Beyond the Basics: Updates in Treatment of Resistant Gram Negative Infections

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Disclosures

- Research funding from Merck

What we will cover: Key points

- IDSA has new expert guidance on management of GNRs – use it! For serious infections:
  - ESBLs: carbapenems >>> other beta-lactams
  - AmpC producers: carbapenems ~ cefepime
  - *Pseudomonas*: dose-optimized beta-lactams or CTOL/TZB, CTZ/AVI, IMI/REL
  - KPCs: MER/VBR, CTZ/AVI, IMI/REL, CFDC
  - NDMs: CTZ/AVI + Aztreonam, CFDC
  - Carbapenem-resistant Acinetobacter: AMP/SUL + (something), [SUL/DUR]
- Mechanism and MIC both matter
  - S does not always equal success & sometimes R can be overcome!

What we won't cover:

- Effectiveness of non-beta-lactams for serious MDR infections
- IDSA expert guidance on:
  - *Stenotrophomonas maltophila*

First, quick β-lactamase refresher

	Beta-lactamase Groups						
Functional Group	1		2				3
Molecular Class	C		A			D	B
Subclass	(WT)	(DR)	2b	2be (ESBL)	2f	2df	
Example Enzymes Names you should know	AmpC		TEM-1, SHV-1	CTX-M, SHV-2, TEM-2	KPC-1	OXA-48	NDM-1
Hydrolytic activity (predicted phenotype) vs beta-lactams							
Aminopenicillins	+++ (R)	+++ (R)	+++ (R)	+++ (R)	+++ (R)	+++ (R)	+++ (R)
Piperacillin	+ (s)	++ (r/R)	++ (r)	+++ (R)	+++ (R)	+++ (R)	+++ (R)
1st/2nd GC	+++ (R)	+++ (R)	+ (s)	+++ (R)	+++ (R)	++ (r/R)	+++ (R)
3rd/4th GC	+ (s)	++ (r/R)	-- (S)	++ (r/R)	+++ (R)	+ (s/r)	+++ (R)
Monobactams	+ (s)	+++ (R)	-- (S)	+++ (R)	+++ (R)	-- (S)	-- (S)
Penems	-- (S)	-- (S)	-- (S)	-- (S)	++ (r/R)	++ (r/R)	++ (r/R)
Other characteristics							
Inhibition by clavulanate	--	--	+++	++	--	--	--
Inhibition by avibactam	+++	++	+++	+++	++	++	--
Typical Location/Expression	Chromosomal/ Inducible →Constitutive		Plasmid / Constitutive				
Active site	Serine						Metallo (Zn)

How well enzyme hydrolyzes drug

Likely bug-drug phenotype

How well inhibitor inhibits BLmase

AY is a 77 yo M nursing home resident with DM2, HTN and recent paraplegia c/b urinary incontinence with a new fever and hypotension. He was transferred to UCSF, admitted to the ICU, & started on vanco and cefepime. UCX & BCX are growing *Proteus mirabilis,* with susceptibility results show below.

<u>Urine: >100,000 *Proteus mirabilis*</u>
Ampicillin >16 R
Ampicillin/sulbactam >16/8 R
Aztreonam >16 R
Cefazolin>16 R
Ceftazidime >16 R
Ceftriaxone >32 R
Cefepime 4 S-DD
Ertapenem <=0.25 S
Imipenem 2 I
Meropenem <=0.5 S
Piperacillin/tazobactam 16/4 S-DD

<u>Blood: *Proteus mirabilis*</u>
Ertapenem ≤0.25

What beta-lactamase enzyme do you think this organism is producing?
What antibiotic(s) would you recommend for AY?

a) Cefepime
b) Ertapenem
c) Imipenem
d) Meropenem
e) Piperacillin/tazobactam

Urine (UCSF) >100,000 *Proteus mirabilis*
Ampicillin >16 R
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Piperacillin/tazobactam 16/4 S-DD

Blood (UCSF) *Proteus mirabilis*
Ertapenem ≤0.25

-3rd-gen cephalosporin resistance but not carbapenem resistance
-Variable activity of cefepime, pip/tazo, and amp/sulbactam
*-**NOTE: Proteus has low intrinsic susceptibility to imipenem specifically – this is not indicative of carbapenemase production***

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Functional Group	1		2				3
Molecular Class	C		A			D	B
Subclass	(WT)	(DR)	2b	2be (ESBL)	2f	2df	
Example Enzymes	AmpC		TEM-1, SHV-1	TEM-3, SHV-2, CTX-M	KPC-1	OXA-48	NDM-1
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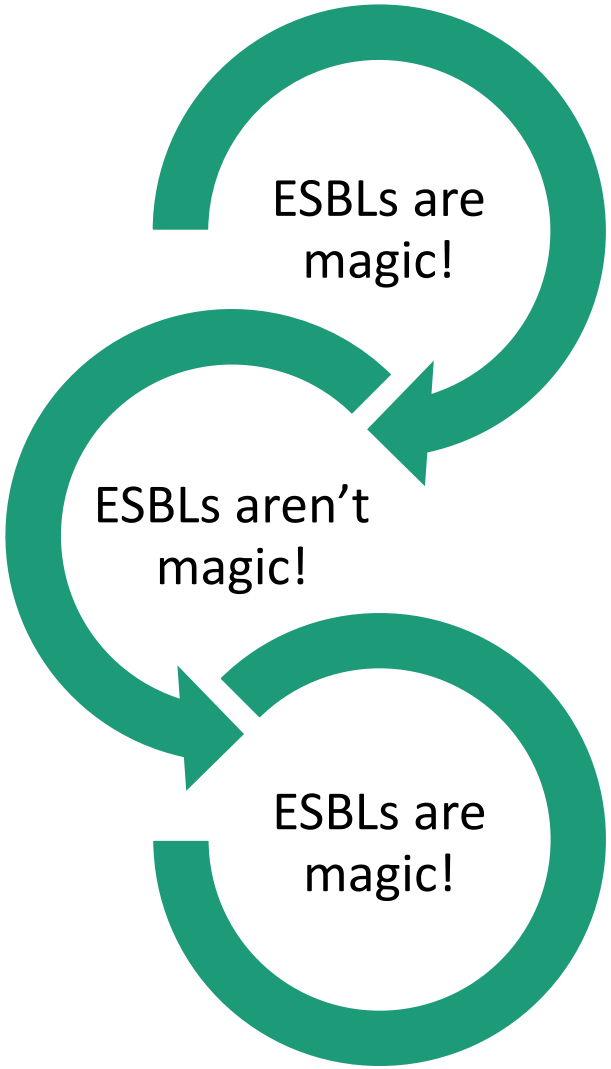
1st/2nd GC	+++ (R)	+++ (R)	+ (s)	+++ (R)	+++ (R)	++ (R)	+++ (R)
3rd/4th GC	+ (s)	++ (r/R)	-- (S)	++ (r/R)	+++ (R)	+ (s/r)	+++ (R)
Monobactams	+ (s)	+++ (R)	-- (S)	+++ (R)	+++ (R)	-- (S)	-- (S)
Penems	-- (S)	-- (S)	-- (S)	-- (S)	++ (r/R)	++ (r/R)	++ (R)
Other characteristics							
Inhibition by clavulanate	--	--	+++	++	--	--	--
Inhibition by avibactam	+++	++	+++	+++	++	++	--
Common organisms	CAPES		*Enterobacteriaceae*				
Location	Chromosomal		Plasmid			Plasmid	Plasmid
Expression	Inducible →Constitutive		Constitutive			Constitutive	Constitutive

Perceived relationships between susceptibility results and clinical outcomes for ESBLs have see-sawed over the years

Finding: Association of CTX MIC with clinical failures with or without ESBLs, cohort studies of pip/tazo showing OK outcomes
Response: Lower breakpoints, get rid of phenotypic tests, CTX-R as ESBL surrogate in PEK
Problem: Can we really use pip/tazo or cefepime?
Key Reference: J Clin Micro 2019;56:e01917



Finding: Clinical failures in patients with CTX-S, ESBL + isolates
Response: Phenotypic test for ESBL → change cephalosporin S → R
Problem: Breaks the S paradigm, requires extra testing
Key Reference: J Clin Micro 2001;39:2206-2212

Finding: Association of pip/tazo with increased mortality vs mero for definitive tx of ESBL BSI
Response: Carbapenems preferred for serious ESBL infections
Problem: Less-severe infections, empiric therapy, re-breaks the S paradigm
Key Reference: JAMA 2018;10:984-994 **(MERINO I)**

MERINO I *doesn't necessarily rule out all BLICs for ESBLs* – CTOL is easier to protect than PIP & AVI is much better guardian of CTZ

So… if you have another reason to use a novel BLIC, it ***should*** cover ESBLs

Study	Drug	Vs	n (%) "ESBL"	Outcomes "ESBLs"
ASPECT-NP	CTOL/TZB	MER	157 (31%)	Clinical cure: 57.1% vs 61.6% (-4.5%, -19.3% - 10.7%)
ASPECT-cUTI	CTOL/TZB	LEVO	118 (14.8%)	Clinical cure: 62.3% vs 35.1% (27.2%, 9.2% - 42.9%)
MERINO III	CTOL/TZB	MER	100%	*TERMINATED (lack of CTOL/TZB + COVID)*
REPROVE	CTZ/AVI	MER	75 (21.1%)	Clinical cure: 82.4% vs 70.7% (11.6%, -8.32% – 30.2%)
RECAPTURE	CTZ/AVI	DOR	155 (19.1%)	Clinical cure: 63.2% vs 58.2% (5.0%, -10.9% - 20.5%)

The ***story likely isn't over yet*** as MERINO subgroup analyses proceed and a confirmatory trial is underway (PETERPEN)

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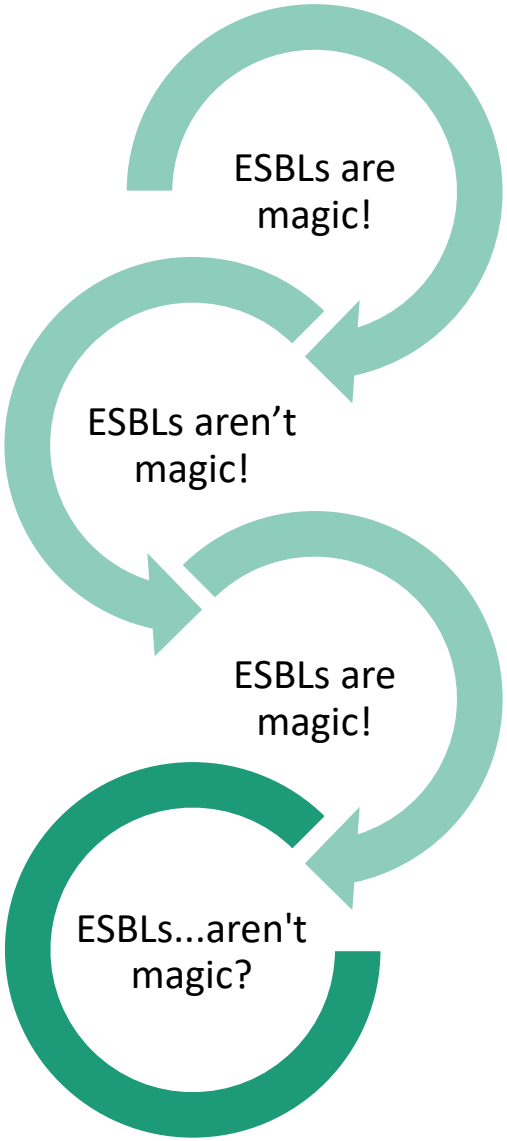
Finding: Post hoc analysis of MERINO found smaller differences & influence of secondary beta-lactamases on pip/tazo outcomes
Response: Back to phenotypic/genotypic beta-lactamase detection? Pip/tazo MIC of 16 now S-DD. **PETERPEN trial underway (**NCT03671967)
Key Reference: CID 2021;73:e3842



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IDSA Guidance Recommendations for ESBL-EB come down hard for team carbapenem

Syndrome	First-line	Alternative	Avoid
Uncomplicated cystitis	Nitrofurantoin TMP/SMX	Amox/clav Aminoglycoside x1 Fosfomycin Cefepime Pip/tazo	Doxycycline
Pyelo/complicated UTI	Carbapenem Cipro/levo TMP/SMX	Pip/tazo	Cefepime Doxycycline
Infections outside the urinary tract	Carbapenem (Transition to FQ or TMP/SMX after clinical response if PO desired)		Pip/tazo Cefepime Amox/clav Doxycycline Omadacycline

Tamma et al. IDSA Guidance on the Treatment of Antimicrobial-Resistant Gram-Negative Infections:
https://www.idsociety.org/practice-guideline/amr-guidance/#

A 68 yo F hospitalized for ICH develops fever, increased WBC and dyspnea on day 10 of hospitalization. Empiric ceftriaxone and vancomycin are initiated. Blood cultures are growing *Enterobacter cloacae*, with a presumed pulmonary source. Patient has defervesced and respiratory status is improving on 48 hours of vancomycin + ceftriaxone.

