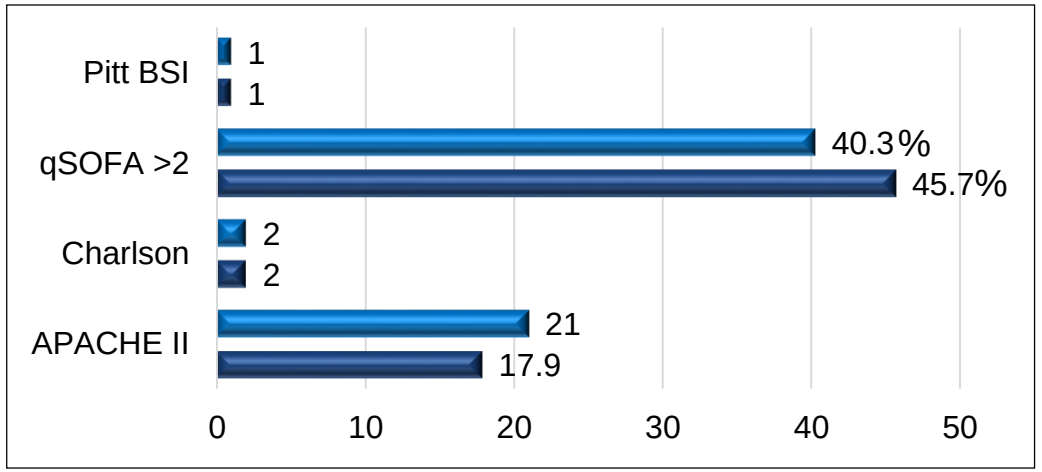

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PTZ MER

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The ~~Spaghetti~~ Pre-Specified Stopping Incident

Interim analysis at 340 patients approaching pre-specified stopping rule

30-Day Mortality:

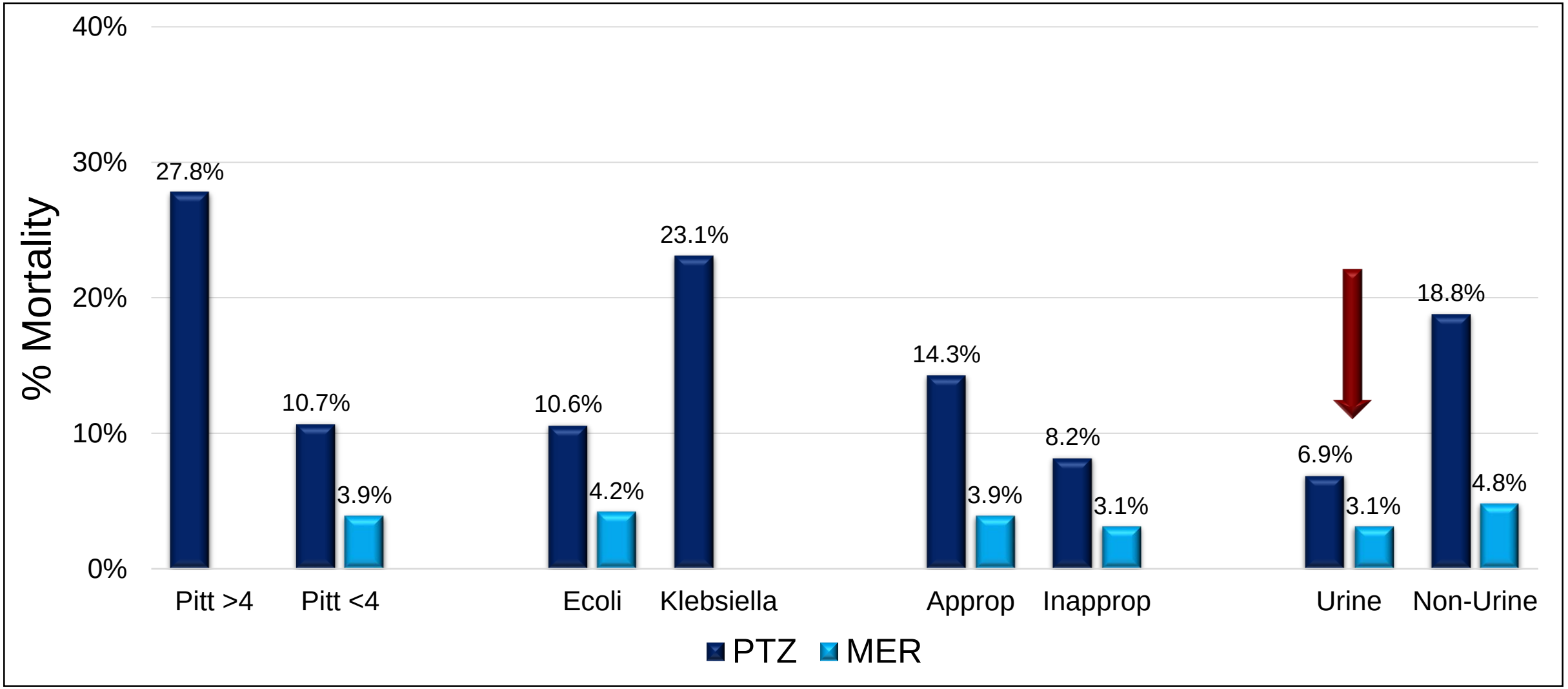
The ~~Spaghetti~~ Pre-Specified Stopping Incident

Interim analysis at 340 patients approaching pre-specified stopping rule

30-Day Mortality:

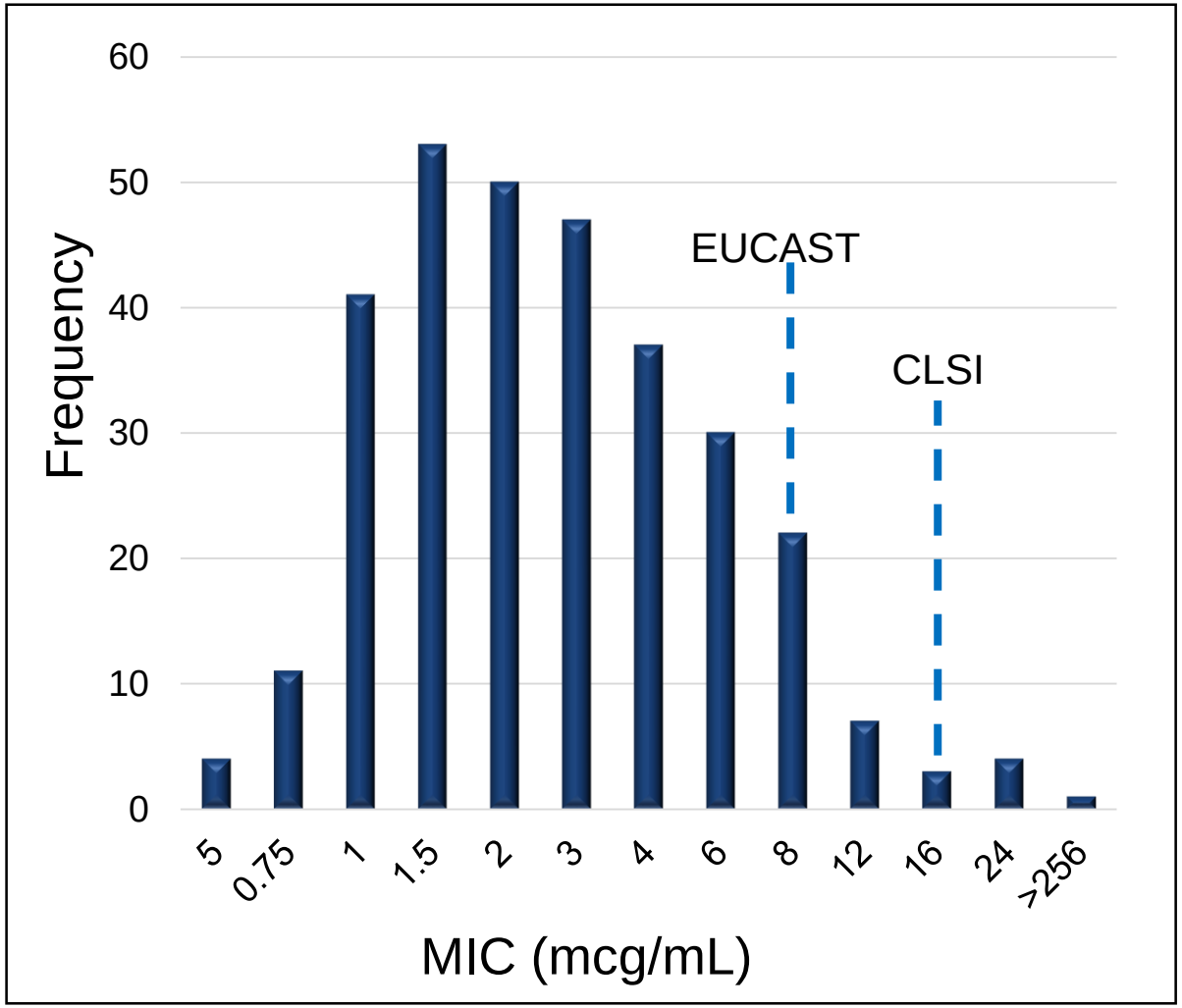
Piperacillin/tazobactam	Meropenem
12.3% (23/187)	3.7% (7/191)

Subgroup Analysis – 30d Mortality



Harris PNA. JAMA 2018;320:984-94

Piperacillin/tazobactam Distribution



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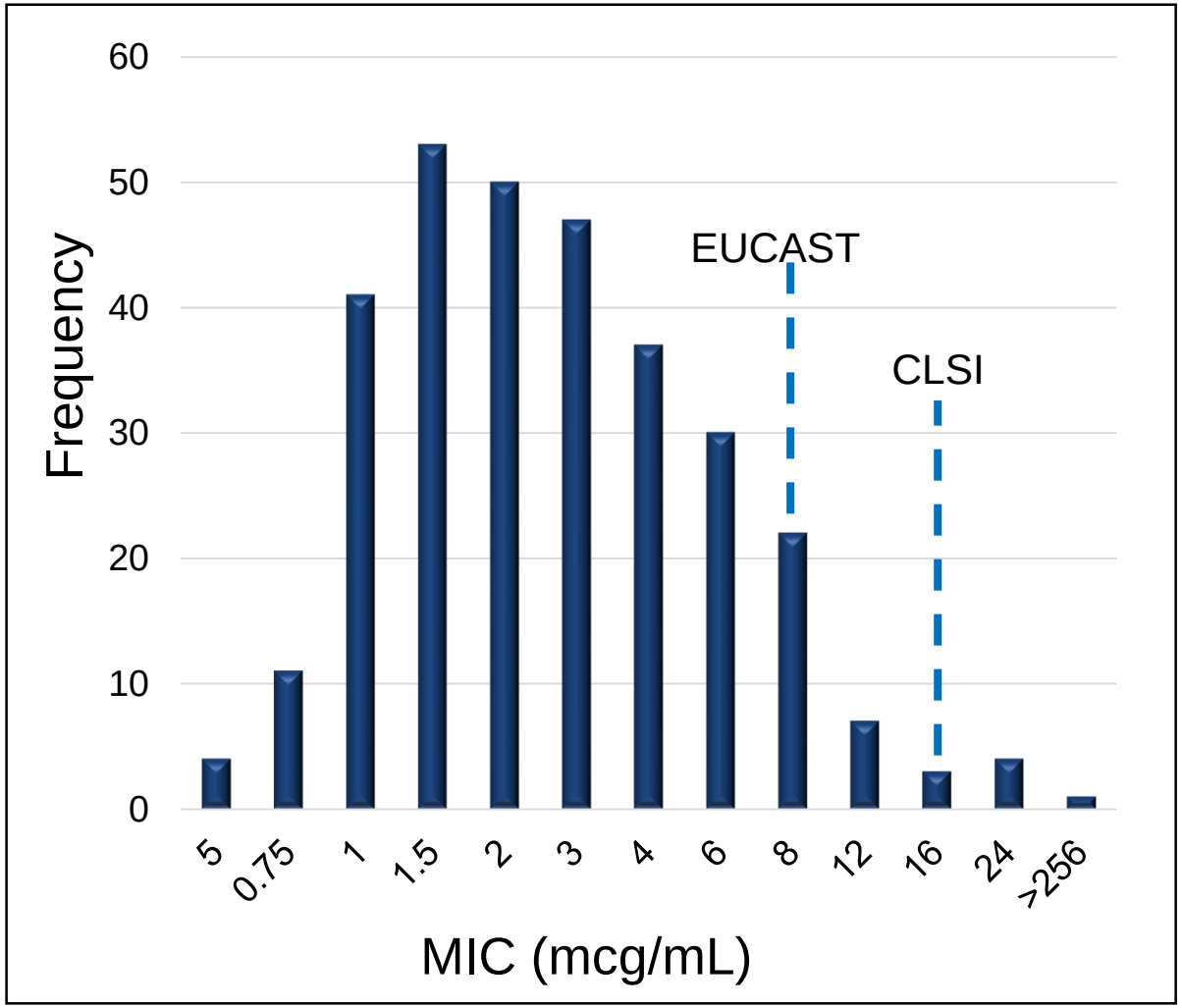
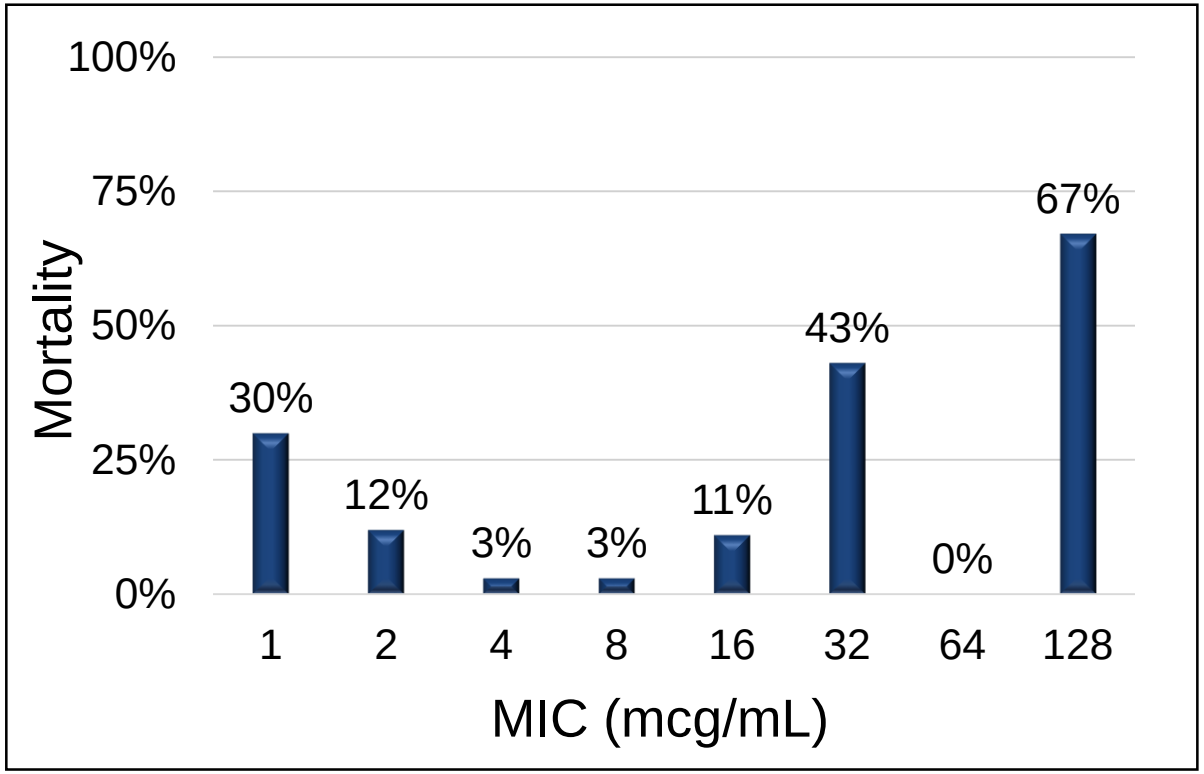
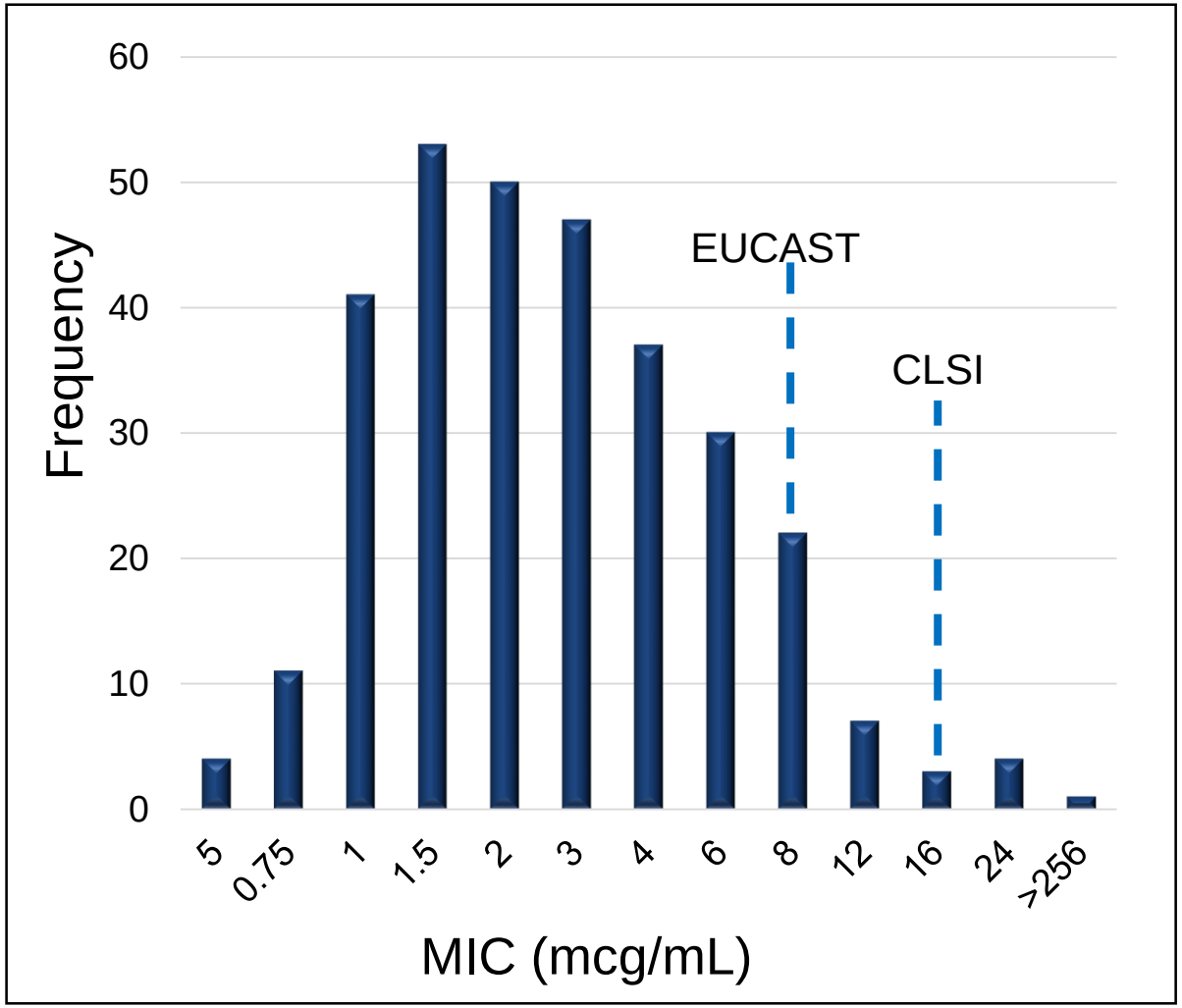
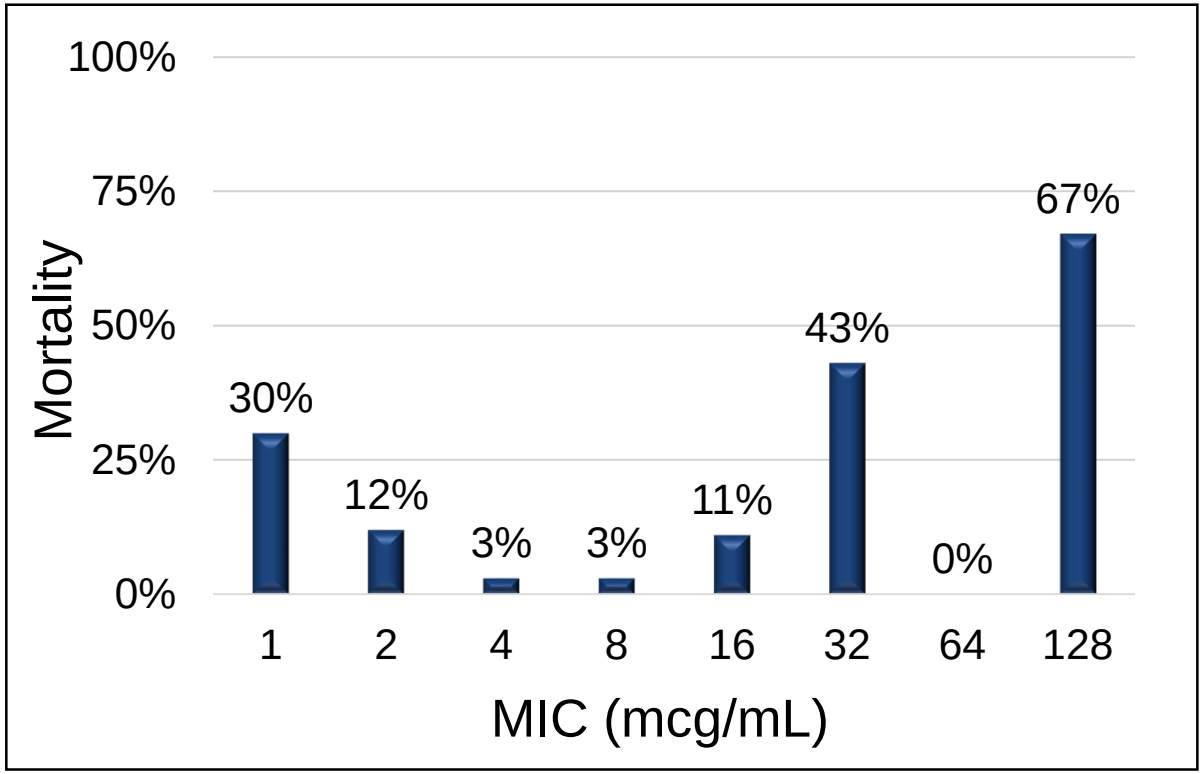