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What beta-lactamase enzyme do you think this organism is producing?
What antibiotic(s) would you recommend for AY?

a) Ceftriaxone
b) Cefepime
c) Ertapenem
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-"HECK-Yes":
Hafnia alvei
Enterobacter cloacae
Citrobacter freundii
Klebsiella aerogenes-
YErSinia enterocolitica;
Pseudomonas
-1st gen cephalosporin & amp/sulbactam resistance

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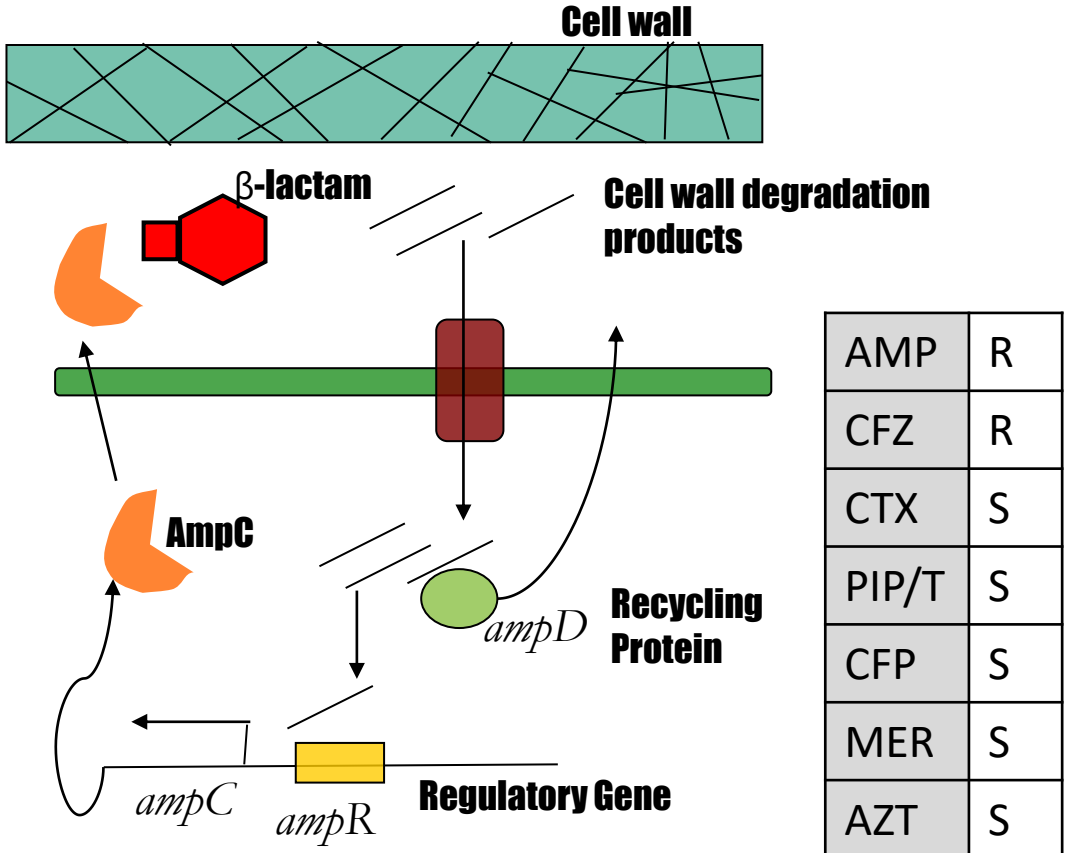
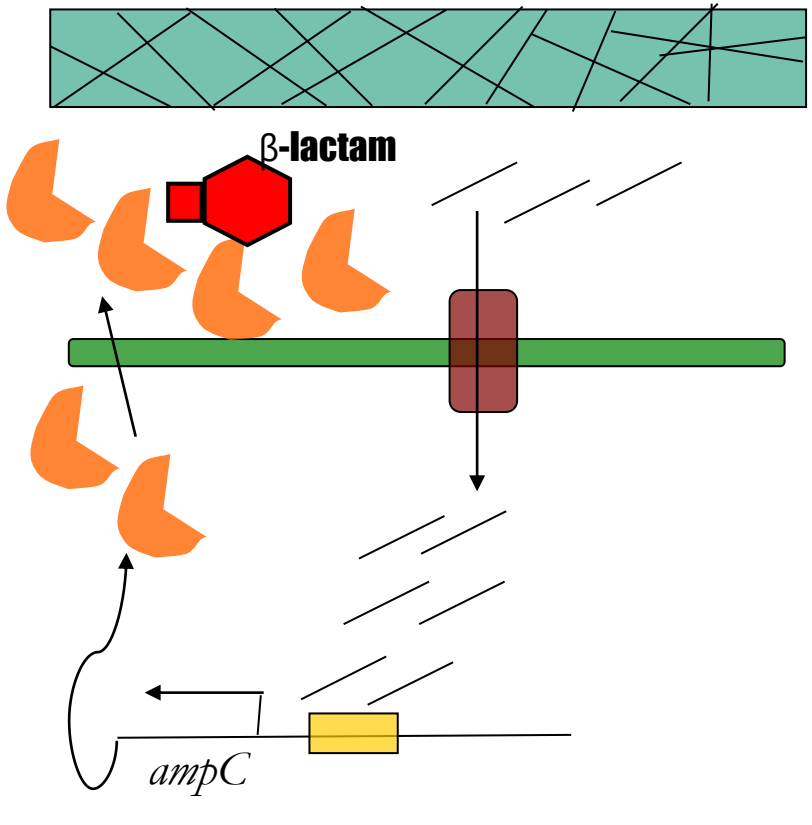
Monobactams	+ (s)	+++ (R)	-- (S)	+++ (R)	+++ (R)	-- (S)	-- (S)
Penems	-- (S)	-- (S)	-- (S)	-- (S)	++ (r/R)	++ (r/R)	++ (R)
Other characteristics							
Inhibition by clavulanate	--	--	+++	++	--	--	--
Inhibition by avibactam	+++	++	+++	+++	++	++	--
Location	Chromosomal		Plasmid				
Expression	Inducible →Constitutive		Constitutive				

Many Gram-negatives possess AmpC type β-lactamase that is (usually) chromosomal, (usually) inducible & hydrolyzes PCNs, 1-3rd GC, aztreonam



AMP	R
CFZ	R
CTX	S
PIP/T	S
CFP	S
MER	S
AZT	S

- Induction
  - Antibiotics increase # of peptide degradation products, which bind to regulatory element, leading to production of modest amounts of β-lactamase in presence of antibiotic

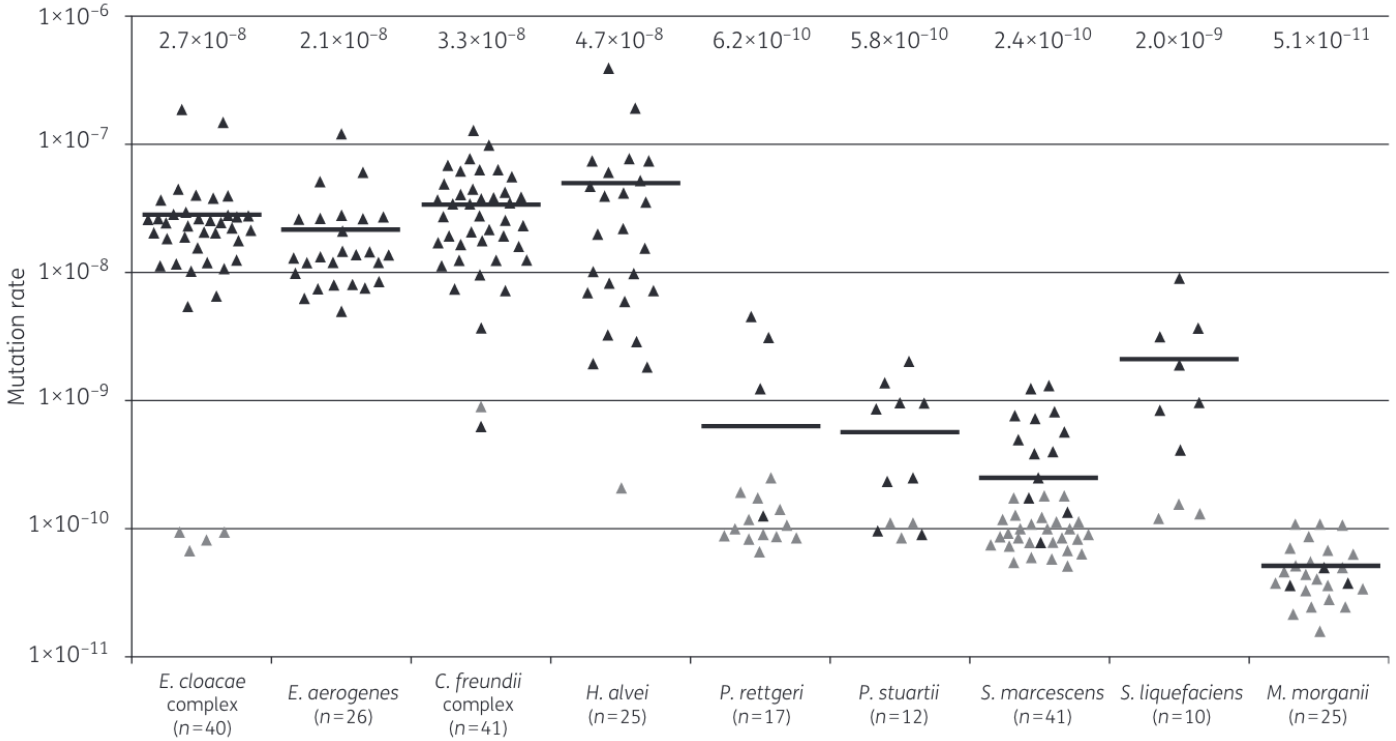


AMP	R
CFZ	R
CTX	**R**
PIP/T	**R**
CFP	S
MER	S
AZT	**R**

- Stable Derepression
  - Spontaneous mutant with defect in recycling pathway triggering high-level constitutive β-lactamase production (in presence or absence of inducers)

↑ risk of mutations → AmpC derepression and ***emergent resistance*** in clinical isolates for ***Hafnia, Enterobacter, Citrobacter, Klebs (aerogenes)***

So…SPACE/SPICE is out – HECK-Yes is in!