Piperacillin/tazobactam Distribution





Piperacillin/tazobactam	Meropenem
11.5% (18/157)	3.7% (6/164)

Question

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D. Change to oral therapy because this is an uncomplicated infection.

Use Your ~~Illusion~~ II: CRE

Antibiotics

Question

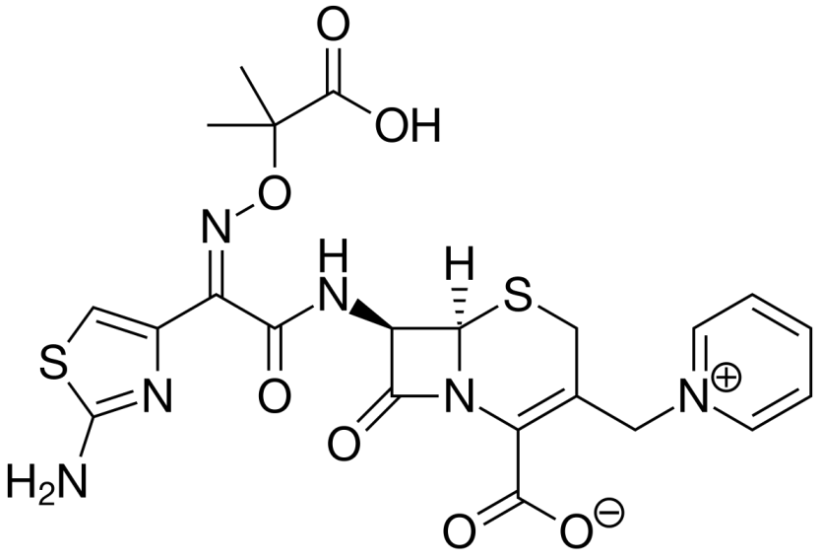
Which of the following medications has activity against carbapenem-resistant Enterobacteriaceae?

A. Ceftolozane/tazobactam
B. Meropenem/vaborbactam
C. Aztreonam
D. Ertapenem

Ceftazidime/avibactam

Ceftazidime

- Existing anti-Psa cephalosporin
- Stable against porin channel changes (carbapenems)
- Inactivated by ESBL, KPC enzymes

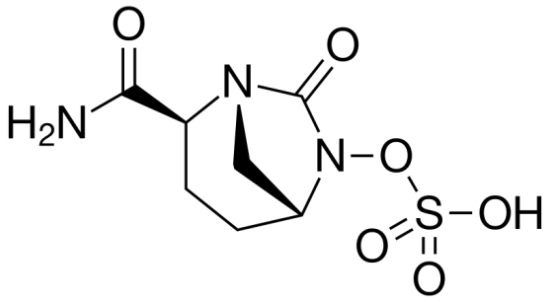


Ceftazidime

Avibactam

New!

- Novel non-β-lactam β-lactamase inhibitor
- Stable against ESBLs, KPC & OXA-48 enzymes
- Inactivated by MBLs



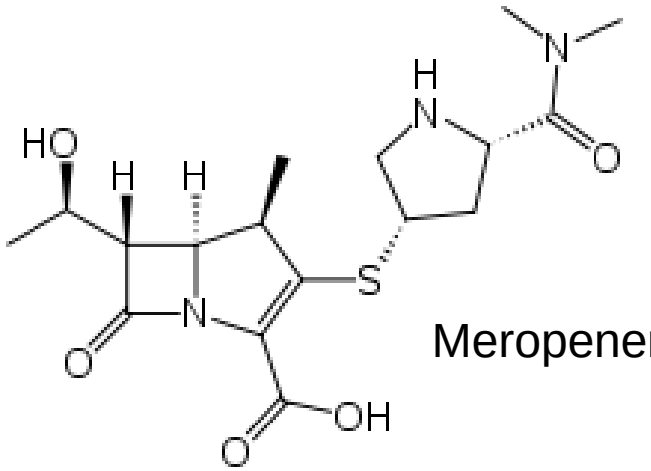
Avibactam

Avycaz PI. Allergan. Madison, NJ 2019; Liscio JL. *IJAA* 2015;46:266-71

Meropenem/vaborbactam

Meropenem

- Existing anti-Psa carbapenem
- Stable against ESBL, cephalosporinases
- Inactivated by carbapenemases

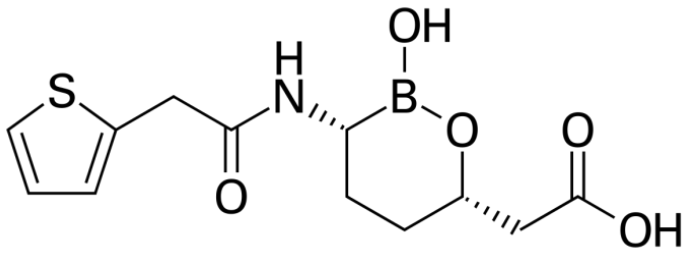


Meropenem

Vaborbactam

New!

- Novel boronic-acid β-lactamase inhibitor
- Stable against ESBLs, KPC enzymes
- Inactivated by MBLs



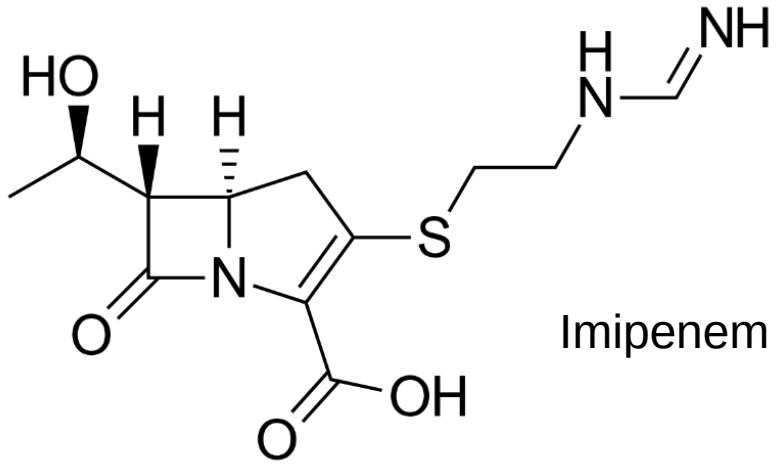
Vaborbactam

Vabomere PI. Melinta. Lincolnshire, IL. 2018

Imipenem-cilastatin/relebactam

Imipenem-cilastatin

- Existing anti-Psa carbapenem
- Stable against AmpC, ESBL
- Inactivated by carbapenemases

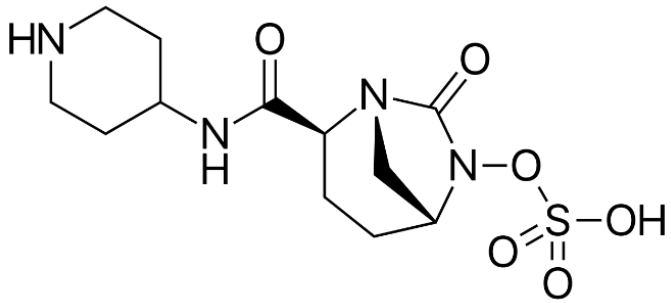


Imipenem

Relebactam

New!

- Novel diazabicyclooctane, non-β-lactam, β-lactamase inhibitor
- Stable against AmpC, ESBL, KPC
- Inactivated by MBL, OXA



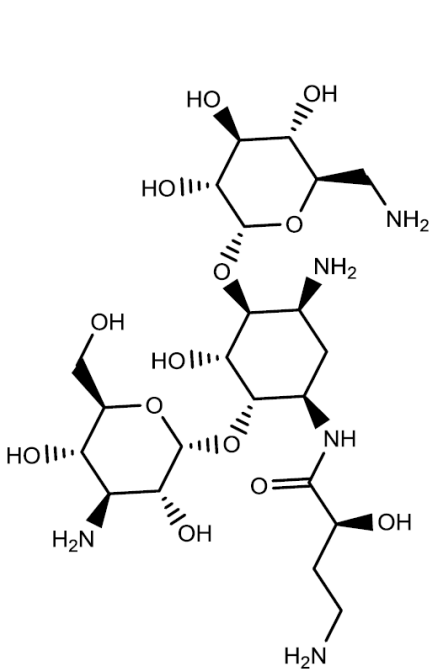
Relebactam

Sims M. *J Antimicrob Chemother* 2017;72:2616-26; Lucasti C. *Antimicrob Agents Chemother* 2016;60:6234-43

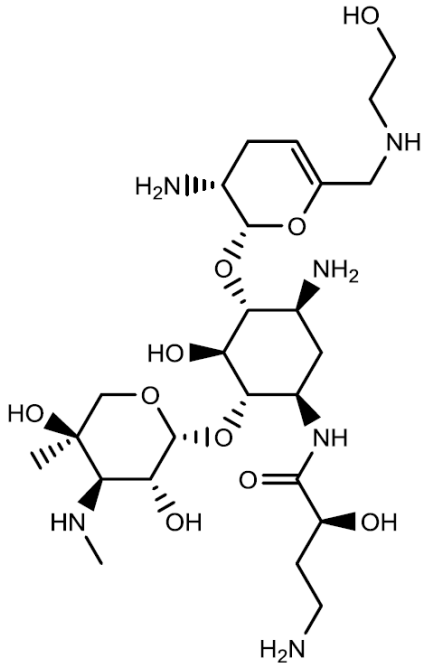
Plazomicin

New!

- Semisynthetic aminoglycoside
- 3 key modifications protect against most AMEs
  - No hydroxyl group at 3’ and 4’
  - Unsaturated hydroxyethyl group at 6’
  - 4-amino-3-hydroxybutanoic acid at N-1 substitution
- MOA:
  - Binds to 30S subunit
  - Inhibits protein synthesis
- Dose: 15 mg/kg IV q24h



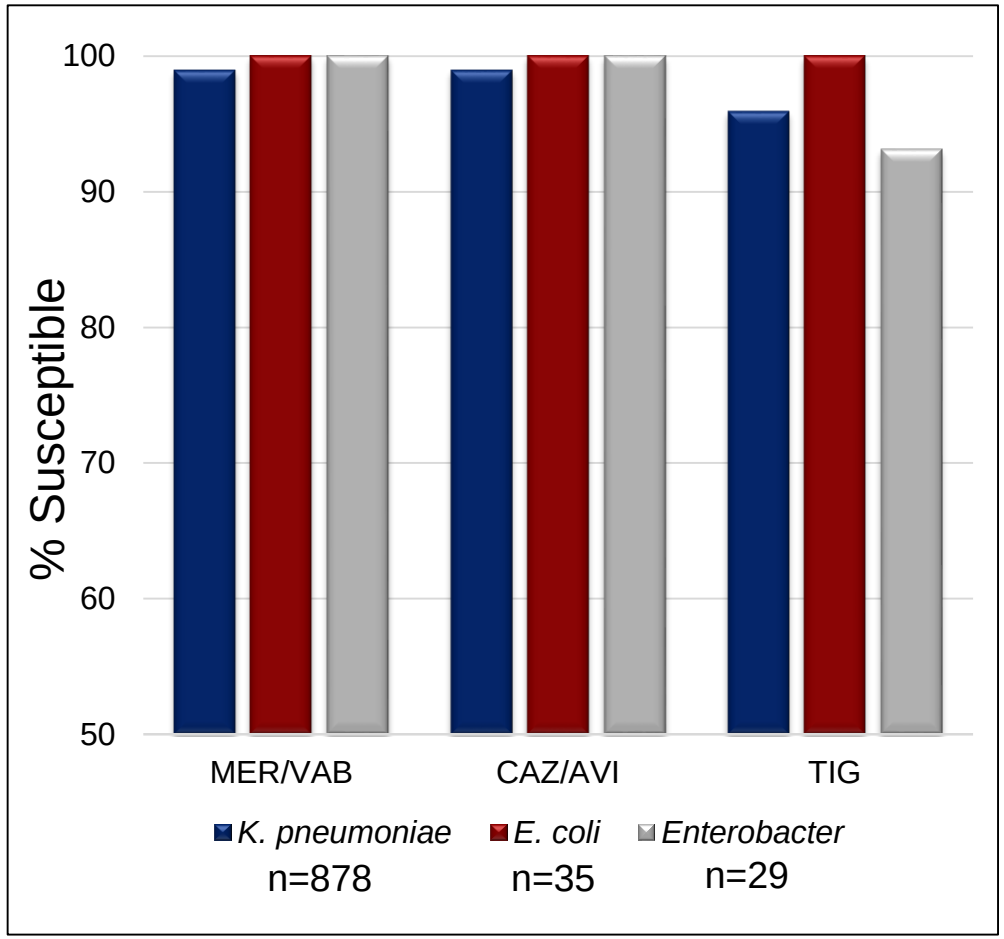
Amikacin

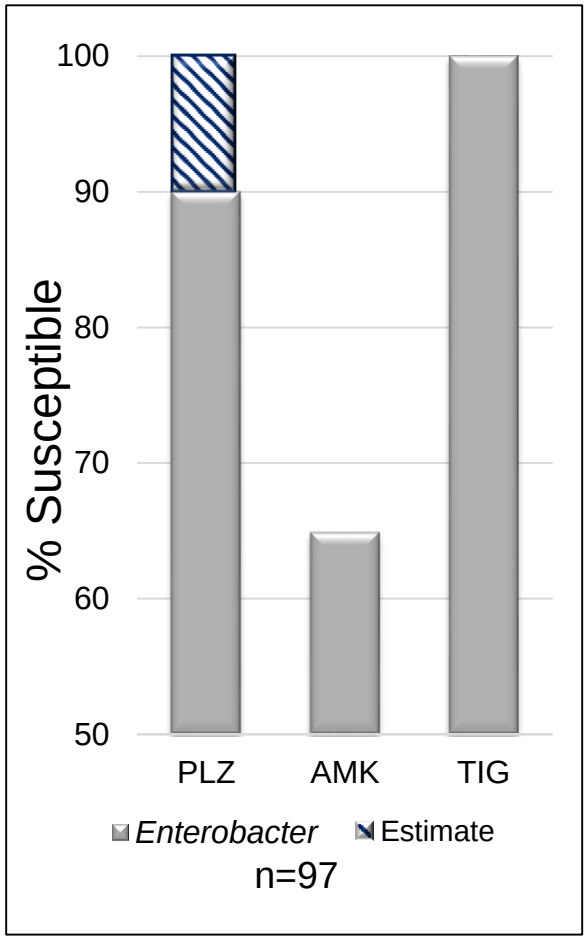


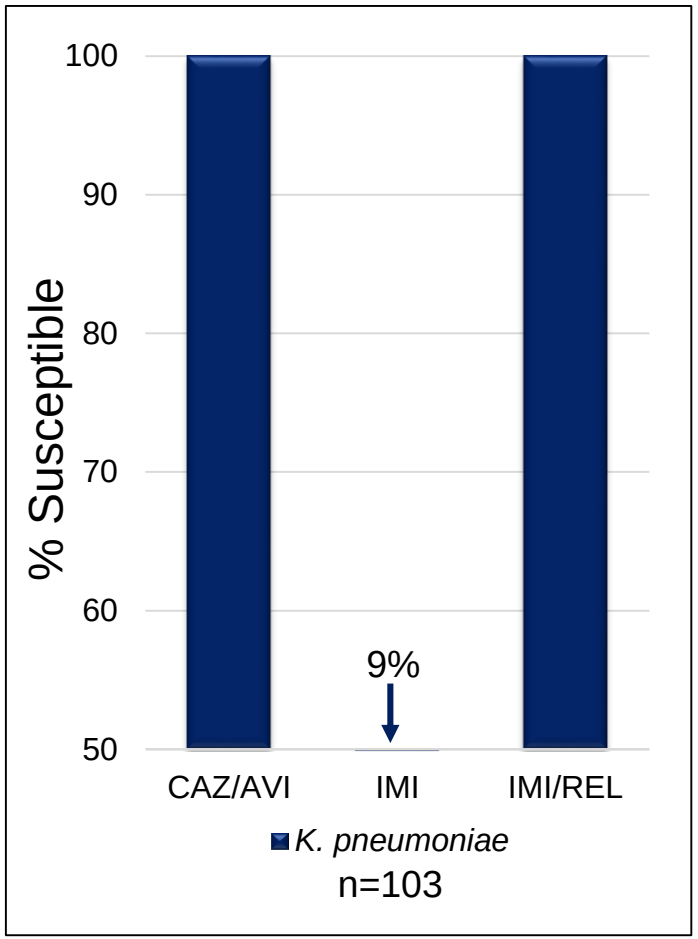
Plazomicin

Zemdri PI. Achaogen. South San Francisco, CA. 2018; ElJaaly K. *Drugs* 2019 doi: 10.1007/s40265-019-1054-3

In Vitro CRE Studies







Hackel MA. *AAC* 2017;62:e01904-17; Castanheira M *AAC* 2018;62:e00313-18; Papp-Wallace KM. AAC 2018;62:e00174-18

In vivo CRE Studies: CAZ/AVI

CRACKLE **Consortium on Resistance Against Carbapenems in *Klebsiella* and Other Enterobacteriaceae**

van Duin D et al. *CID* 2018;66:163-71

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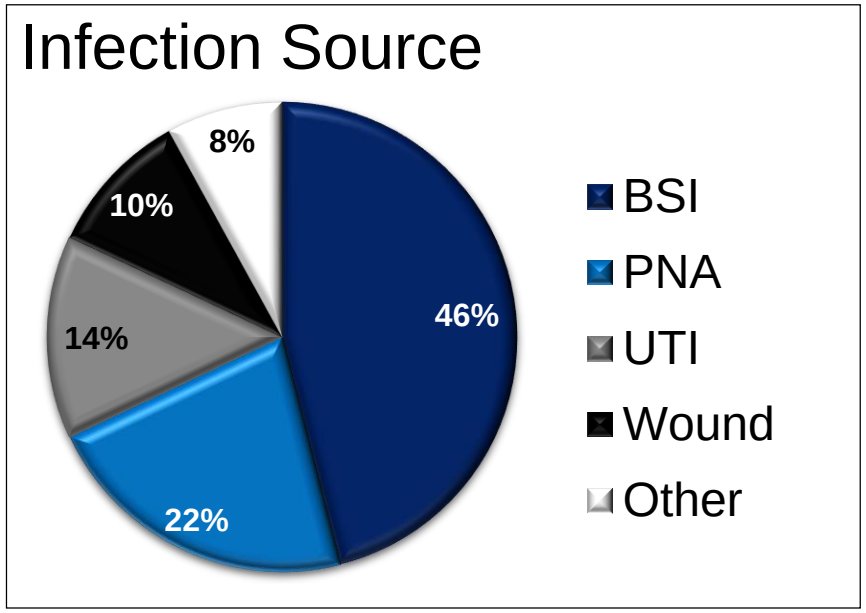

van Duin D et al. *CID* 2018;66:163-71

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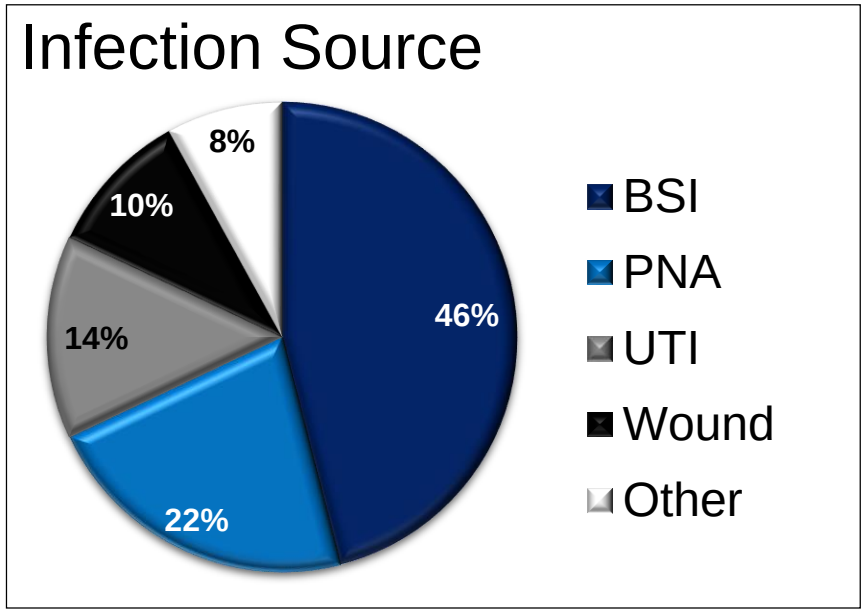
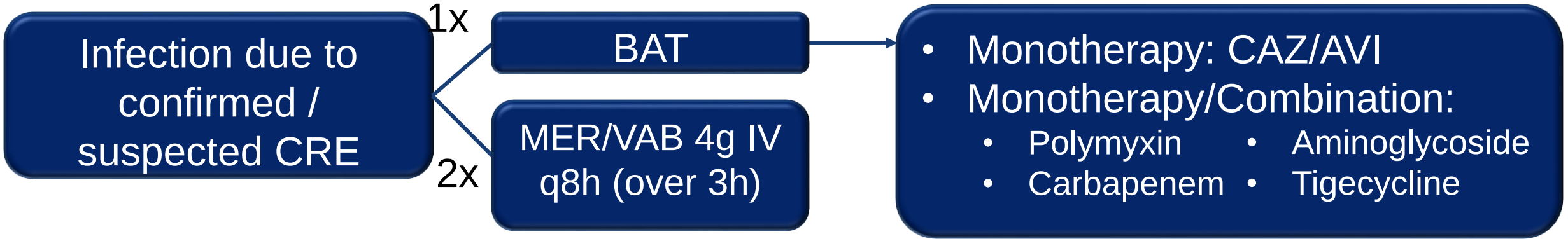


	CAZ/AVI (n=38)	COL (n=99)
Hospital mortality	3 (8%)	33 (33%)
AKI	1 (4%)	5 (11%)

van Duin D et al. *CID* 2018;66:163-71

In vivo CRE Studies: MER/VAB



Wunderink R. *Infect Dis Ther* 2018;7:439-55

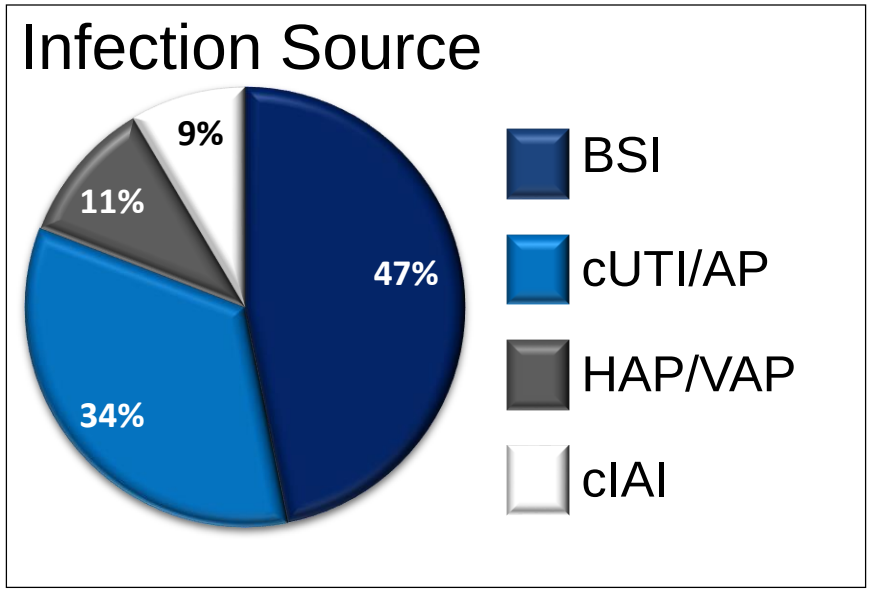
In vivo CRE Studies: MER/VAB

Infection due to confirmed / suspected CRE

1x BAT

2x MER/VAB 4g IV q8h (over 3h)

- Monotherapy: CAZ/AVI
- Monotherapy/Combination:
  - Polymyxin
  - Aminoglycoside
  - Carbapenem
  - Tigecycline



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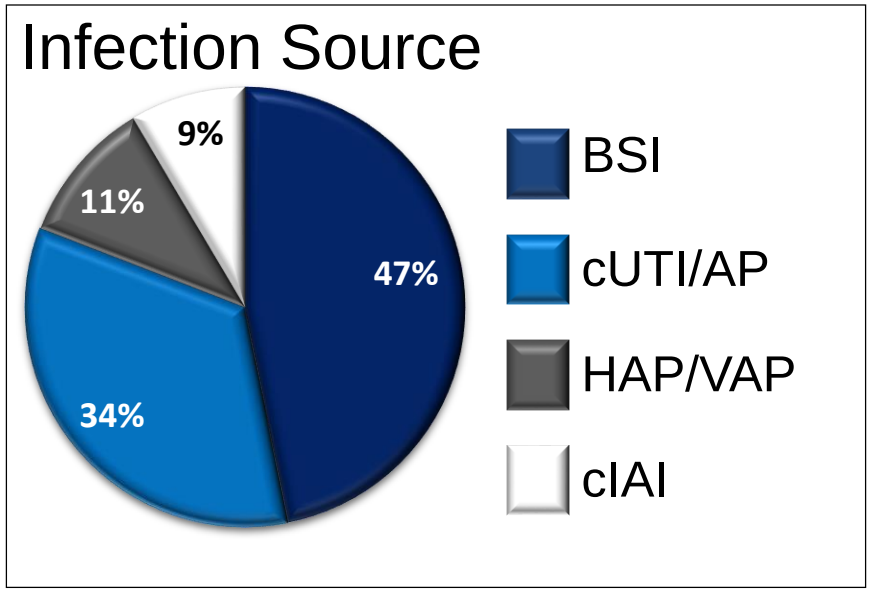
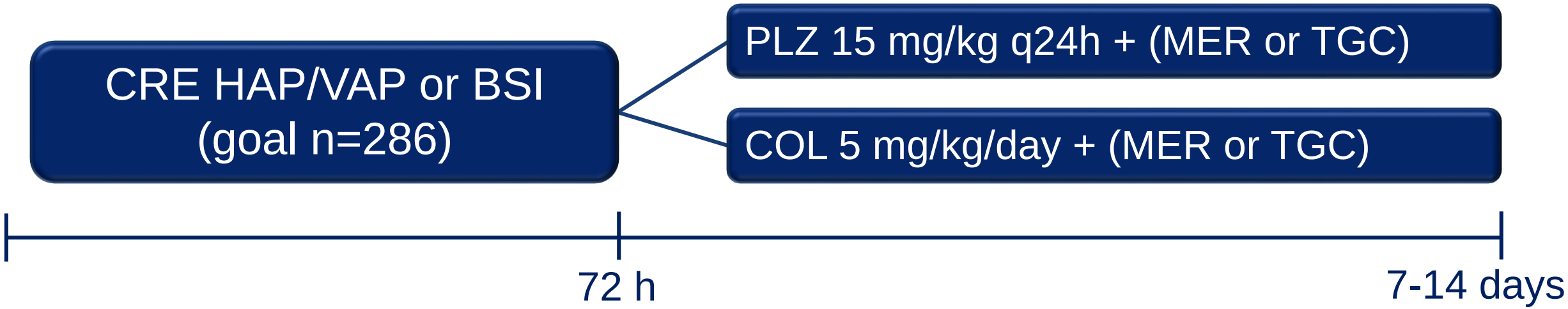


	MER/VAB (n=32)	BAT (n=15)
Cure EOT	21 (65.6%)	5 (33.3%)
Cure TOC	19 (59.4%0	4 (26.7%)
Micro cure EOT	21 (65.6%)	6 (40.0%)
Micro cure TOC	17 (53.1%)	5 (33.3%)
28d mortality	5 (15.6%)	5 (33.3%)

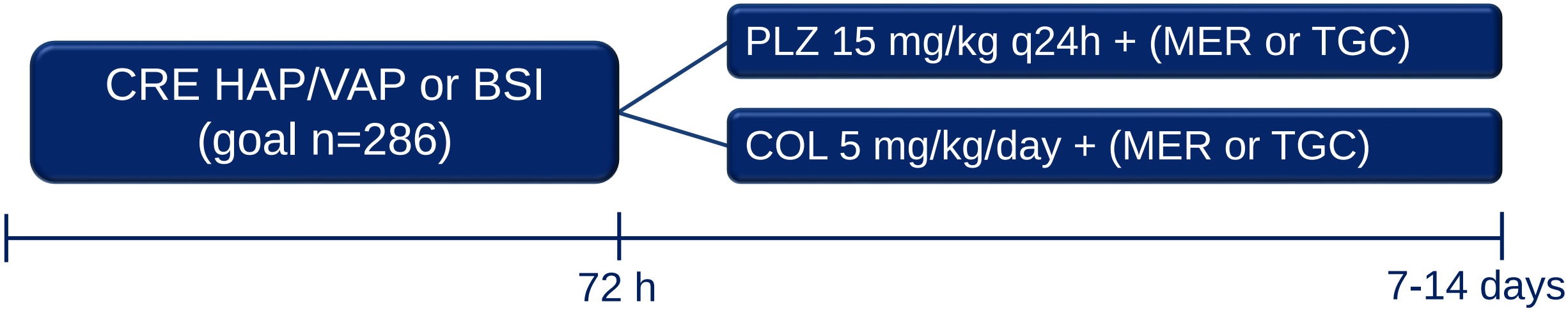
Wunderink R. *Infect Dis Ther* 2018;7:439-55

In vivo CRE Studies: Plazomicin



McKinnell NEJM 2019;380:

In vivo CRE Studies: Plazomicin



	PLZ (n=17)	COL (n=20)	%Δ (90% CI)
28d mortality	4/17 (23.5%)	10/20 (50%)	-26.5 (-51.2 to 0.7)
d5 BSI clearance	12/14 (85.7%)	7/15 (46.7%)	39 (9.4 to 65.5)
ADRs	9/18 (50%)	17/21 (81%)	
AKI	2/12 (16.7%)	8/16 (50%)	

McKinnell NEJM 2019;380:

Question

Which of the following medications has activity against carbapenem-resistant Enterobacteriaceae?