Population	Emergent 3rd-generation Cephalosporin Resistance	
	Bacteremic	Non-bacteremic
All species	4/54 (7.4%)	7/164 (4.3%)
Enterobacter cloacae	2/18 (11.1%)	6/71(12.7%)
Klebsiella aerogenes	2/10 (20.0%)	0/41 (0%)
Citrobacter freundii	0/8 (0.0%)	1/31 (3.2%)
Serratia marcescens	0/10 (0.0%)	0/27 (0.0%)
Morganella morganii	0/6 (0.0%)	0/15 (0.0%)

Kohlmann R, et al. J Antimicrob Chemother 2018; 73: 1530–1536
Choi S-H, et al. Antimicrob Agents Chemother 2008;52:995-1000.

Pip-tazo similar outcomes to carbapenems in cohort studies – is it a viable option? There's a MERINO for that! Sort of…

_So…_pip/tazo probably not a drug of choice for severe HECK-Yes infections

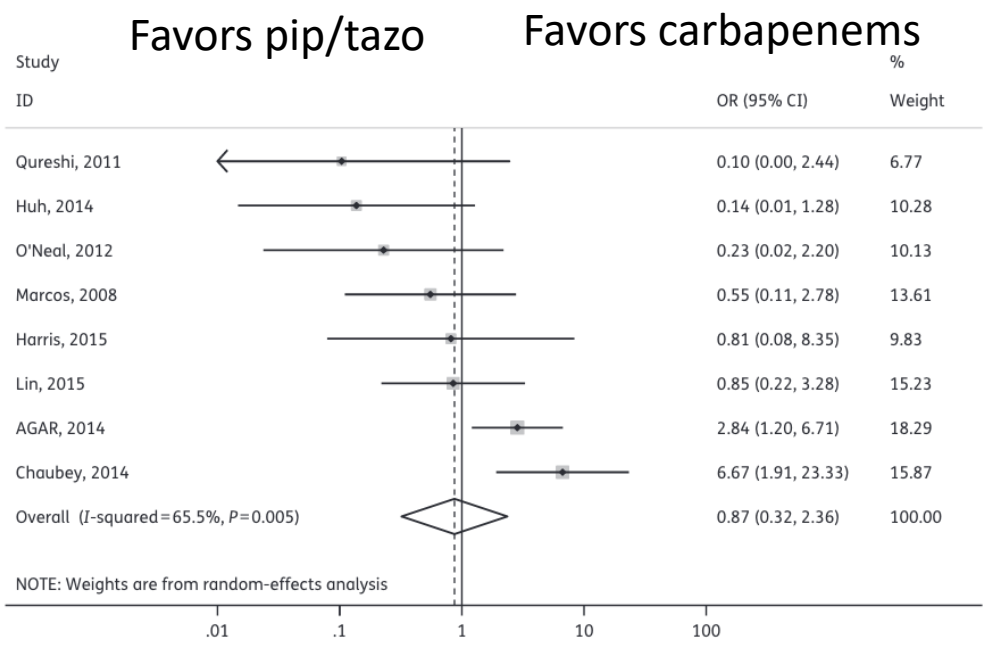


Figure 2. Forest plot of unadjusted ORs for mortality in patients given definitive therapy with BLBLIs versus carbapenems.

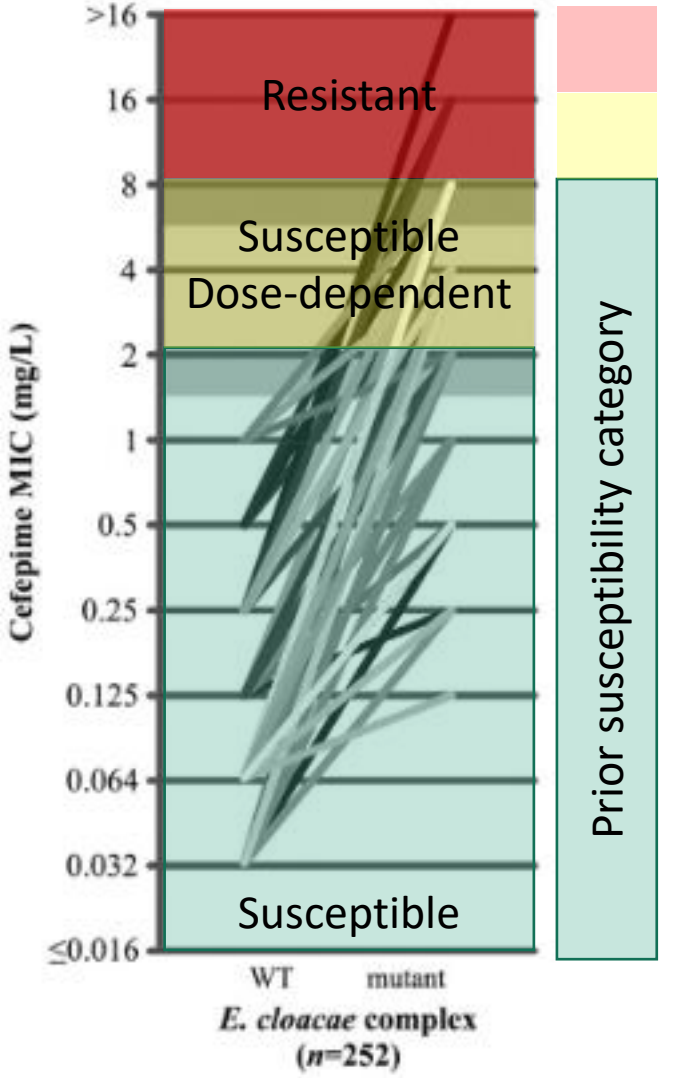
Harris PNA, et al. J Antimicrob Chemother 2016; 71:296 – 306

Stewart AG, et al OFID 2021

Meropenem Versus Piperacillin-Tazobactam for Definitive Treatment of Bloodstream Infections Caused by AmpC β-Lactamase–Producing *Enterobacter* spp, *Citrobacter freundii*, *Morganella morganii*, *Providencia* spp, or *Serratia marcescens*: A Pilot Multicenter Randomized Controlled Trial (MERINO-2)	Pip/tazo (n=38)	Mero (n=34)
Primary outcome: Death or clinical failure or micro failure or micro relapse	29%	21%
Death day 30	0%	6%
Clinical failure day 5	21%	12%
Micro failure days 3-5	13%	0%
Micro relapse days 5-30	0%	9%
Primary outcome by organism		
Enterobacter	28% (5/18)	7% (1/14)
Non-*Enterobacter*	30% (6/20)	30% (6/20)

Cefepime better AmpC stability though MICs do rise with derepressed isolates – **cohort studies favorable**; no RCTs available/ongoing

So…cefepime may be an option for AmpC infections but pay attention to MIC



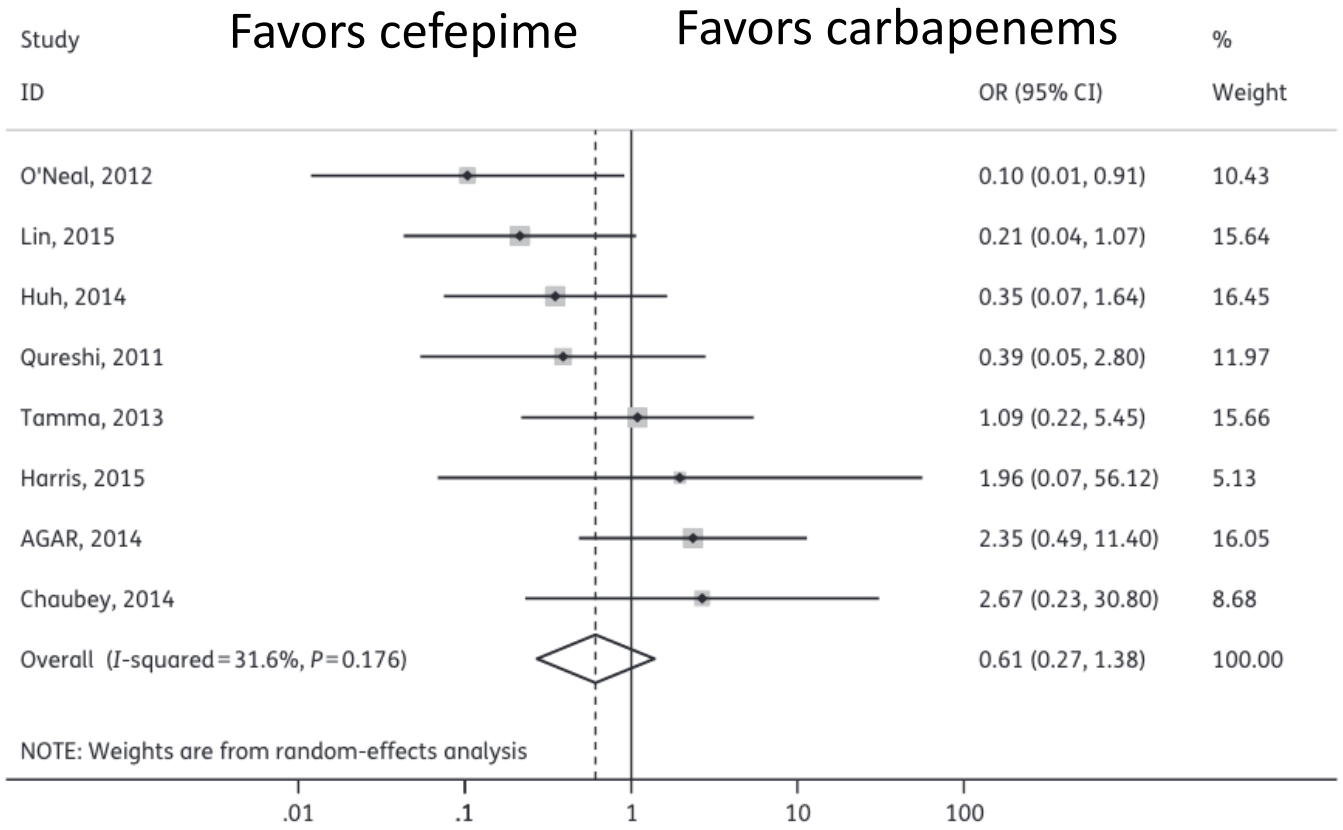


Figure 4. Forest plot of unadjusted ORs for mortality in patients given definitive therapy with cefepime versus carbapenems.

Kohlmann R, et al. Clin Micro Infect 2019;25:1158

Harris PNA, et al. J Antimicrob Chemother 2016; 71:296 – 306

IDSA Guidance Recommendations for Enterobacterales at significant risk of AmpC-emergent resistance

Syndrome	Recommended	Consider	Avoid
Uncomplicated cystitis	Nitrofurantoin TMP/SMX	Ceftriaxone Ceftazidime Pip/tazo Fosfomycin	Doxycycline
Infections besides uncomplicated cystitis	Cefepime (MIC <=2) Ertapenem Meropenem Imipenem Fluoroquinolones	Ceftaz/avi Imi/rel Mero/vabor Cefiderocol TMP/SMX	Ceftol/tazo Amox/clav Doxycycline Fosfomycin Nitrofurantoin Ceftriaxone Pip/tazo

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https://www.idsociety.org/practice-guideline/amr-guidance-2.0/

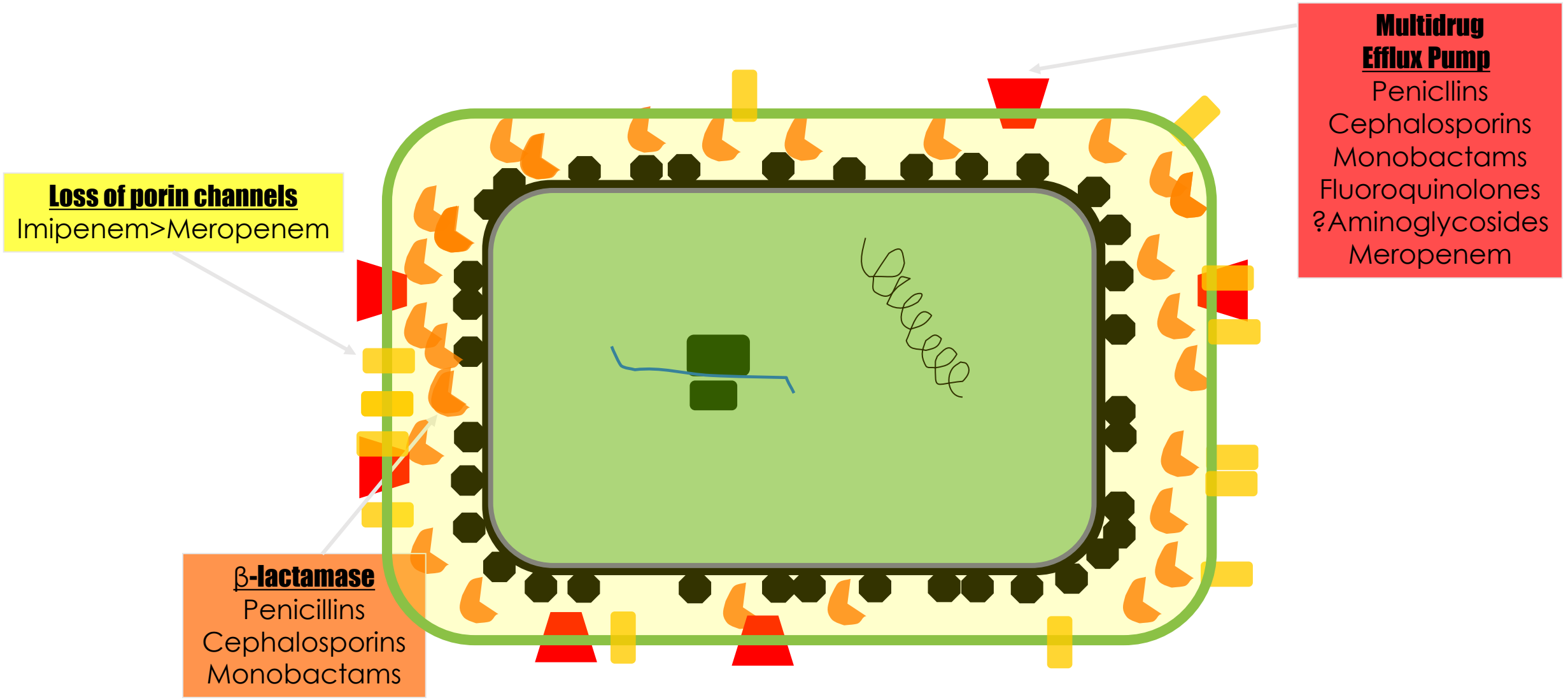
A 68 yo F hospitalized for ICH develops fever, increased WBC and dyspnea on day 10 of hospitalization. Empiric **ceftazidime** and vancomycin are initiated. Blood cultures are growing ***Pseudomonas aeruginosa***, with a presumed pulmonary source. Patient has defervesced and respiratory status is improving on 48 hours of vancomycin + **ceftazidime**.

Blood, ***Pseudomonas aeruginosa***
Aztreonam 2 S
Ceftazidime 2 S
Cefepime <=2 S
Meropenem <=0.5 S
Piperacillin/tazobactam 16/4 S

What beta-lactamase enzyme do you think this organism is producing?
What antibiotic(s) would you recommend for AY?

a) Ceftazidime
b) Cefepime
c) Meropenem
d) Piperacillin/tazobactam

In addition to upregulation of AmpC, *Pseudomonas* can express ***other intrinsic resistance mechanisms*** that work synergistically to promote resistance



Emergent resistance **MORE common with carbapenems** (vs PCNs, cephs) in *Pseudomonas*; clinical outcomes appear similar

So…no advantage of carbapenems for therapy of susceptible *Pseudomonas*

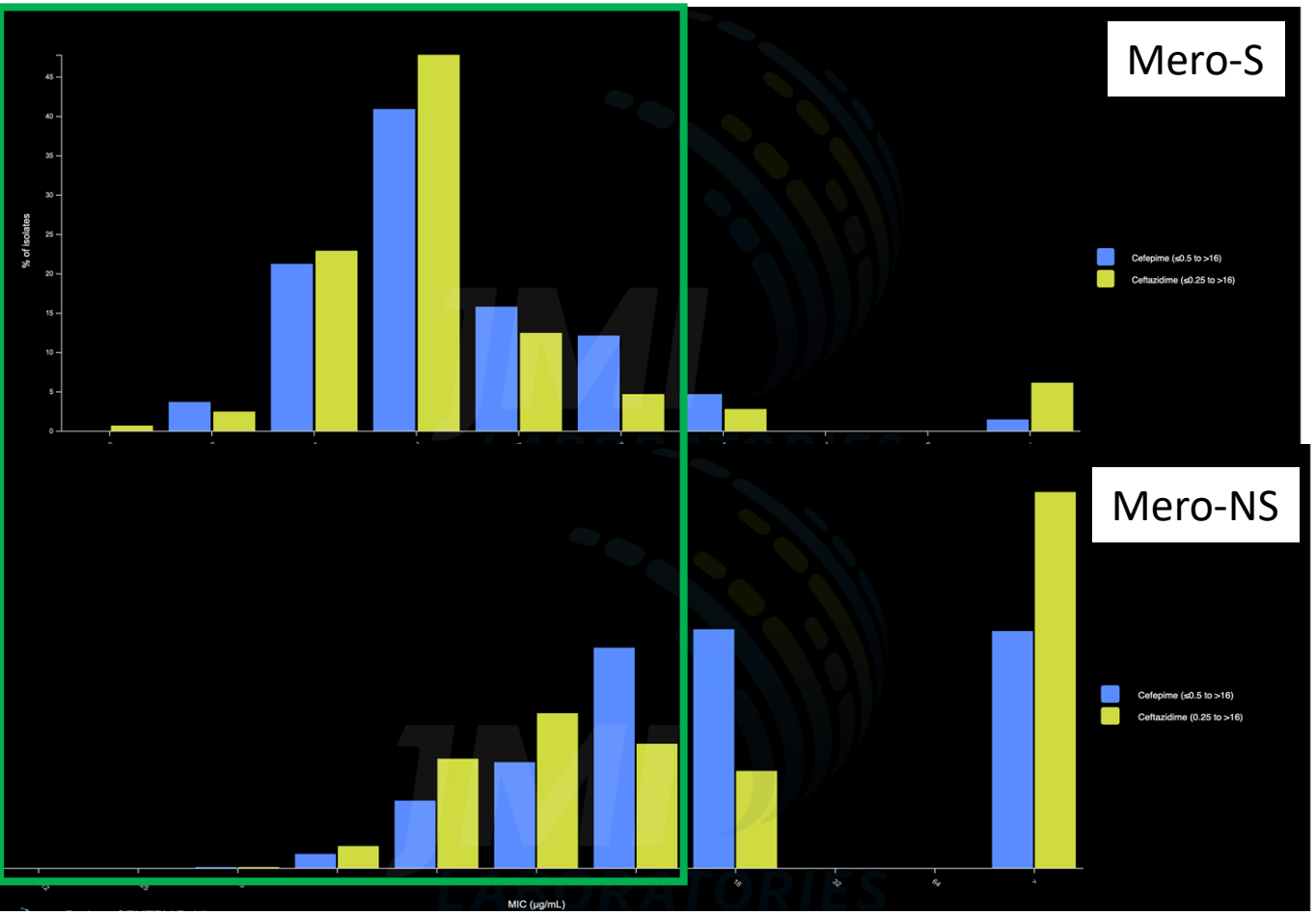
	Emergent Resistance of Initially Susceptible Isolates			
Study	**Cephalosporins**	**Penicillins**	**Carbapenems**	**FQs**
Fish	11% (63/594)	14% (78/542)	35% (78/225)	16% (99/639)
Carmeli	11% (14/125)	8% (7/91)	19% (7/37)	11% (11/98)
Babich	12% (25/201)	8% (28/332)	18% (36/206)	N/R
Clinical Outcomes (Babich et al)				
Outcome	**Ceftazidime**	**Pip/tazo**	**Carbapenem**	**p-value**
30-day mortality	17.4%	16%	20%	0.48
7-day mortality	6.1%	4.9%	7.6%	0.43
Clinical failure	45.9%	37.3%	44.4%	0.12

Fish DN, et al. Pharmacother 1995;15:279-291
Carmeli Y, et al. Antimicrob Ag Chemother 43:1379-1382
Babich T, et al Clin Infect Dis 2020;70

Presence of ***any*** anti-pseudomonal beta-lactam resistance may *increase risk of failure* of **active beta-lactams**