A. Ceftolozane/tazobactam
B. Meropenem/vaborbactam
C. Aztreonam
D. Ertapenem

Take Me Down to the ~~Paradise~~ *Pseudomonas* City

Question

A 55 year old man with epilepsy on valproic acid and levetiracetam presents to the hospital for a suspected pulmonary infection. He has a history of multi-drug resistant *Pseudomonas aeruginosa* infections. Which of the following antibiotics is most appropriate to recommend for empiric therapy?

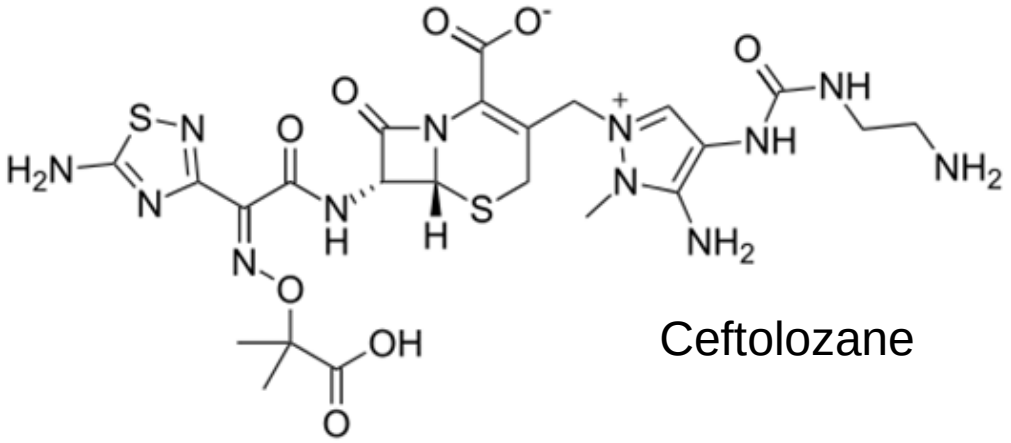
A. Fosfomycin
B. Eravacycline
C. Meropenem/vaborbactam
D. Ceftazidime/avibactam

Ceftolozane/tazobactam

Ceftolozane

New!

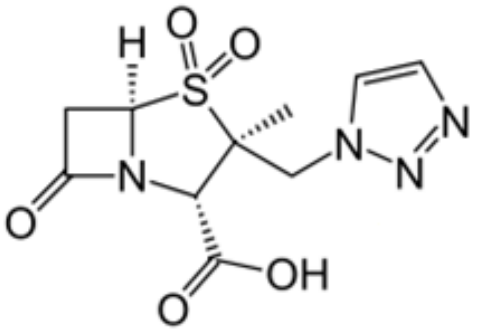
- Novel anti-Psa cephalosporin
- Stable against AmpC
- Inactivated by ESBL, carbapenemases



Ceftolozane

Tazobactam

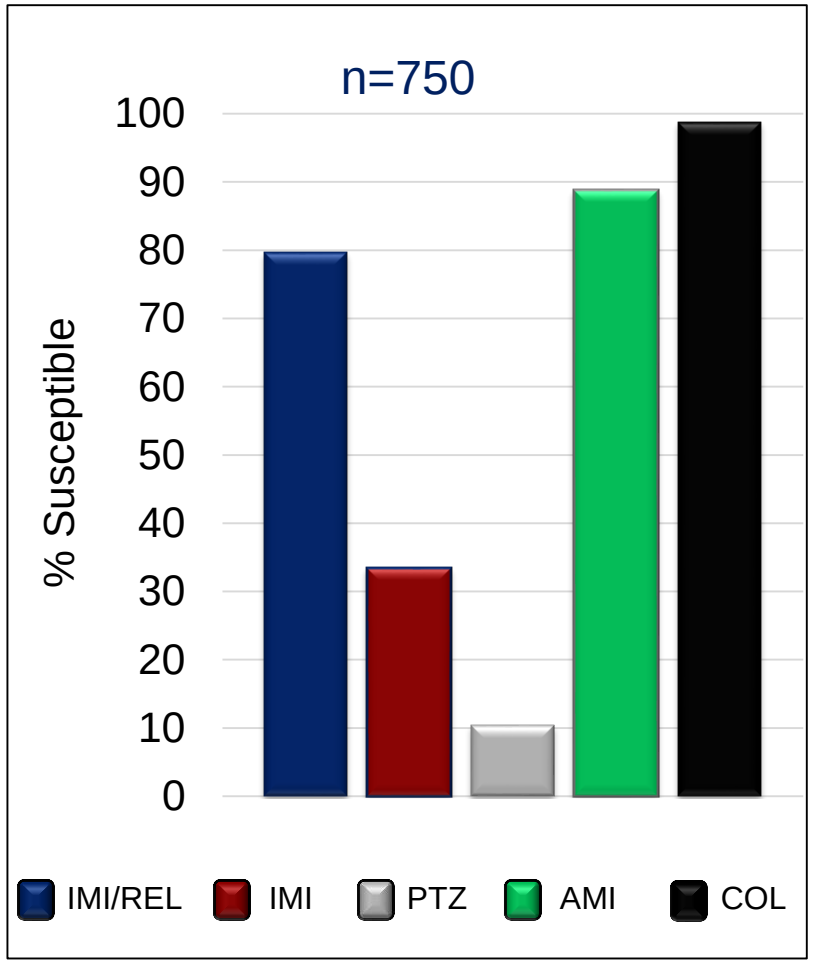
- Existing β-lactamase inhibitor
- Stable against ESBLs, cephasporinases
- Inactivated by AmpC, carbapenemases

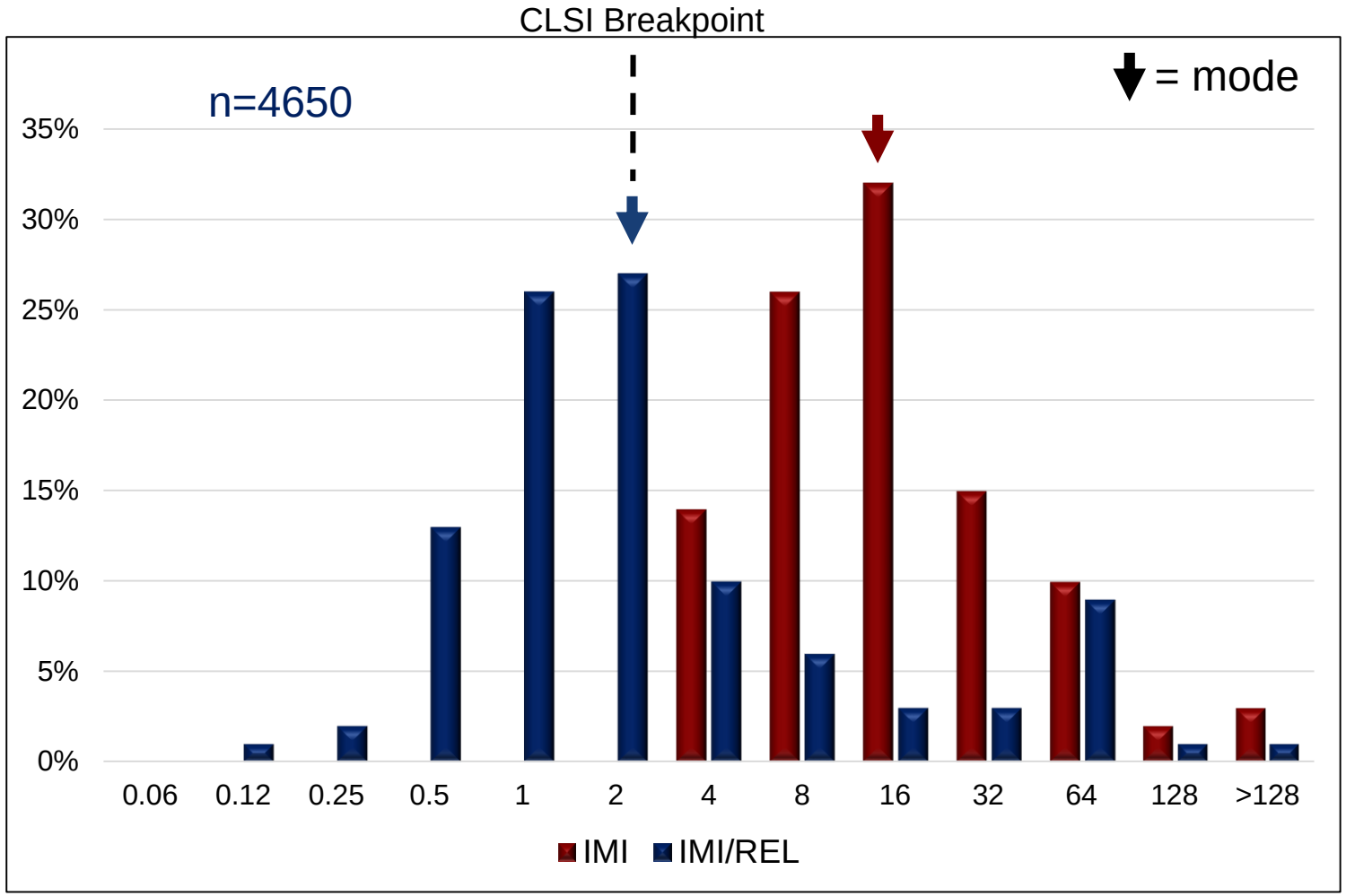


Tazobactam

Zerbaxa PI. Merck. Syracuse, NY. 2018; Liscio JL. *IJAA* 2015;46:266-71

In vitro MDR *Pseudomonas* Studies





Karlowsy JA. DMID doi: 10.1016/j.diagmicrobio.2019.05.001; Young K. BMC Microbiol 2019;19:150

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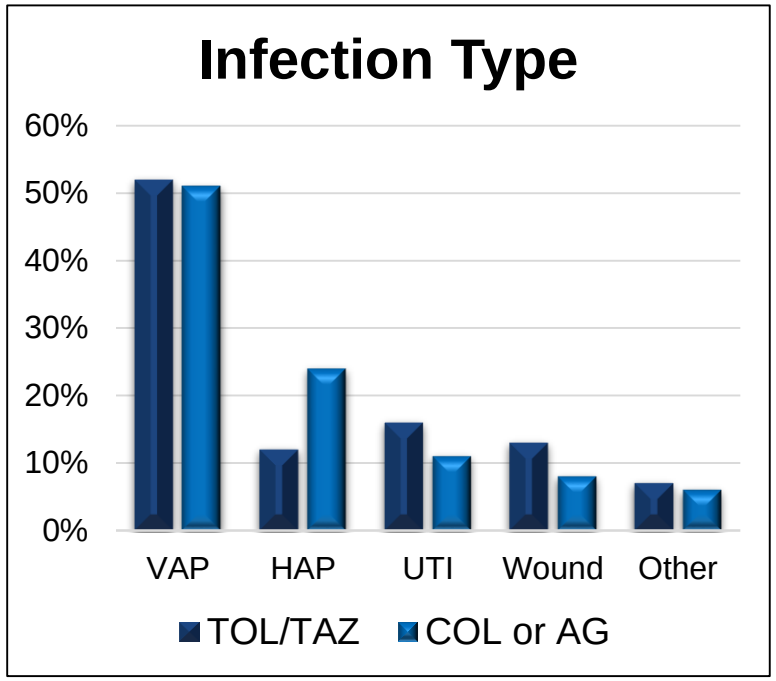
In vivo: MDR *Pseudomonas*

MDR or XDR *Pseudomonas*

retrospective

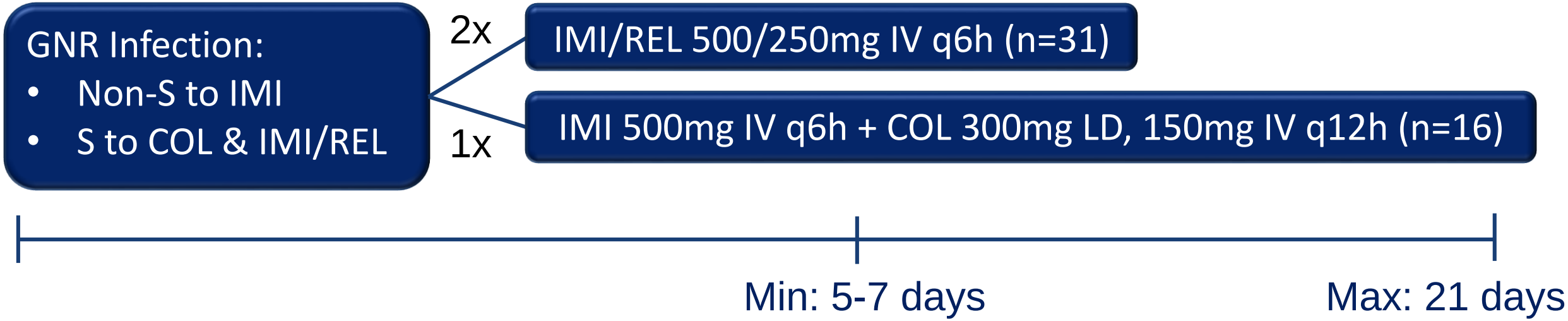
- TOL/TAZ ≥ 48h +/- inhaled COL / AG (n=100)
- COL or AG backbone ≥ 48h +/- inhaled COL / AG (n=100)



	TOL/TAZ n=100	COL or AG n=100	aOR (95% CI)
Clinical cure	81%	61%	2.63 (1.31-5.30)
In-hospital mortality	20%	25%	0.62 (0.30-1.28)
AKI	6%	34%	0.08 (0.03-0.22)

Pogue JM et al. *CID* 2019; doi: 10.1093/cid/ciz816

In vivo CR-*Psa*: IMI/REL vs. IMI+COL

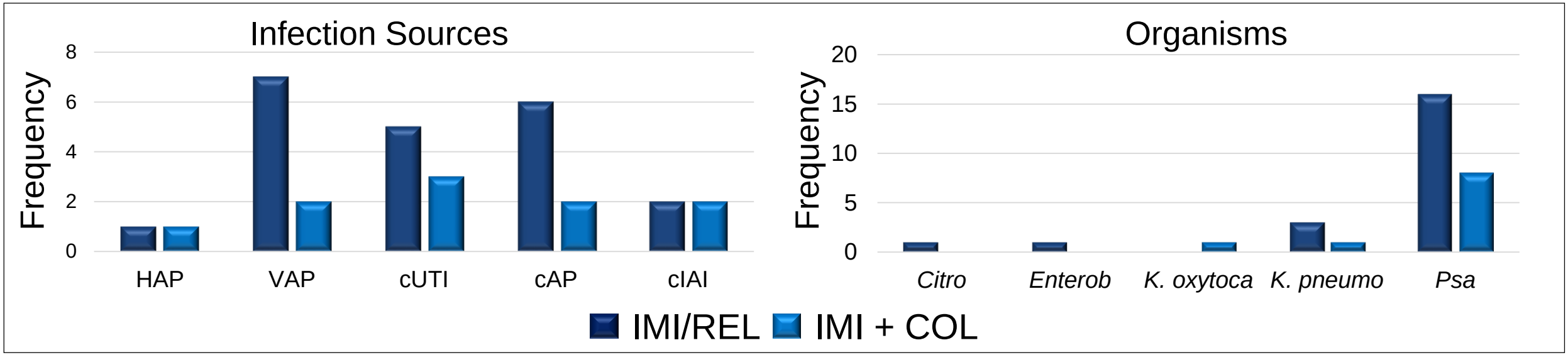


Overall Response:

- HAP/VAP: 28d all-cause mortality
- cIAI: 28d clinical response
- cUTI: clinical/micro response ≤ 24h after last dose