So… if there's any beta-lactam resistance, treat more aggressively

Cefepime & ceftazidime MICs

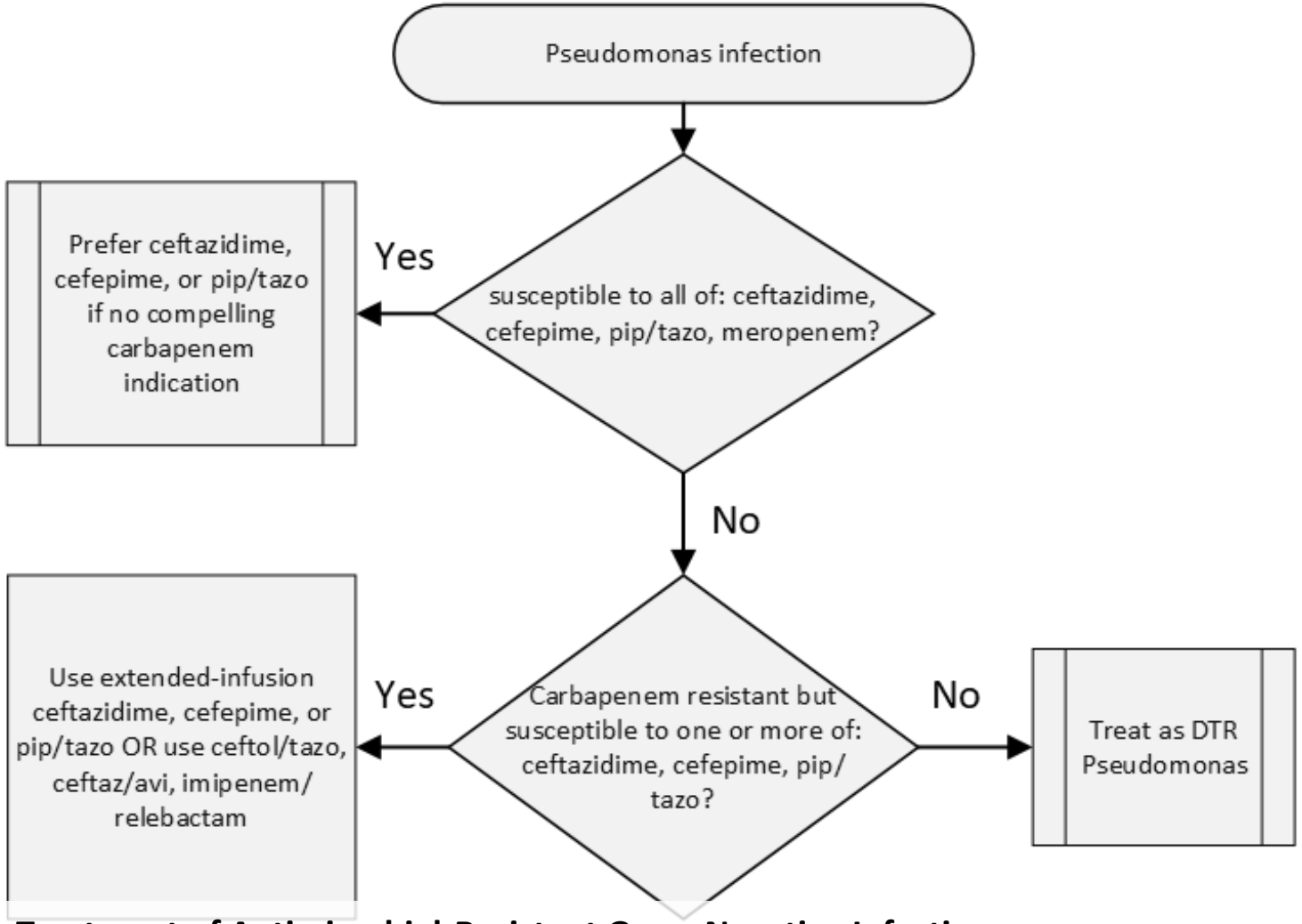


Outcome	No β-lactam resistance	≥1 other β-lactam resistant	Adjusted OR (95% CI)
Hospital mortality or d/c to hospice	29%	35%	1.42 (0.89-2.29)
30-day mortality	27%	33%	1.65 (1.02-2.66)
Discharged alive to home	35%	17%	0.50 (0.29-0.85)

SENTRY data

Lodise et al *Pharmacotherapy*. 2021;41:658–667

IDSA recommends ***non-carbapenems over carbapenems if all S***; dose optimization or consider novel β-lactams if carbapenem resistance



Tamma et al. IDSA Guidance on the Treatment of Antimicrobial-Resistant Gram-Negative Infections: Version 1.0 https://www.idsociety.org/practice-guideline/amr-guidance/#

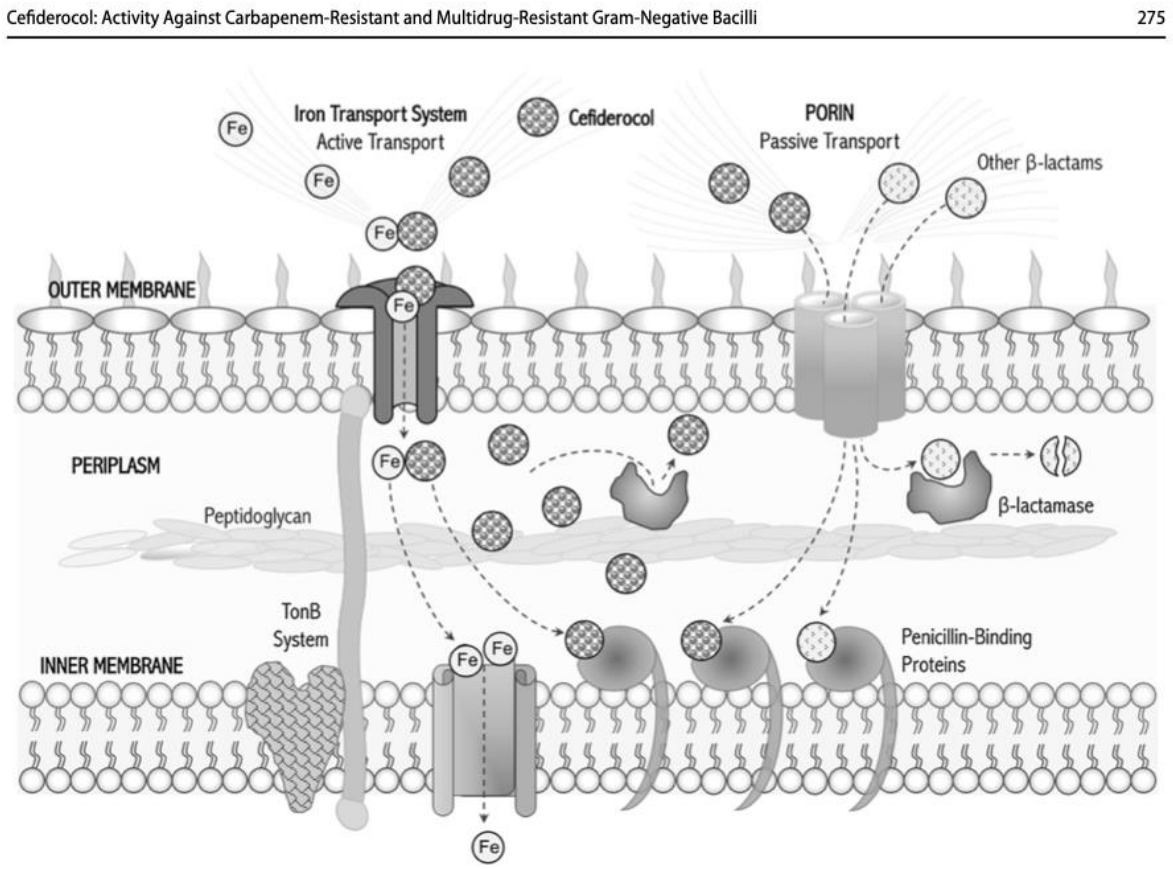
Novel beta-lactams offer *activity against "DTR" Pseudomonas* (except meropenem/vaborbactam)

Novel beta-lactam	% S among ceftazidime/pip-tazo/FQ/carbapenem-R *Pseudomonas*
Ceftazidime/avibactam	82%
Ceftolozane/tazobactam	82%
Imipenem/relebactam	71%
Meropenem/vaborbactam	36%*
Cefiderocol	97%

*No official breakpoint for *Pseudomonas*

Sader HS, et al. Int J ID 2021;113:279-281
Karlowsky JA, et al. Microbiol Spect 2022;10:01724-22

Cefiderocol is a novel cephalosporin combining β-lactamase stability & ↑ target site concentration & ? clinical data



APEKS NP		CREDIBLE CR	
Multicenter DB RCT		Multicenter DB RCT	
VAP (41%) non-VAP HAP (59%)		HAP/VAP (45%) UTI (26%)	
Klebsiella (33%) *Pseudomonas* (17%)		*Acinetobacter* (45%) *Klebsiella* (34%)	
CFDC	MER 2g IV q8h over 3h	**CFDC**	COL combos (66%)
Clinical cure: 65% vs 67% (noninferior); 14-day mortality: 12.4% vs 11.6% (noninferior)		**28-day mortality: 25% vs 18% (p=NS); Clinical response: 53% vs 50% (p=NS)**	

IDSA Guidance Recommendations for "DTR *Pseudomonas* infections"

"Difficult to treat Resistance (DTR)" =
non-susceptibility to all of the following: piperacillin-tazobactam, ceftazidime, cefepime, aztreonam, meropenem, imipenem-cilastatin, ciprofloxacin, and levofloxacin

Syndrome	Recommended	Consider	Avoid
Urinary tract infection	Ceftol/tazo Ceftaz/avi Imi/rel Cefiderocol Tobramycin x1 (uncomplicated cystitis)	Colistin	Plazomicin Fosfomycin
Infections besides UTI	Ceftol/tazo Ceftaz/avi Imi/rel	Cefiderocol Polymyxin B	Plazomicin Polymyxin B Adjunctive inhaled antibiotics

Tamma et al. IDSA Guidance on the Treatment of Antimicrobial-Resistant Gram-Negative Infections

RF is a 45 yo M s/p liver transplant with a complicated post-operative course with suspicion for VAP, on empiric linezolid, meropenem, and caspofungin x3 days without improvement. A bronchoalveolar lavage is performed and grows *Klebsiella pneumoniae*.

Amikacin 16 S
Ampicillin >16 R
Ampicillin/sulbactam >16/8 R
Aztreonam >16 R
Cefazolin>16 R
Ceftazidime >16 R
Ceftazidime/avibactam <=2/2 S
Ceftolozane/tazobactam >16/4 R
Ceftriaxone >32 R
Cefepime >16 R
Ciprofloxacin >2 R
Colistin 1
Ertapenem >8 R
Meropenem 4 R
Minocycline 8 I
Piperacillin/tazobactam >128/4 R
Tigecycline 2
Tobramycin >8 R

What beta-lactamase enzyme do you think this organism is producing?

What antibiotic(s) would you recommend for AY?

a) Colistin
b) Ceftazidime/avibactam
c) Extended-infusion meropenem
d) Tigecycline

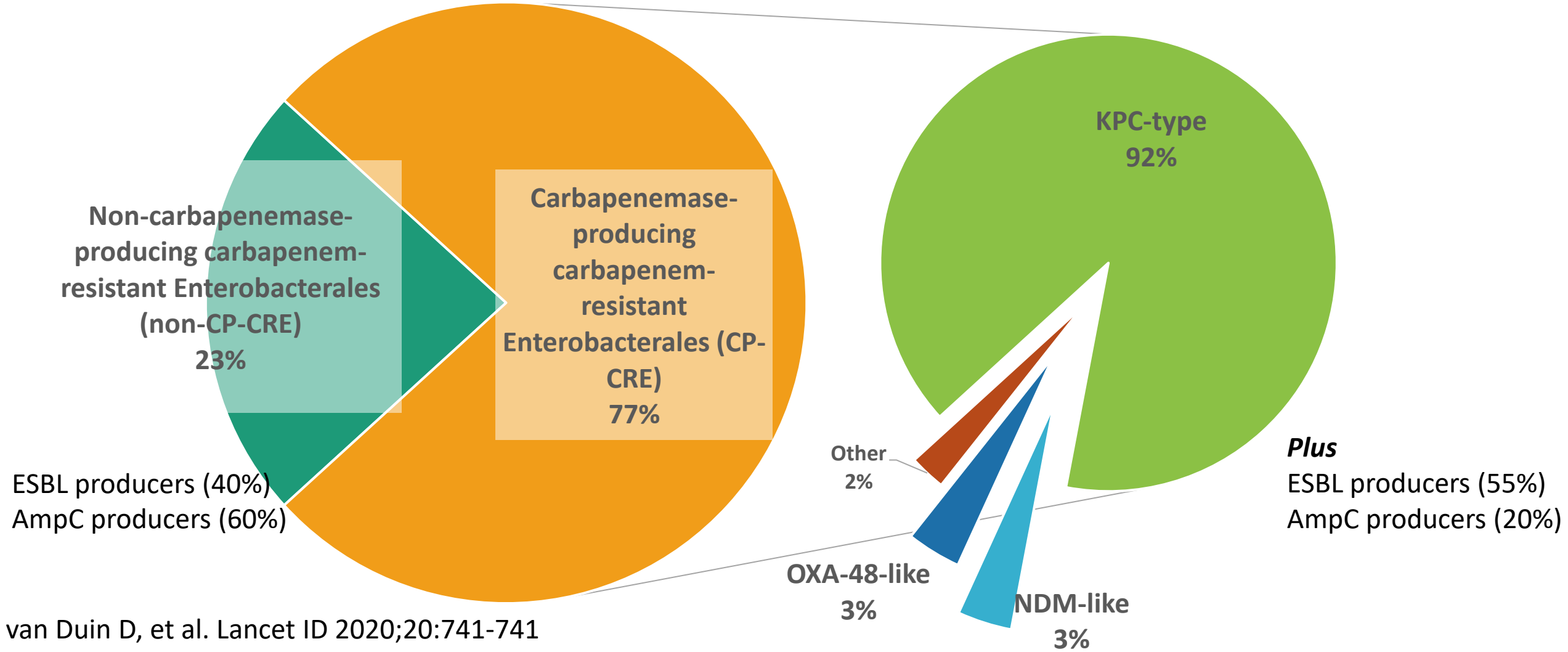
BAL, *Klebsiella pneumoniae*
Amikacin 16 S
Ampicillin >16 R
Ampicillin/sulbactam >16/8 R
Aztreonam >16 R
Cefazolin>16 R
Ceftazidime >16 R
Ceftazidime/avibactam <=2/2 S
Ceftolozane/tazobactam >16/4 R
Ceftriaxone >32 R
Cefepime >16 R
Ciprofloxacin >2 R
Colistin 1
Ertapenem >8 R
Meropenem 4 R
Minocycline 8 I
Piperacillin/tazobactam >128/4 R
Tigecycline 2
Tobramycin >8 R