Matsch J. CID 2019 doi: 10.1093/cid/ciz530

In vivo CR-*Psa*: IMI/REL vs. IMI+COL



Matsch J. CID 2019 doi: 10.1093/cid/ciz530

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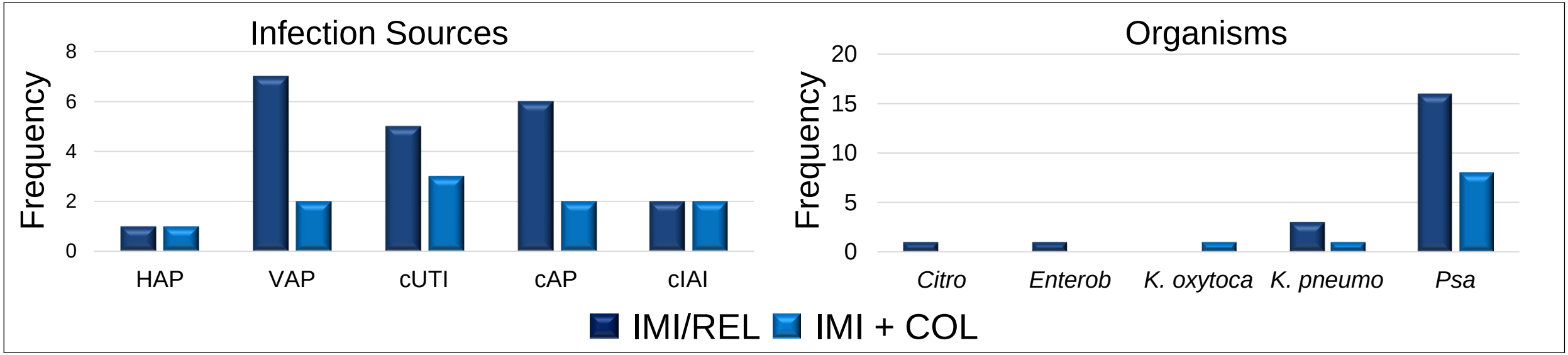

	IMI/REL	IMI + COL	%Δ (95% CI)
Overall Response	15/21 (71.4%)	7/10 (70.0%)	-7.3 (-2.75 to 21.4)
Day 28 response	15/21 (71.4%)	4/10 (40.0%)	26.3 (1.3 to 51.5)
28d all-cause mortality	2/21 (9.5%)	3/10 (30.0%)	-17.3 (-46.4 to 6.7)
Txt-related AKI	3/29 (10.3%)	9/16 (56.3%)	-45.9 (-69.1 to -18.4)

Matsch J. CID 2019 doi: 10.1093/cid/ciz530

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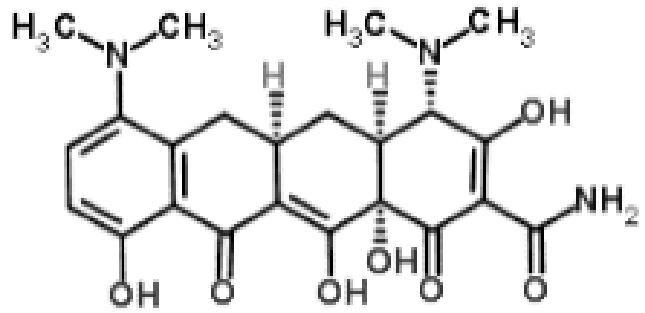
A. Fosfomycin
B. Eravacycline
C. Meropenem/vaborbactam
D. Ceftazidime/avibactam

Sweet Child o' Mine: *Acinetobacter*

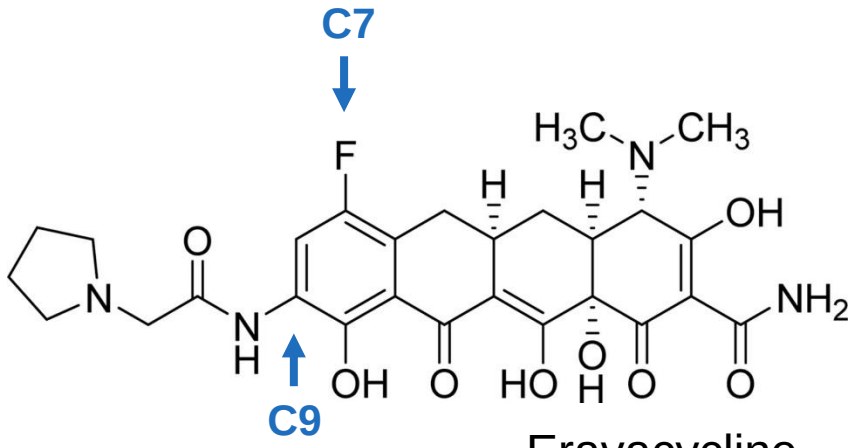
Eravacycline

New!

- Fluorocycline
- Stable against tetracycline resistance mechanisms:
  - Fluorine at C7
  - Pyrrolidinoacetamido at C9
- MOA:
  - Bind to 30s subunit
  - Inhibit protein synthesis



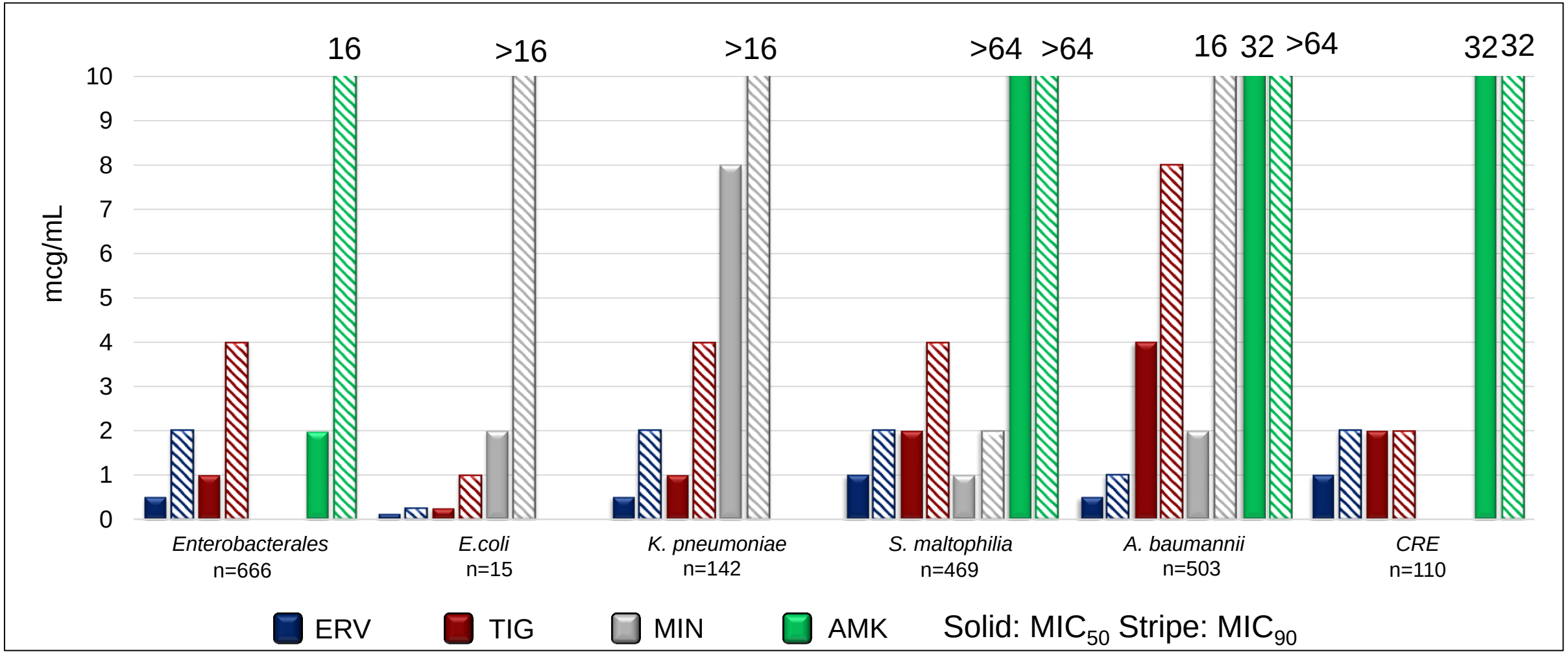
Minocycline



Eravacycline

Heaney M. *Annals Pharmacother* 2019;53:1124-35; Xerava PI. Tetraphase. Watertown, MA. 2018

In vitro MDR GNR Studies



Lawrence KR. ASM Microbe 2018. Poster 630; Zhang Y. *J Antibiotics* 2016;69:600-4

Eravacycline: *In vivo Acinetobacter*

IGNITE 1:

	ERV	ETP
Acinetobacter	8/8	6/6
Cepha-R	8/8	5/5
ESBL	5/5	1/1
CR-Ab	2/2	4/4
MDR	7/7	4/4

IGNITE 4:

	ERV	MER
Acinetobacter	5/5	2/2

Solomkin JS. *JAMA Surgery* 2017;152:224-32; Solomkin JS. *CID* 2018 doi: 10.1093/cid/ciy1029

Meta-analysis for MDR, XDR *Acinetobacter*

Systematic Review: 29 studies

Network Meta-analysis 26 studies

Patients: 2529	Media age: 60 years	Pneumonia: 58.5%	XDR *Acinetobacter:* 45.0% MDR *Acinetobacter:* 41.0%

Kengkla K et al. *J Antimicrob Chemother* 2018;73:22-32

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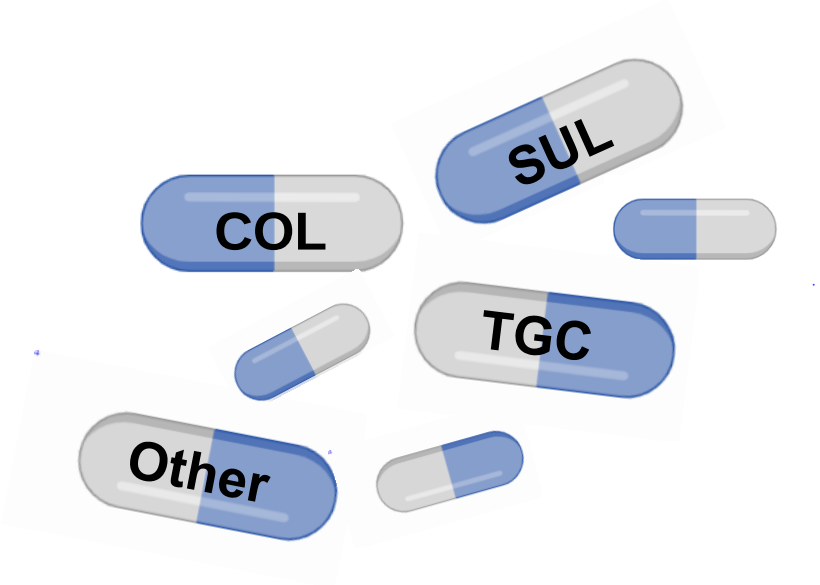

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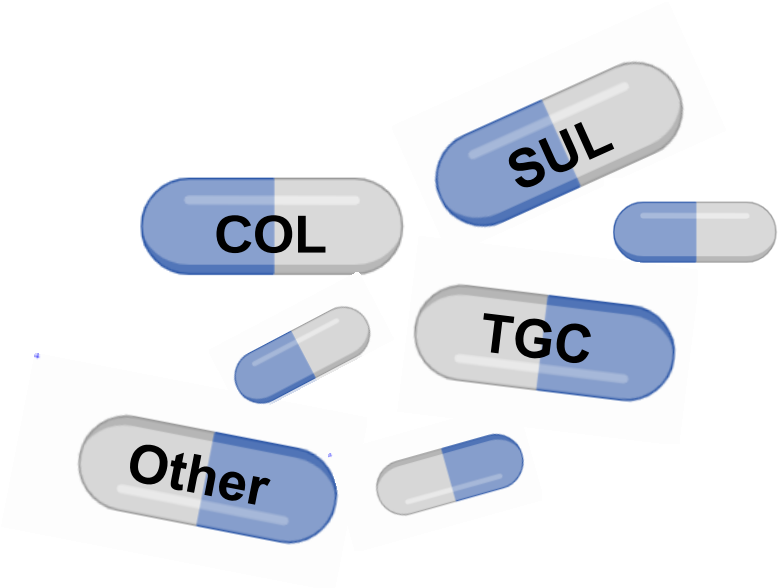


Clinical cure	**COL + SUL + TGC** = best
Micro cure	**COL + other** >> COL; TGC; TGC + other
All-cause mortality	**COL + other** >> SUL + other
Nephrotoxicity	**COL** >> TGC; TGC + other

Kengkla K et al. *J Antimicrob Chemother* 2018;73:22-32

Don’t You Cry: Review of Current Agents

Summary of Current Agents

Drug	ESBL	CRE (KPC)	CRE (MBL)	CR *Pseudo*	MDR *Acineto*
TOL/TAZ					
CAZ/AVI					
MER/VAB					
IMI/REL					
Plazomicin					
Eravacycline					

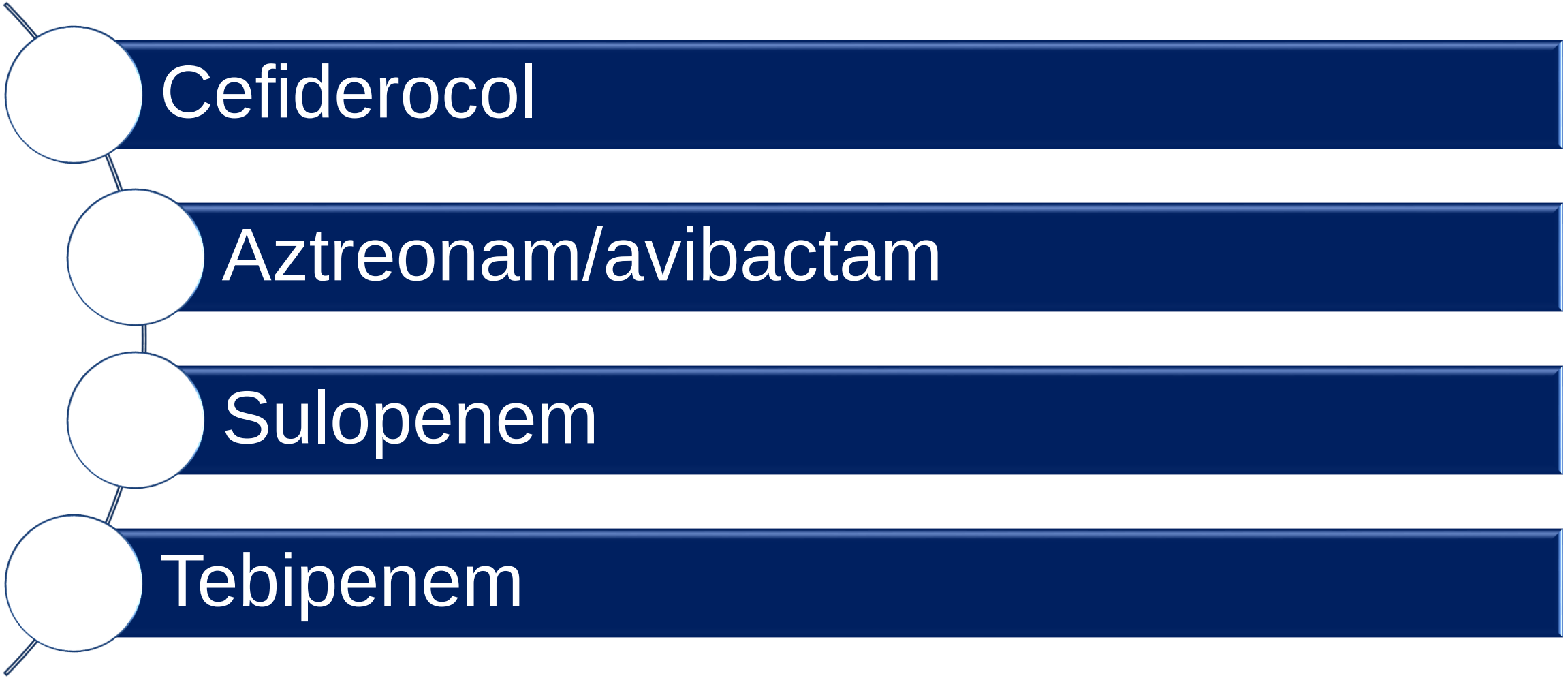
All We Need is Just a Little Patience

Question

Which of the following antimicrobials uses iron transport mechanisms and a “trojan horse” approach as part of its mechanism of action?

A. Eravacycline
B. Cefiderocol
C. Fosfomycin
D. Quinupristin/dalfopristin

Coming Attractions



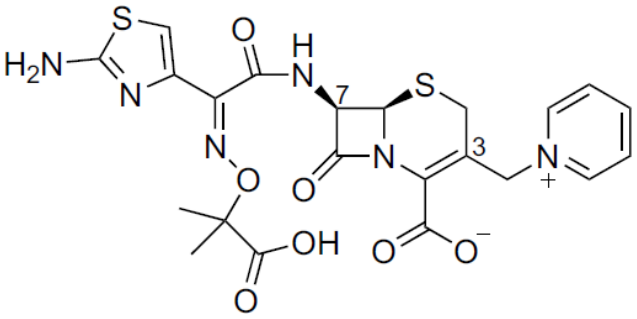
Cefiderocol

New!