Genotypic probe positive for KPC-1 gene

-Carbapenem resistance (mero>erta), restoration of ceftazidime by avibactam

	Beta-lactamase Groups						
Functional Group	1		2				3
Molecular Class	C		A			D	B
Subclass	(WT)	(DR)	2b	2be (ESBL)	2f	2df	
Example Enzymes	AmpC		TEM-1, SHV-1	TEM-3, SHV-2, CTX-M	KPC-1	OXA-48	NDM-1
Hydrolytic activity vs beta-lactams (predicted phenotype)							
Aminopenicillins	+++ (R)	+++ (R)	+++ (R)	+++ (R)	+++ (R)	+++ (R)	+++ (R)
Piperacillin	+ (s)	++ (r/R)	++ (r)	++ (r/R)	+++ (R)	+++ (R)	+++ (R)
1st/2nd GC	+++ (R)	+++ (R)	+ (s)	+++ (R)	+++ (R)	++ (R)	+++ (R)
3rd/4th GC	+ (s)	++ (r/R)	-- (S)	++ (r/R)	+++ (R)	+ (s/r)	+++ (R)
Monobactams	+ (s)	+++ (R)	-- (S)	+++ (R)	+++ (R)	-- (S)	-- (S)
Penems	-- (S)	-- (S)	-- (S)	-- (S)	++ (r/R)	++ (r/R)	++ (R)
Other characteristics							
Inhibition by clavulanate	--	--	+++	++	--	--	--
Inhibition by avibactam	+++	++	+++	+++	++	++	--
Common organisms	CAPES		*Enterobacteriaceae*				
Location	Chromosomal		Plasmid			Plasmid	Plasmid
Expression	Inducible →Constitutive		Constitutive			Constitutive	Constitutive

About ¾ of carbpenemase-resistant Enterobacterales (CRE) are *carbapenemase producers (CP-CRE),* most commonly KPC-type



van Duin D, et al. Lancet ID 2020;20:741-741

Novel BLI combinations (BLICs) appear ***superior to standard salvage therapies*** for CRE based on cohorts & "pathogen-directed" trials

CRACKLE		TANGO II (RCT)		RESTORE IMI-1 (RCT)	
Multicenter cohort		Multicenter OL RCT		Multicenter DB RCT	
BSI (45%) HAP/VAP (22%)		BSI (47%) UTI (34%)		UTI (50%) HAP/VAP (35%)	
Klebsiella (97%)		*Klebsiella* (87%)		*Pseudomonas* (77%) *Klebsiella* (15%)	
CTZ/AVI (37%), **+** TIG (32%), CARB (29%)	COL (6%), + TIG (61%), CARB (60%)	**MER/VBR (100%)**	COL (7%) + AG (20%), TIG (13%), AG/TG (7%)	**IMI/REL**	IMI + COL
30-day mortality: 9% vs 32% (p=0.001)		**28-day mortality: 15% vs 33% (p=0.20); Clinical cure: 66% vs 33% (p=0.03)**		**28-day mortality: 9% vs 30% (p=0.15); Clinical response: 71% vs 40%**	
van Duin D et al. Clin Infect Dis. 2018 Jan 6;66(2):163-171.		Wunderink RG, et al. Infect Dis Ther. 2018 Dec;7(4):439-455.		Motsch J, et al Clin Infect Dis. 2020 Apr 15;70(9):1799-1808.	

Emergent CTZ/AVI resistance already a concern; MER/VBR possibly more robust vs resistance

Table 6. Post-Hoc Subgroup Analysis	CZA Monotherapy (N=41)	CZA Combination Therapy (N=64)	MVB Monotherapy (N= 22)	*p*-value
Clinical success [n (%)]	26 (63.4)	39 (60.9)	15 (68.2)	0.83
90-day mortality [n (%)]	9 (22.0)	20 (31.2)	6 (27.3)	0.58
Recurrence of CRE infection [n (%)]	9 (22.0)	6 (9.4)	3 (13.6)	0.20
Increase in study drug MIC	5 (12.2)	1 (1.6)	0	0.03
Emergence of study drug resistance	3 (7.3)	0	0	0.07
Any adverse event [n (%)]	14 (34.2)	22 (34.4)	5 (22.7)	0.57
Nephrotoxicity [n (%)]	10 (24.4)	16 (25.0)[a]	2 (9.1)	0.27
Initiation of RRT [n (%)]	1 (2.4)	2 (3.1)	0	1.0
Time to start RRT from study drug initiation days) (median [IQR])	13.6	7.2 [4.7-9.7]	0	
Leukopenia [n (%)]	4 (9.8)	7 (10.9)	2 (9.1)	1.0
Rash [n (%)]	3 (7.3)	1 (1.6)	1 (4.6)	0.31
Neurotoxicity [n (%)]	0	1 (1.6)	0	1.0

Abbreviations: CRE, carbapenem-resistant Enterobacteriaceae; ICU, intensive care unit; IQR, interquartile range; MIC, minimum inhibitory concentration; RRT, renal replacement therapy.
[a] Combination therapy use with CZA: colistin (37.5%), polymyxin B (25%), tigecycline (25%), fluoroquinolone (18.8%), aminoglycoside (6.3%).

"Although all three agents are preferred agents for the treatment of KPC-producing infections, the panel slightly favors meropenem-vaborbactam, followed by ceftazidime-avibactam, and then imipenem-cilastatin-relebactam, based on available data regarding clinical outcomes and emergence of resistance."

Ackley R, et al AAC 2029

Tamma et al. IDSA Guidance on the Treatment of Antimicrobial-Resistant Gram-Negative Infections

What about those non-CP-CRE? Depends on differential carbapenem susceptibility

Susceptibility

	Escherichia coli (ESBL Producer) MIC (Preliminary)	
Amikacin	<=8	Susceptible *
Ampicillin	>16	Resistant *
Ampicillin and Sulbactam	>16	Resistant *
Aztreonam	>16	Resistant *
Caspofungin acetate		
Cefazolin	>16	Resistant *
Cefepime	>16	Resistant *
Ceftazidime	>16	Resistant *
Ceftazidime and Avibactam	<=2	Susceptible *
Ceftolozane and Tazobactam	>16	Resistant *
Ceftriaxone	>32	Resistant *
Ciprofloxacin	<=0.25	Susceptible *
Doripenem	<=0.5	Susceptible *
Ertapenem	8	Resistant
Fluconazole		
Gentamicin	<=2	Susceptible *
Imipenem	2	Intermediate *
Levofloxacin	<=0.5	Susceptible *
Meropenem	1	Susceptible
Minocycline	<=1	Susceptible *
Piperacillin and Tazobactam	>64	Resistant *
Tigecycline	<=1 *	
Tobramycin	<=2	Susceptible *
Trimethoprim and Sulfamethoxazole	<=2	Susceptible *

9 Carbapenemase gene not detected.
(Genes tested: KPC, NDM, OXA48, VIM, IMP 1)

Question 3.1: What is the preferred treatment approach for infections caused by Enterobacterales isolates without carbapenemase production that remain susceptible to meropenem and imipenem but are not susceptible to ertapenem?

Suggested approach: For infections caused by Enterobacterales isolates that exhibit susceptibility to meropenem and imipenem (i.e., MICs ≤1 µg/mL), but are not susceptible to ertapenem (i.e., MICs ≥1 µg/mL), the use of extended-infusion meropenem (or imipenem-cilastatin) is suggested, assuming no carbapenemase has been identified.

For isolates susceptible to meropenem but not susceptible to imipenem (and vice versa), in the absence of data to inform the optimal treatment approach, the panel suggests basing the treatment decision on the severity of illness of the patient and site of infection. For example, in this scenario, meropenem may be a reasonable treatment for urinary tract infection but not for a complex intra-abdominal infection. The panel suggests against the use of meropenem-vaborbactam or imipenem-cilastatin-relebactam to treat ertapenem-resistant, meropenem-susceptible and imipenem-susceptible infections since these agents are unlikely to offer any substantial benefit beyond that of extended-infusion meropenem or imipenem-cilastatin alone.

IDSA Guidance Recommendations for KPC-producing Enterobacterales

Syndrome	Recommended	Consider
Urinary tract infection	Cipro & levo TMP/SMX Meropenem EI (if erta-R but mero-S) Nitrofurantoin (Ucystitis) Fosfomycin (Ucystitis) Aminoglycoside x1 (Ucystitis)	Ceftaz/avi Mero/vabor Imi/rel Cefiderocol
Infections besides uncomplicated cystitis	Mero/vabor Ceftaz/avi Imi/rel	Tigecycline Eravacycline Cefiderocol

Tamma et al. IDSA Guidance on the Treatment of Antimicrobial-Resistant Gram-Negative Infections:
https://www.idsociety.org/practice-guideline/amr-guidance/#

PK is a 58 yo F hx morbid obesity, DVTs, AFib, with hx of multiple intra-abdominal surgeries with placement of ventral hernia mesh unable to be removed with adjacent fluid collections growing *Klebsiella pneumoniae*, susceptibilities below.

Amikacin >32 R
Ampicillin >16 R
Ampicillin/sulbactam >16/8 R
Aztreonam >16 R
Cefazolin>16 R
Ceftazidime >16 R
Ceftazidime/avibactam >16/4 R
Ceftolozane/tazobactam >16/4 R
Ceftriaxone >32 R
Cefepime >16 R
Ciprofloxacin >2 R
Colistin >32 R
Ertapenem >8 R
Meropenem >8 R
Minocycline 2 S
Piperacillin/tazobactam >128/4 R
Tigecycline 2
Tobramycin >8 R

What beta-lactamase enzyme do you think this organism is producing?
What antibiotic(s) would you recommend for AY?

a) Minocycline
b) Tigecycline
c) Polymyxin B & stuff
d) ….