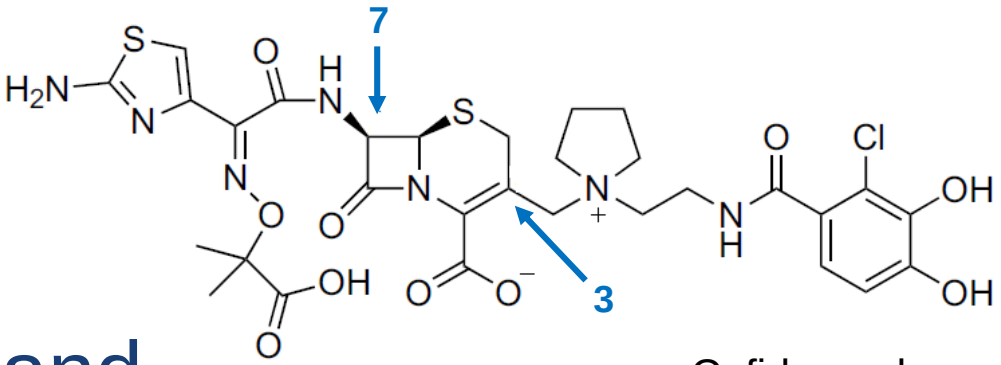
Siderophore cephalosporin

- 3’ catechol substitution
  - Utilizes iron transport mechanisms to ↑ periplasmic [ ]
- 7’ carboxypropyl-oxyimino group
  - Stable against broad β-lactamases

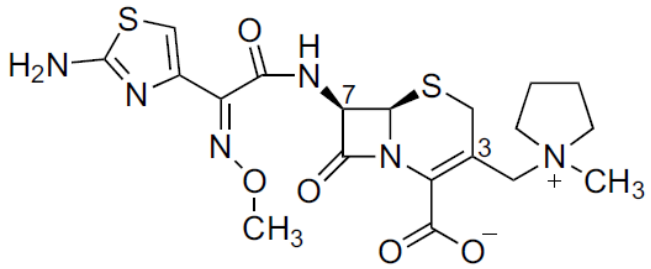
Structurally similar to ceftazidime and cefepime



Ceftazidime



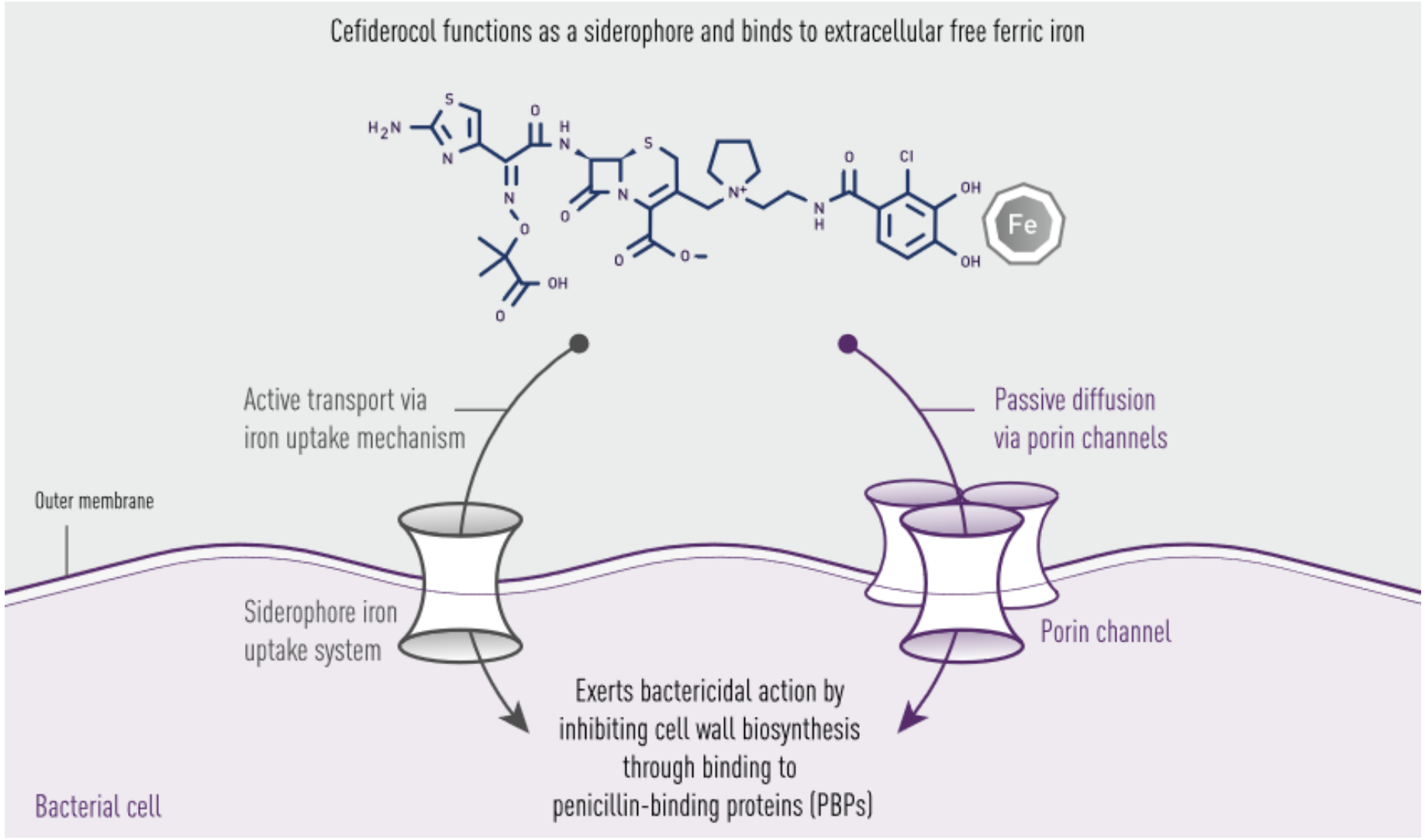
Cefiderocol



Cefepime

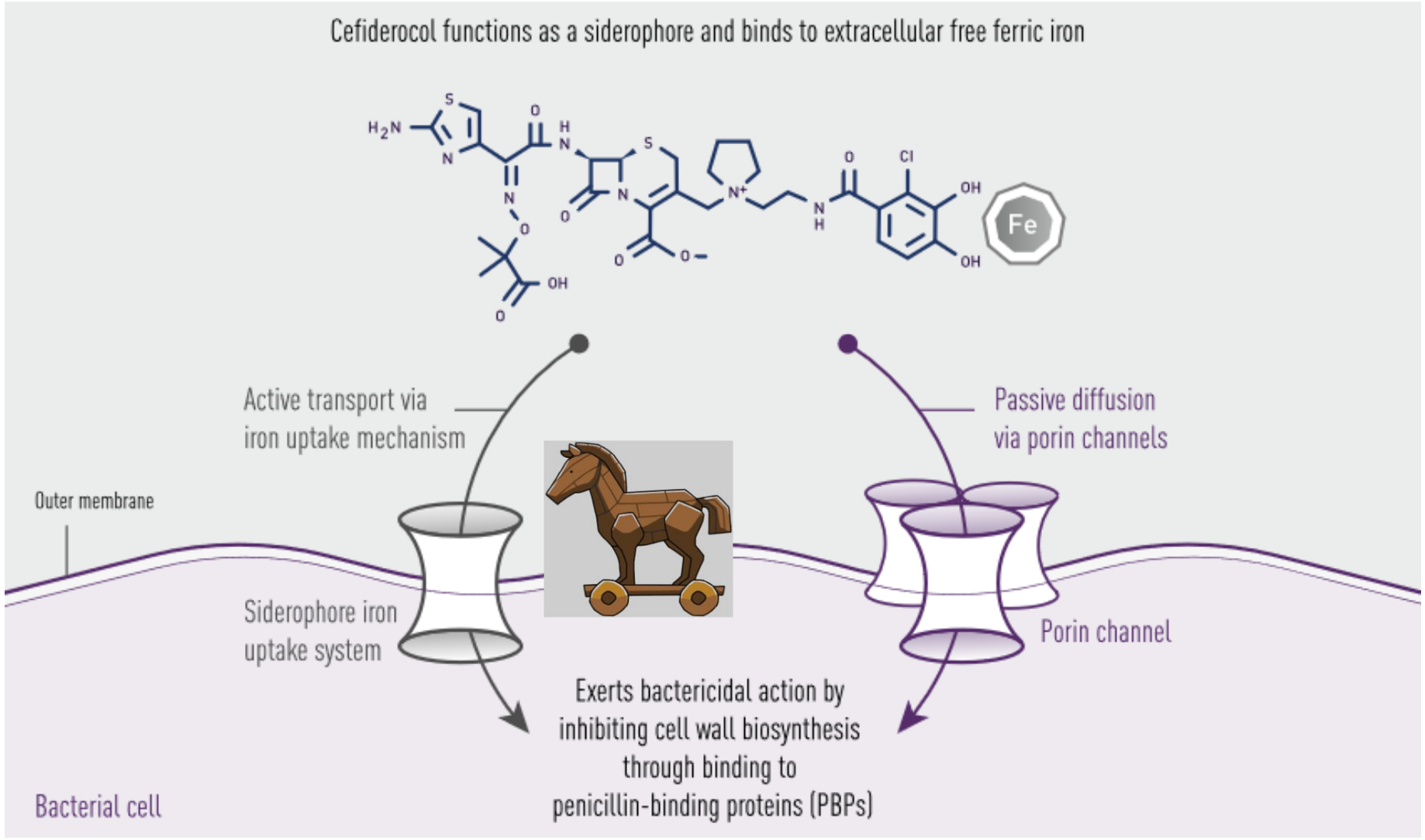
Zhanel GA. *Drugs* 2019;79:271-89

Cefiderocol: MOA



www.fetroja.com Accessed: 12/15/19

Cefiderocol: MOA



www.fetroja.com Accessed: 12/15/19

Cefiderocol

Mechanisms of Resistance:

- Enzymatic hydrolysis
- Porin channel mutations
- Efflux pump override
- Target site mutations

β-lactamases:

- CTX-M
- KPC
- NDM
- OXA
- VIM

Organisms:

- *Acinetobacter*
- *Pseudomonas*
- *Stenotrophomonas*
- Gram-positive
- Anaerobes

Zhanel GA. *Drugs* 2019;79:271-89

Cefiderocol

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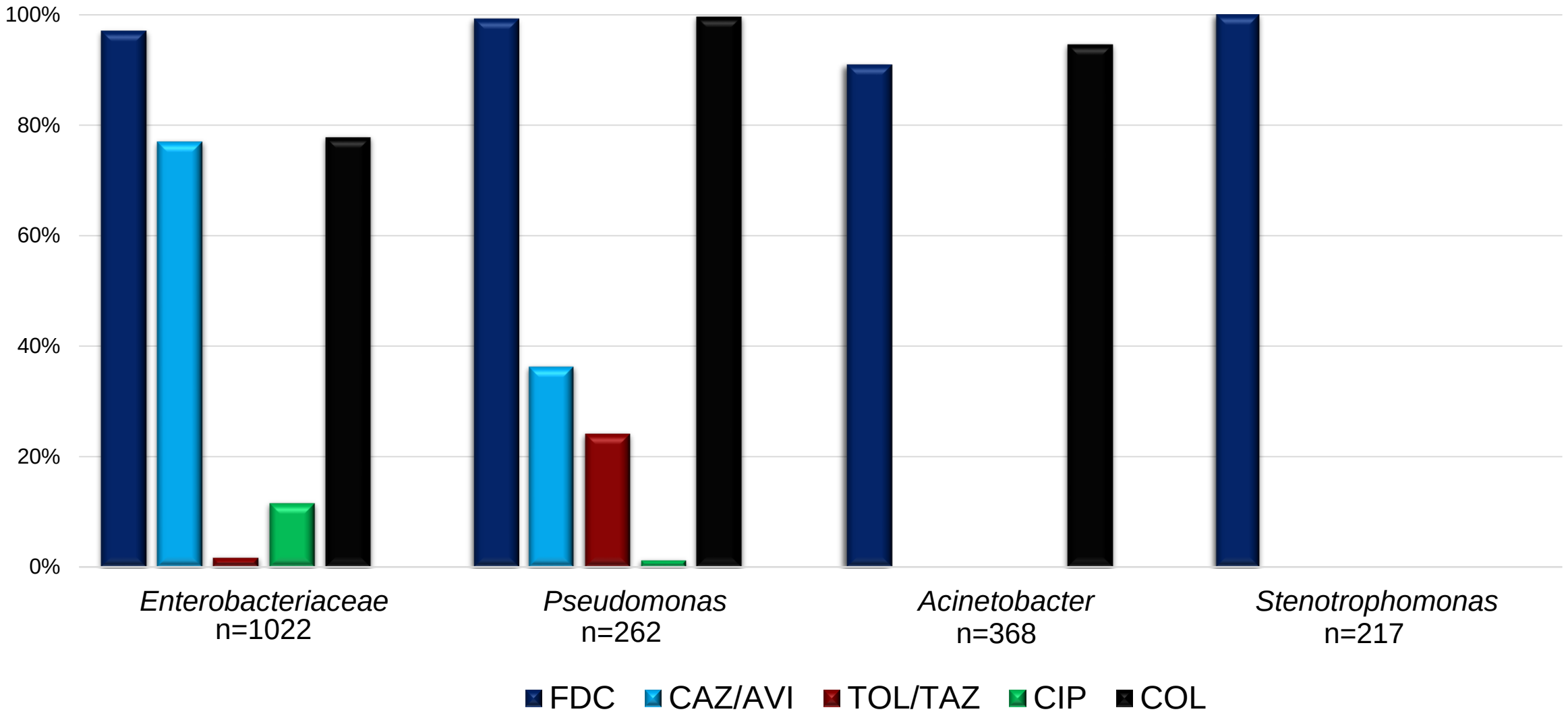
- *Pseudomonas* ✓
- *Stenotrophomonas* ✓
- Gram-positive ✗
- Anaerobes ✗

Zhanel GA. *Drugs* 2019;79:271-89

CR-GNRs: *In Vitro*



Yamano Y. CID 2019;69:S544-51

Cefiderocol (Resistant Pathogens)

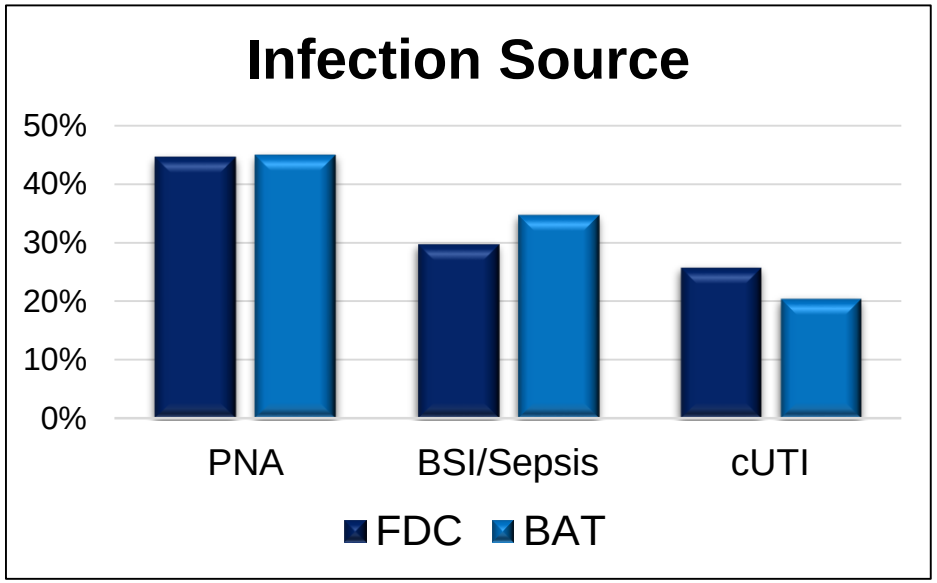
CREDIBLE-CR

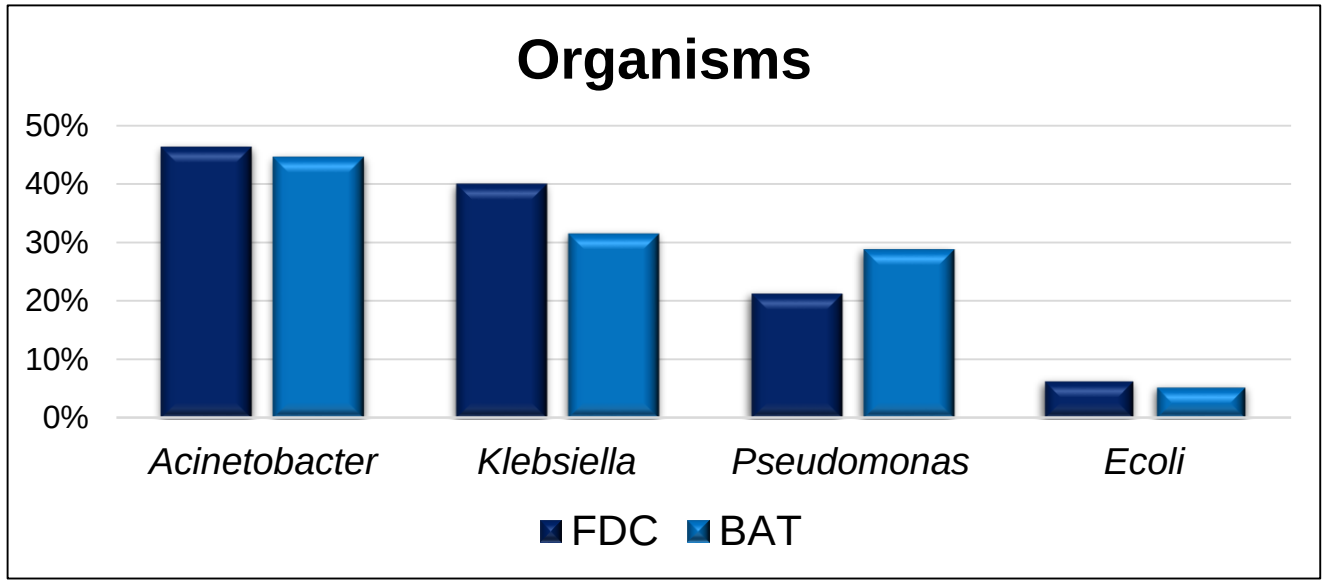
Infection due to CRE

1x → BAT (n=49)