Peritoneal fluid, *Klebsiella pneumoniae*
Amikacin >32 R
Ampicillin >16 R
Ampicillin/sulbactam >16/8 R
Aztreonam >16 R
Cefazolin>16 R
Ceftazidime >16 R
Ceftazidime/avibactam >16/4 R
Ceftolozane/tazobactam >16/4 R
Ceftriaxone >32 R
Cefepime >16 R
Ciprofloxacin >2 R
Colistin >32 R
Ertapenem >8 R
Meropenem >8 R
Minocycline 2 S
Piperacillin/tazobactam >128/4 R
Tigecycline 2
Tobramycin >8 R

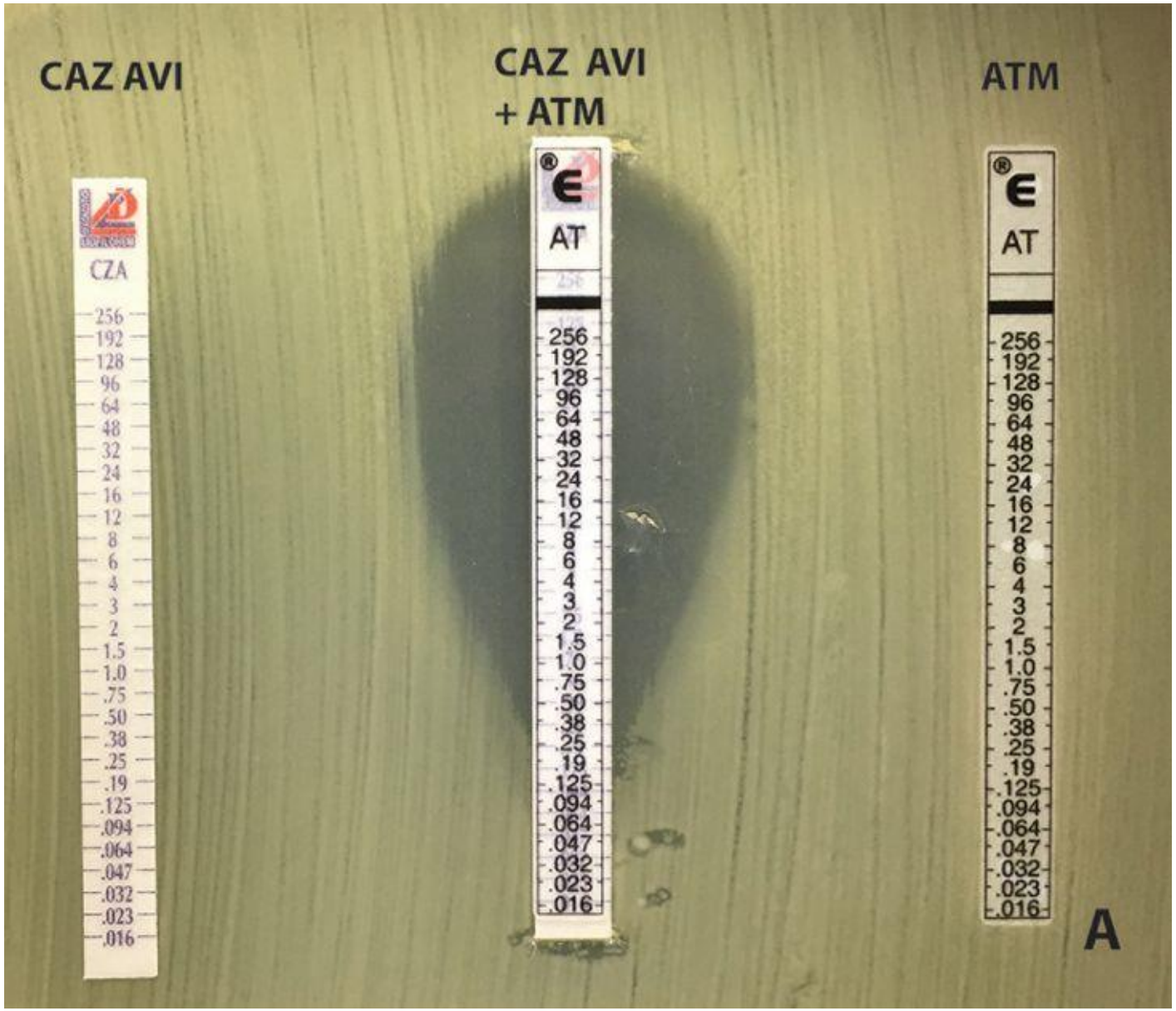
Genotypic probes positive for NDM-1 and OXA-48 genes

Synergy testing for aztreonam + ceftazidime/avibactam
MIC: CTZ/AVI (alone): >256 CTZ/AVI (combination): 1 Aztreonam (alone): 32 Aztreonam (combination): 0.01
Fractional inhibitory combination index: 0.01.
Interpretation: synergistic

	Beta-lactamase Groups						
Functional Group	1		2				3
Molecular Class	C		A			D	B
Subclass	(WT)	(DR)	2b	2be (ESBL)	2f	2df	
Example Enzymes	AmpC		TEM-1, SHV-1	TEM-3, SHV-2, CTX-M	KPC-1	OXA-48	NDM-1
Hydrolytic activity vs beta-l							
Aminopenicillins	+++ (R)				+++ (R)	+++ (R)	+++ (R)
Piperacillin	+ (s)		++ (r/R)	++ (r)	++ (r/R)	+++ (R)	+++ (R)	+++ (R)
1st/2nd GC	+++ (R)		+++ (R)	+ (s)	+++ (R)	+++ (R)	++ (R)	+++ (R)
3rd/4th GC	+ (s)		+++ (R)	+ (s)	+++ (R)	+++ (R)	+ (s/r)	+++ (R)
Monobactams	+ (s)		+++ (R)	-- (S)	+++ (R)	+++ (R)	-- (S)	-- (S)
Penems	-- (S)		-- (S)	-- (S)	-- (S)	++ (r/R)	++ (r/R)	+++ (R)
Other characteristics							
Inhibition by clavulanate	--		--	--	--	--	--	--
Inhibition by avibactam	+++		+++	+++	++	++	++	--
Common organisms	CAPES						Enterobacteriaceae	
Location	Chromosomal				Plasmid		Plasmid	Plasmid
Expression	Inducible →Constitutive		Constitutive			Constitutive	Constitutive	

NDM-1
-High-level carbapenem resistance
-Lack of restoration of ceftaz by avi (or mero by vabor)
-Aztreonam susceptibility (often "hidden" by 2nd beta-lactamase)

OXA-48
-Moderate-level carbapenem resistance
-Possibly CTZ or CFP susceptibility
-Aztreonam susceptibility (often "hidden" by 2nd beta-lactamase)
-Inhibited by avibactam (but not vaborbactam)

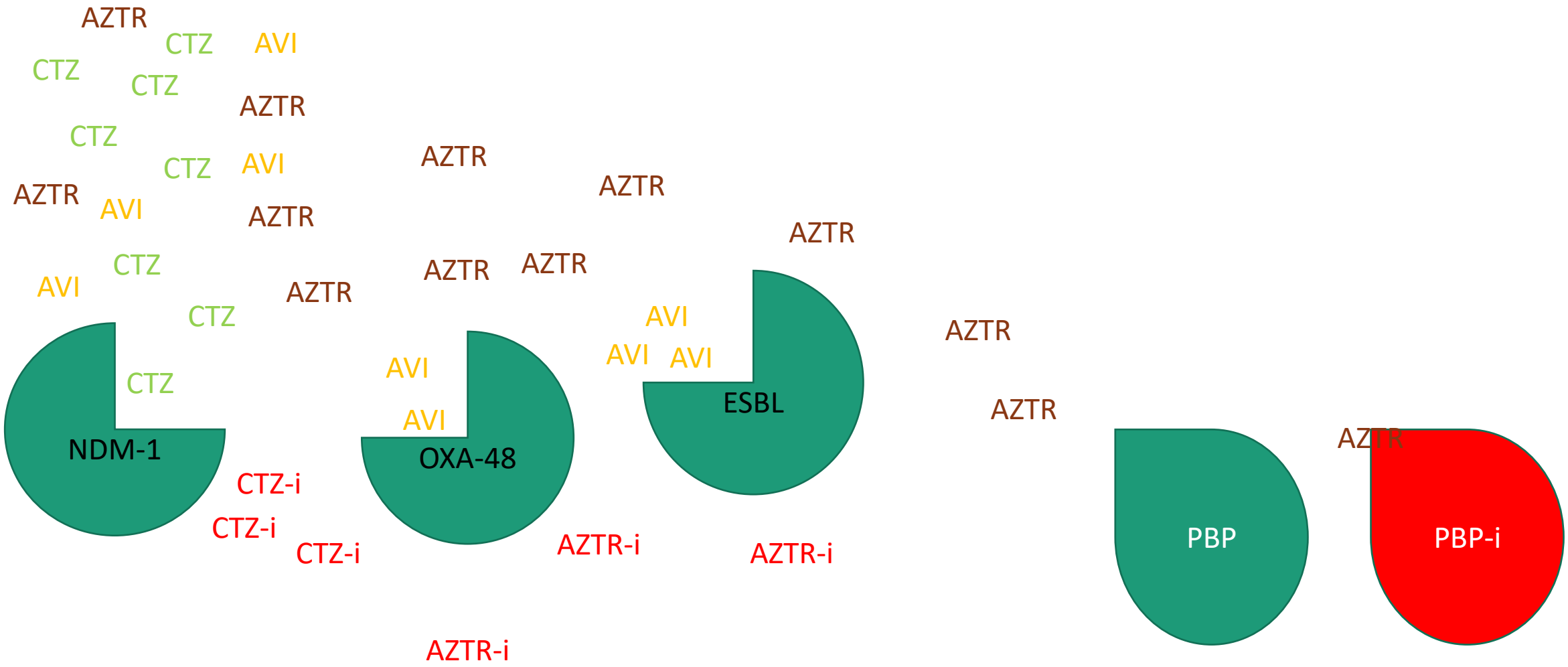


Ceftazidime-Avibactam and Aztreonam, an Interesting Strategy To Overcome β-Lactam Resistance Conferred by Metallo-β-Lactamases in *Enterobacteriaceae* and *Pseudomonas aeruginosa*

Benjamin Davido,[a] Lesly Fellous,[b] Christine Lawrence,[c,d] Virginie Maxime,[e] Martin Rottman,[d,f] Aurélien Dinh[a]

Davido B, et al. AAC 2017;61

Aztreonam avoids MBLs while avibactam protects it from serine beta-lactamases, while the ceftazidime is cannon fodder



Nonrandomized clinical data and IDSA guidance supports *CTZ/AVI + aztreonam* for MBL-producing GNRs; aztreo/AVI in RCTs

Question 3.6: What are the preferred antibiotics for the treatment of infections outside of the urinary tract caused by CRE if NDM production is present?

Suggested approach: Ceftazidime-avibactam in combination with aztreonam, or cefiderocol as monotherapy, are preferred treatment options for NDM and other metallo-β-lactamase-producing infections.