2x → FDC 2g IV q8h* (n=101)

- COL monotherapy (15.8%)
- COL + TCG (7.9%)
- COL + AMP/SUL (5.3%)
- COL + FOS (5.3%)
- Non-COL (21.1%)





*could receive 1 additional GNR agent

FDA submission dossier: https://www.fda.gov/media/131705/download

Cefiderocol Results

FDA submission dossier: https://www.fda.gov/media/131705/download

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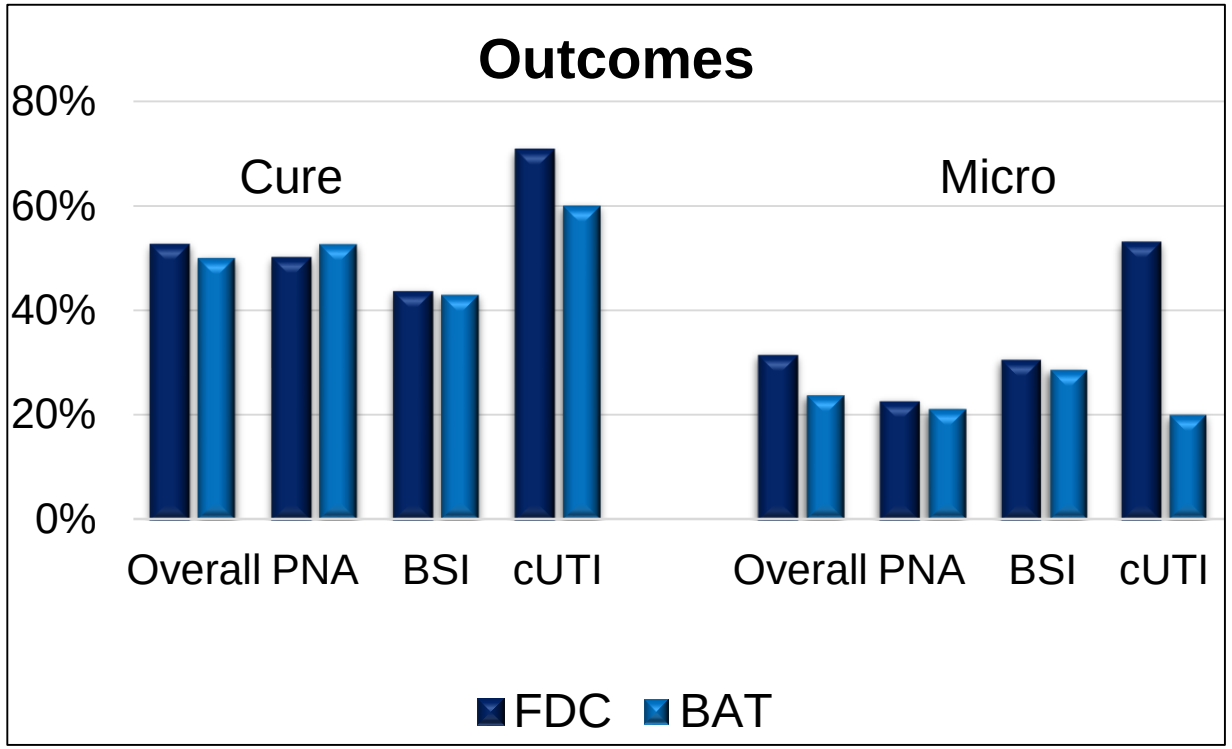
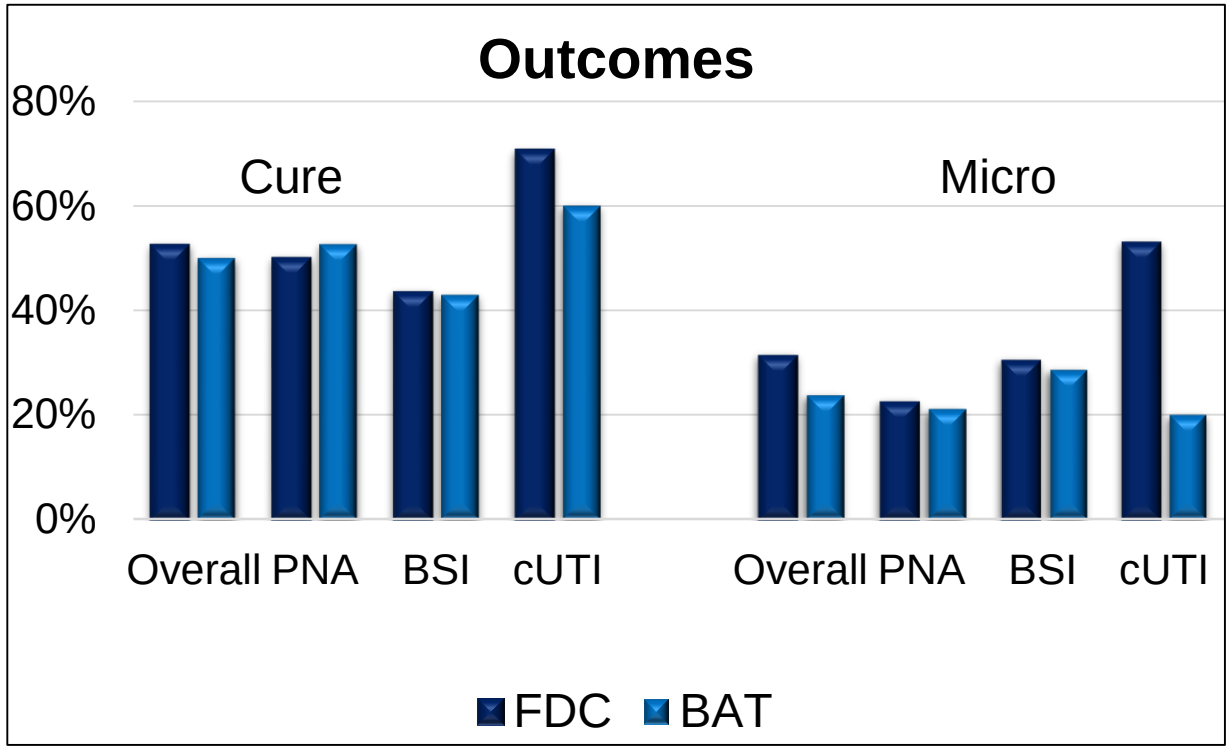
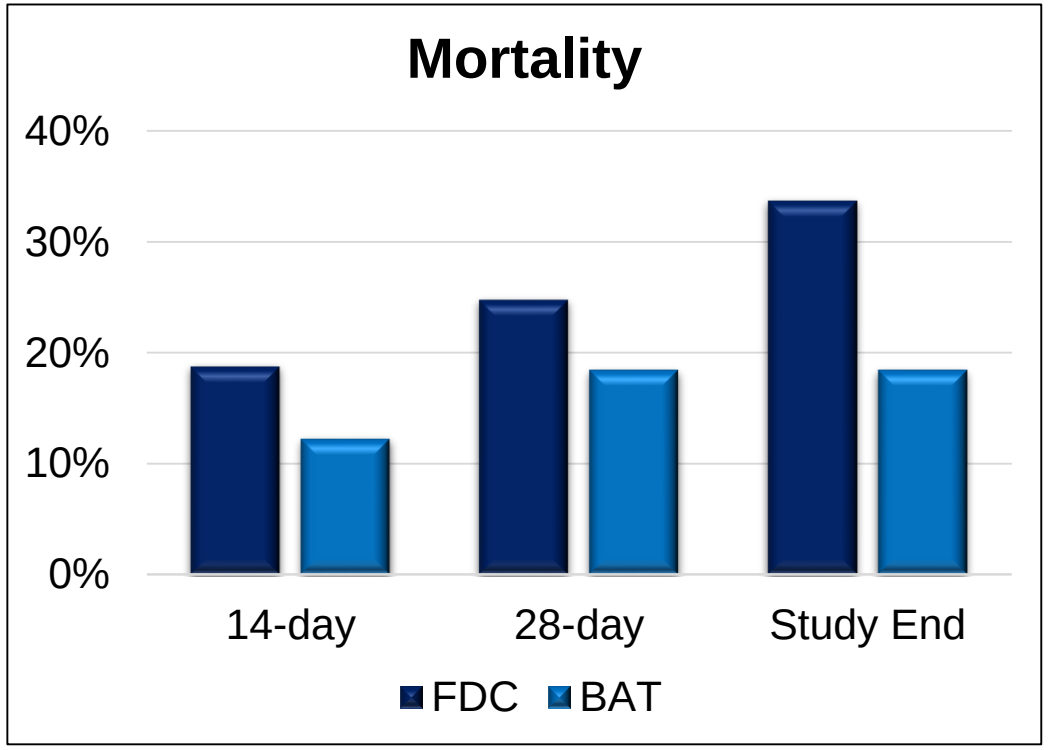
Cefiderocol Results



FDA submission dossier: https://www.fda.gov/media/131705/download

Cefiderocol Results





FDA submission dossier: https://www.fda.gov/media/131705/download

Beth Israel Lahey Health
Beth Israel Deaconess Medical Center

Aztreonam/Avibactam

Ambler Class	Example
A	TEM-1, TEM-2, SHV-1
A	SHV, CTX, KLUG
A	KPC
B	VIM, IMP, NDM
C	AmpC
D	OXA

Castanheira M. ECCMID 2013. Poster P1615

Aztreonam/Avibactam

Ambler Class	Example	
A	TEM-1, TEM-2, SHV-1	Avibactam
A	SHV, CTX, KLUG	Avibactam
A	KPC	Avibactam
B	VIM, IMP, NDM	
C	AmpC	Avibactam
D	OXA	Avibactam

Castanheira M. ECCMID 2013. Poster P1615

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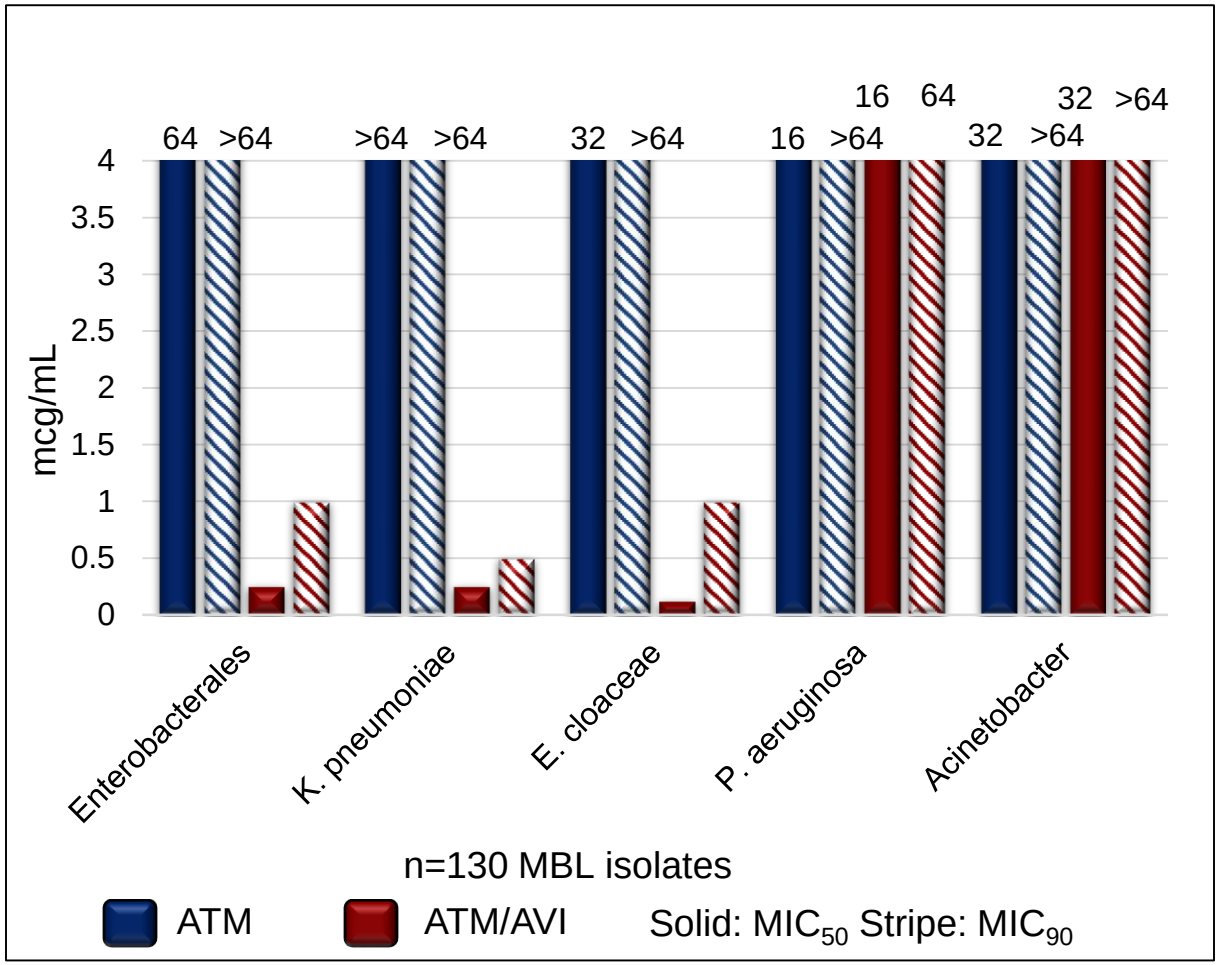
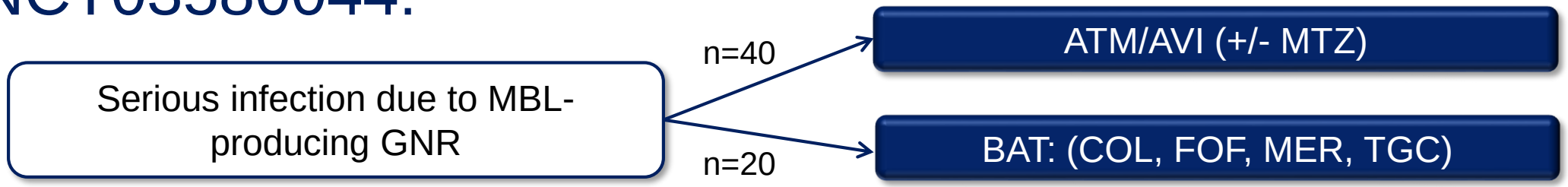


Castanheira M. ECCMID 2013. Poster P1615

Aztreonam/Avibactam: Coming Attractions

NCT03580044:



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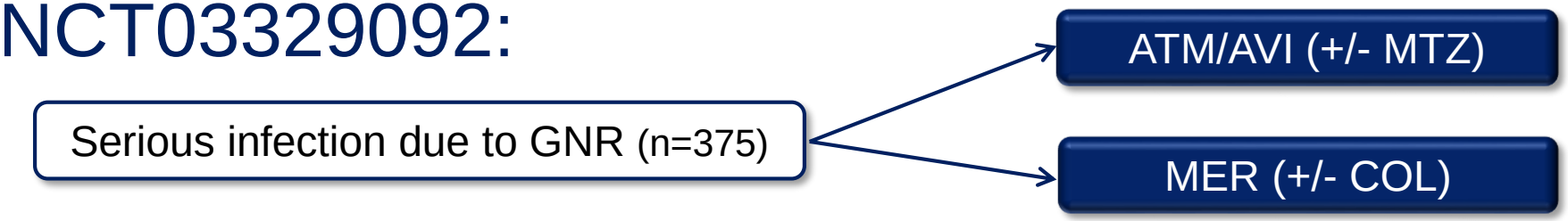


NCT03978091:

www.clinicaltrials.gov Accessed: 7/21/19

Sulopenem New! & Tebipenem New!

Oral carbapenem prodrugs

- Sulopenem-etzadroxil/probenecid
- Tebipenem-pivoxyl

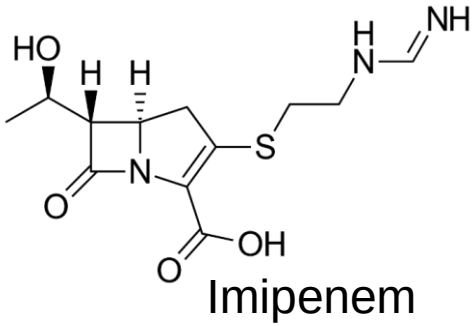
Stable against:

- ESBL, AmpC

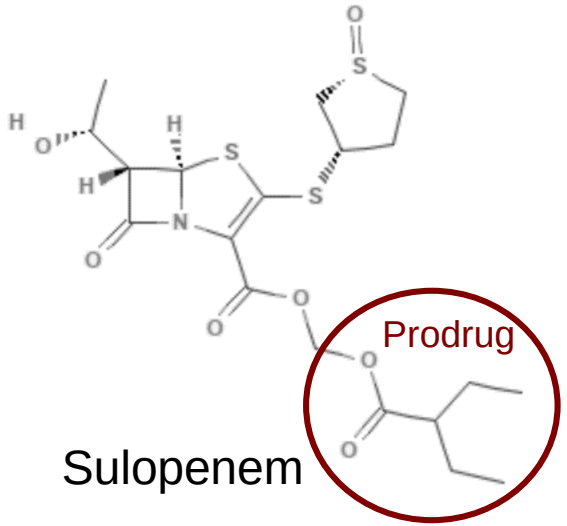
Inactivated by:

- KPC, OXA, MBL

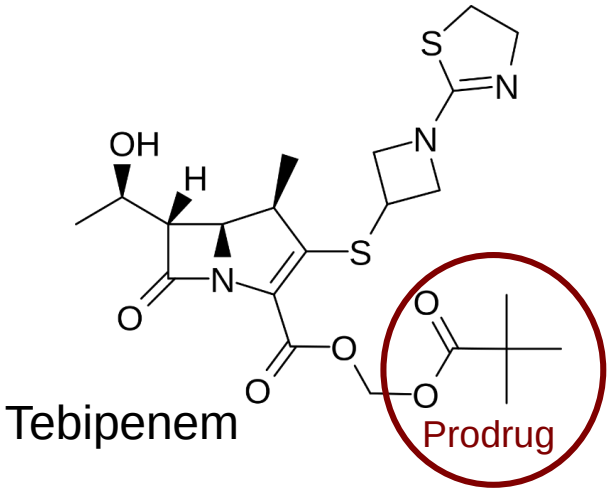
Similar activity to ertapenem



Imipenem



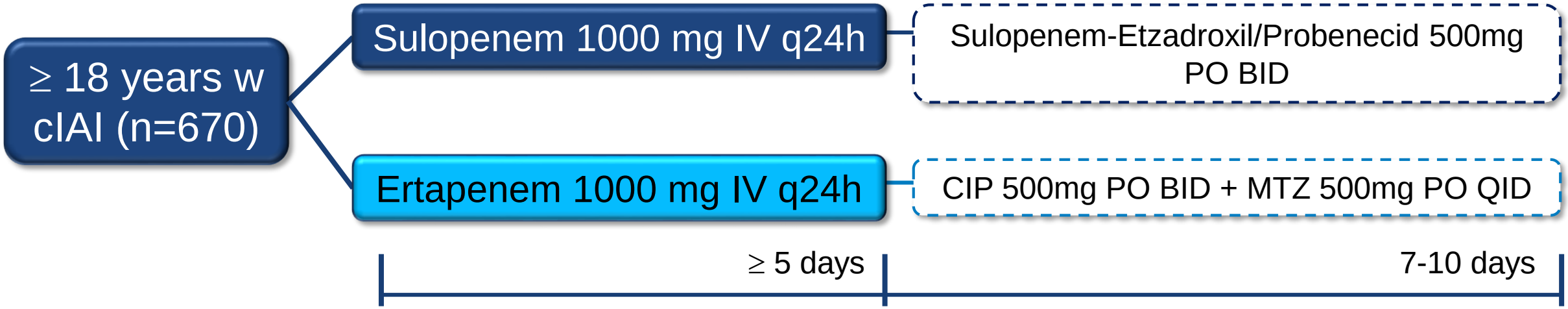
Sulopenem



Tebipenem

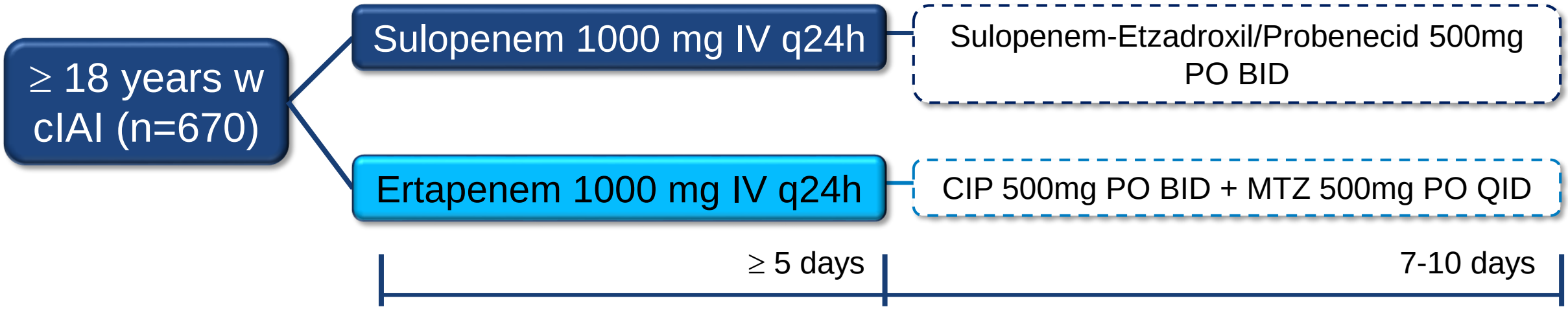
Rubio A *ACS Infect Dis* 2018;4:1436-8; Mendes RE. ASM Microbe 2018 Poster Sunday-560

Sulopenem: SURE-3



Iterum Therapeutics Press Release: 12/10/19; www.clinicaltrials.gov Accessed: 4/15/19

Sulopenem: SURE-3



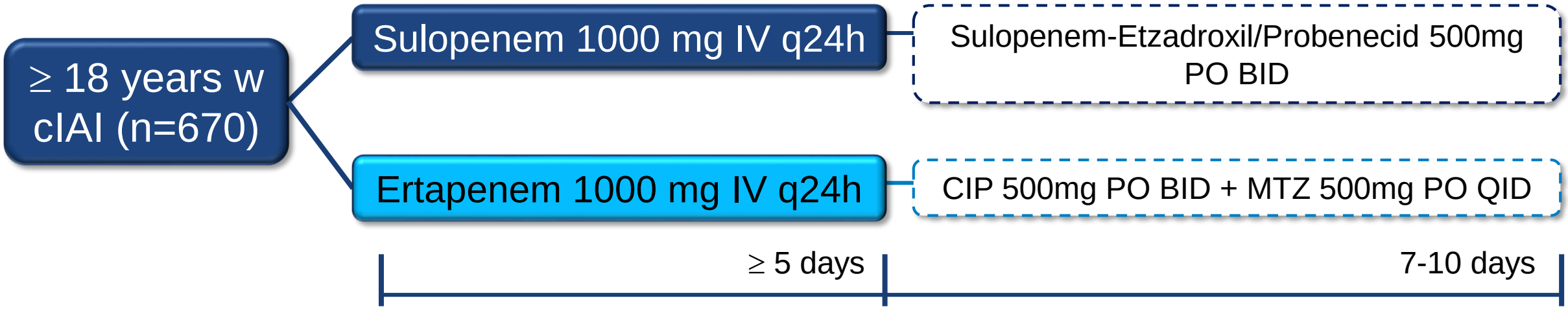
Primary Endpoint:

- 28 day microMITT

Sulopenem	Ertapenem
85.5%	90.2%

Iterum Therapeutics Press Release: 12/10/19; www.clinicaltrials.gov Accessed: 4/15/19

Sulopenem: SURE-3



Primary Endpoint:

- 28 day microMITT

Sulopenem	Ertapenem
85.5%	90.2%

Adverse Events:

	Sulopenem	Ertapenem
Overall	6.0%	5.1%
Diarrhea	4.5%	2.4%

Iterum Therapeutics Press Release: 12/10/19; www.clinicaltrials.gov Accessed: 4/15/19

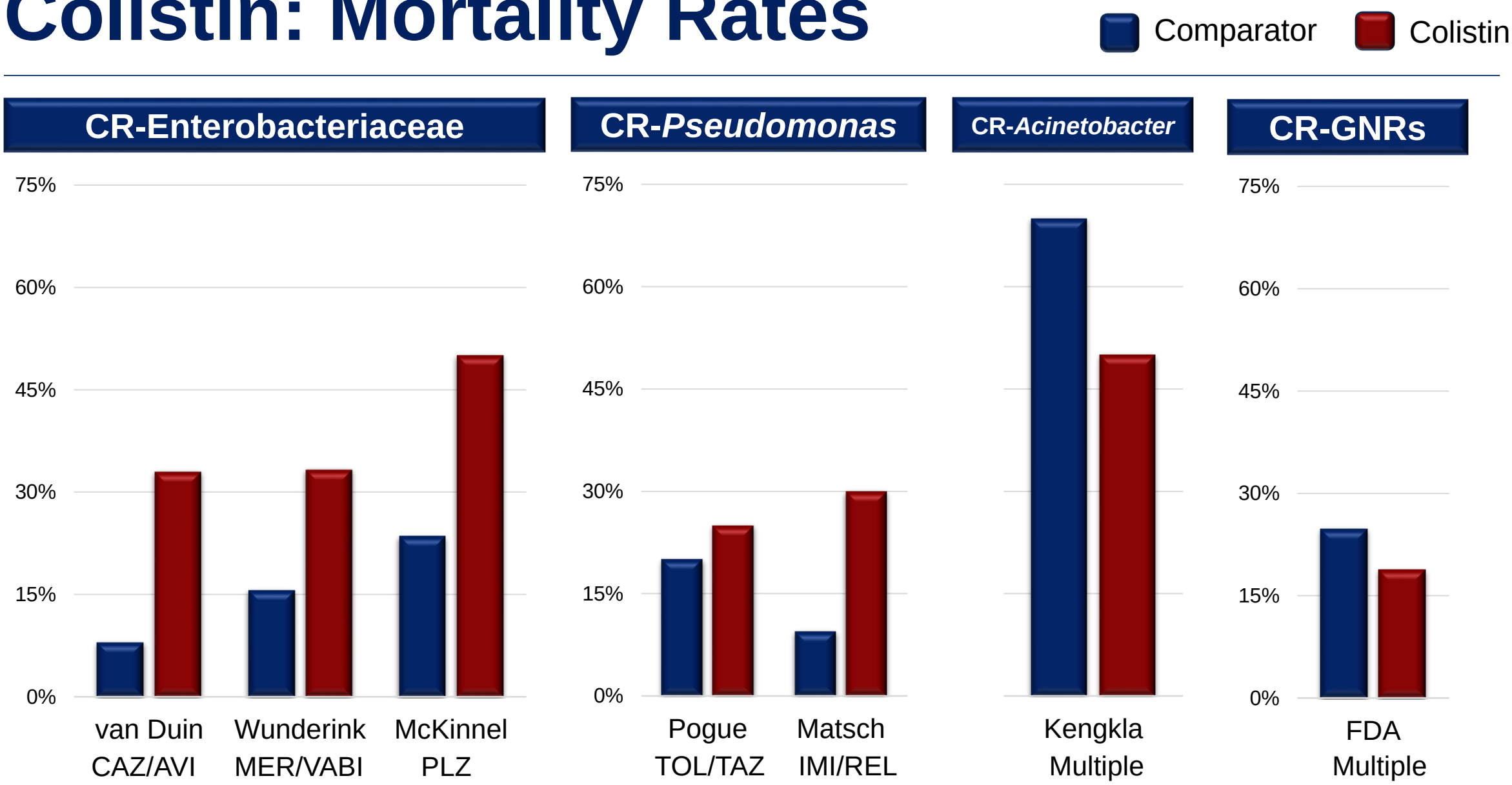
Question

Which of the following antimicrobials uses iron transport mechanisms and a “trojan horse” approach as part of its mechanism of action?

A. Eravacycline
B. Cefiderocol
C. Fosfomycin
D. Quinupristin/dalfopristin

Nothing Lasts Forever, Even Old Colistin's Reign

Colistin: Mortality Rates



Summary of Current/Future Agents

Drug	ESBL	CRE (KPC)	CRE (MBL)	CR *Pseudo*	MDR *Acineto*
TOL/TAZ					
CAZ/AVI					
MER/VAB					
IMI/REL					
Plazomicin					
Eravacycline					
ATM/AVI					
Cefiderocol					
Fosfomycin					
Tebipenem					
Sulopenem					

Blue font indicates PO option

New BL/BLI Comparison

	Ceftolozane / tazobactam	Ceftazidime / avibactam	Meropenem / vaborbactam	Imipenem / relebactam
Dose	1.5 g IV q8h 3 g IV q8h (PNA)	2.5 g IV q8h	4 g IV q8h	1.5 g IV q6h
Infusion time	1 hour	2 hours	3 hours	0.5 hour
Dose adjustments	CrCl < 50 mL/min	CrCl < 50 mL/min	**eGFR** < 50 mL/min/1.73m^2	CrCl < 90 mL/min
Elimination	Renal, mostly as unchanged drug	Renal, mostly unchanged drug	Renal, ~50% as unchanged drug	Renal, ~63% as unchanged drug
Notes	Must add MTZ for IAI	Must add MTZ for IAI	Drug only **stable for 4 hours** (RT) once mixed	
Cost (day)*	$410.19 ($820.38 PNA)	$1291.71	$1188	??

*per UpToDate 12/15/19

Zerbaxa PI. Merck; Syracuse, NY. 2018; Avycaz PI. Allergan; Madison, NJ 2019; Vabomere PI. Melinta; Lincolnshire, IL. 2018

Tetracycline Comparison

	Eravacycline	Tigecycline	Minocycline
Dose	1 mg/kg IV q12h	LD: 100 mg IV x 1 MD: 50 mg IV q12h	LD: 200 mg x 1 MD: 100 mg q12h
Dosage form	IV	IV	IV, PO
Infusion time	60 min	30-60 min	60 min
Dose adjustments	Child-Pugh C: 1 mg/kg q12h x 2; then 1 mg/kg q24h	Child-Pugh C: MD: 25 mg IV q12h	None (Max dose 200 mg/day)
Metabolism	CYP 3A4	Negligible	Hepatic
Excretion	Urine (34%), feces (47%)	Urine (33%), feces (59%)	Urine (5-12%), feces (20-34%)

Xerava PI. Tetraphase. Watertown, MA. 2018; Tygacil PI. Pfizer. Philadelphia, PA. 2018

Tetracycline Comparison

	Eravacycline	Tigecycline	Minocycline
ADRs	Infusion reaction (7.7%) **Nausea (6.5%)** **Vomiting (3.7%)** **Diarrhea (2.3%)** Hypotension (1.3%) Wound dehiscence (1.3%)	**Nausea (26%)** **Vomiting (18%)** **Diarrhea (12%)** Abdominal pain (6%) Headache (6%) AST/ALT increase (3%)	Dizziness (9%) Fatigue (9%) Pruritis (5%) Malaise (4%) *Esophagitis
Cost (day) *	$176.40	~$300.00	$389.12 (IV) $2.76 (PO)

*per UpToDate 12/15/19

Xerava PI. Tetraphase. Watertown, MA. 2018; Tygacil PI. Pfizer. Philadelphia, PA. 2018

Multiplex Resistance Gene Comparison

Resistance Genes	FilmArray	Verigene	PhenoTest	Cepheid Carba-R
Gram-negative				
CTX-M (ESBL)	*	✓		
IMP (carbapenemase)	*	✓		✓
KPC (carbapenemase)	✓	✓		✓
NDM (carbapenemase)	*	✓		✓
OXA (carbapenemase)	*	✓		✓
VIM (carbapenemase)	*	✓		✓
mcr-1	*			

*in development, 2nd generation

Conclusions

ESBL

- Once susceptibilities known, carbapenem preferred

CRE

- Data supports CAZ/AVI, MER/VAB & PLZ over colistin
- Monotherapy may be sufficient
- Potential for ERV, FDC

Pseudomonas

- Data supports TOL/TAZ, CAZ/AVI, IMI/REL over colistin
- FDC??

Acinetobacter

- Still looking for holy grail
- COL triple therapy has data, ERV may be an option
- FDC??

If you weren't a GNR fan before …

Welcome to the jungle,
We've got fun and games.
We got everything you want,
Honey, we know the names.
We are the people that can find,
Whatever you may need.
If you got the money,
Honey, we got your disease.

Rose, Axl. Appetite for Destruction. 1987

Welcome to the Jungle:
Update on New GNR Agents

Monica V. Mahoney, PharmD, BCPS AQ-ID, BCIDP

@mmPharmD

Beth Israel Lahey Health

Beth Israel Deaconess Medical Center