Table 4. Cox Regression Analysis of Factors Independently Associated With 30-Day Mortality

Factor	HR (95% CI)	*P* Value
Cardiovascular disease	6.62 (2.77–15.78)	<.001
Solid organ transplantation	3.52 (1.42–8.69)	.006
SOFA score (1-point increment)	1.21 (1.1–1.32)	<.001
CAZ-AVI + ATM (vs OAAs)	0.17 (.07–.41)	<.001

Abbreviations: ATM, aztreonam; CAZ-AVI, ceftazidime-avibactam; CI, confidence interval; HR, hazard ratio; OAAs, other active antibiotics; SOFA, Sequential Organ Failure Assessment.

Efficacy and Safety of Aztreonam-Avibactam for the Treatment of Serious Infections Due to Gram-Negative Bacteria, Including Metallo-β-Lactamase-Producing Pathogens: Phase 3 REVISIT Study

MBL-positive status

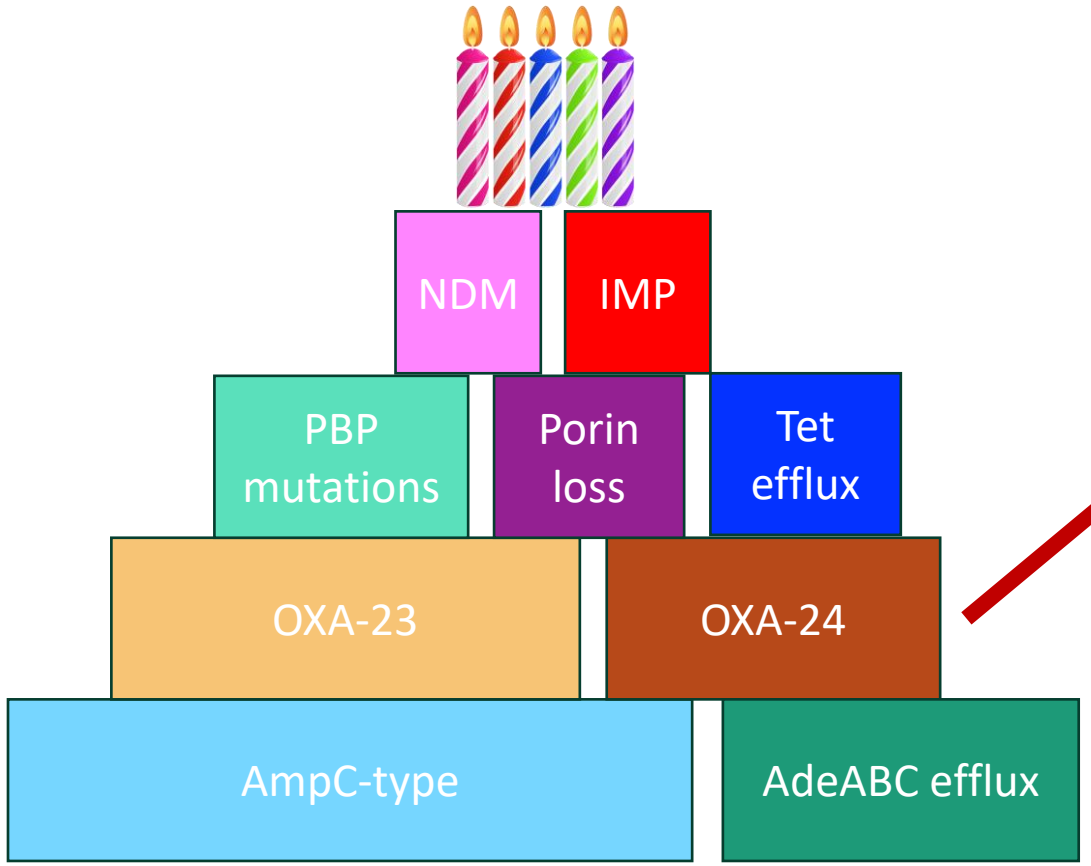
Micro-ITT analysis set		
	ATM-AVI ± MTZ	MER ± COL
N	7	3
Cure n (%)	2 (**28.6**)	2 (**66.7**)
Failure n (%)	3 (42.9)	1 (33.3)
Indeterminate n (%)	2 (28.6)	0

ME analysis set		
	ATM-AVI ± MTZ	MER ± COL
N	4	1
Cure n (%)	**2 (50.0)**	**0 (0)**
Failure n (%)	2 (50.0)	1 (100)

Tamma et al. IDSA Guidance on the Treatment of Antimicrobial-Resistant Gram-Negative Infections
Falcone M, et al . Clin Infect Dis. 2021 Jun 1;72(11):1871-1878. ID Week 2023

A brief word on CRABc (Carbapenem-resistant *Acinetobacter baumanii* complex)

CRAB typically layers ***multiple resistance mechanisms*** which can evade even most newer BLICs



Molecular Class	D	
Example Enzymes	OXA-48	OXA-23/24
Other characteristics		
Inhibition by clavulanate	--	--
Inhibition by avibactam	++	--
Inhibition by vaborbactam	--	--
Inhibition by relebactam	--	--

IDSA recommends *high doses of ampicillin/sulbactam* + second agent for serious CRAB infections

Dose	Daily SUL	AMP/SUL regimen
FDA-approved (max dose)	4 g	2/1 g q6h over 30 mins
IDSA high-dose (low end)	6 g	2/1 g IV q4h over 30 mins
IDSA high-dose (high end)	9 g	6/3 g IV q8h over 4 hours

"When non-susceptibility to ampicillin-sulbactam is demonstrated, the panel believes ***ampicillin-sulbactam may still remain an effective treatment option*** based on the potential for sulbactam to saturate altered PBP targets"

Tamma et al. IDSA Guidance on the Treatment of Antimicrobial-Resistant Gram-Negative Infections

Sulbactam/durlobactam is a ***newly approved*** BLIC with potent activity vs CRAB

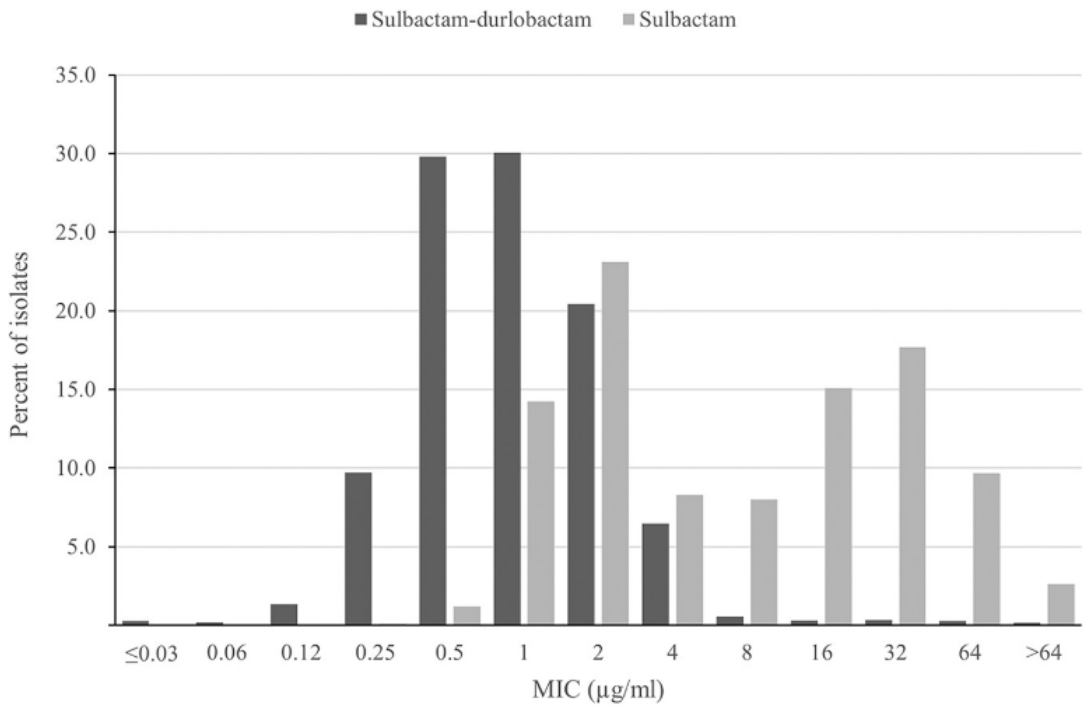
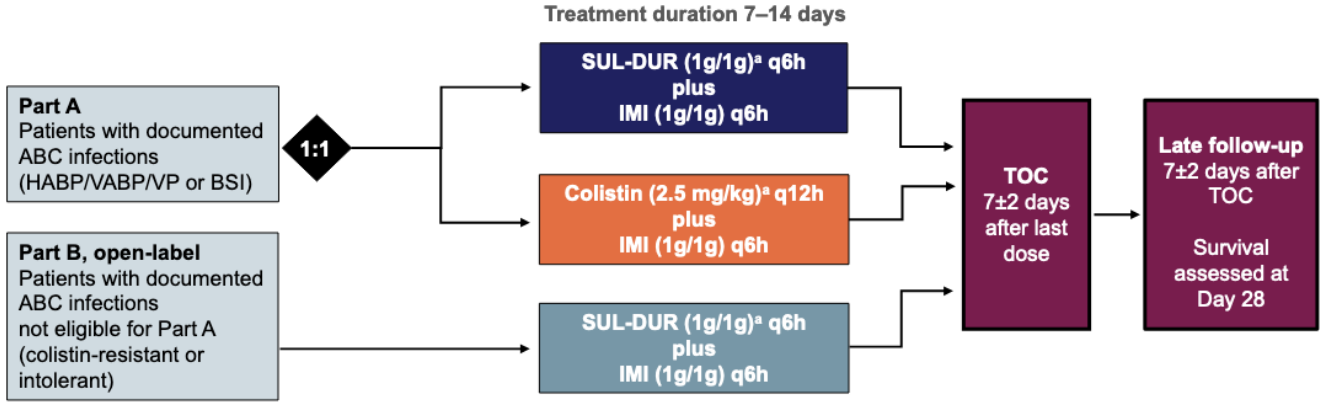


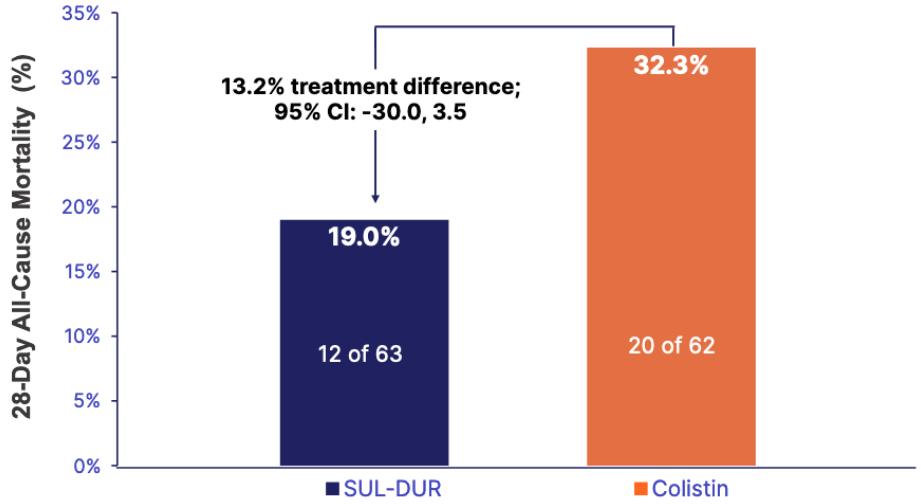
FIG 1 Sulbactam-durlobactam (black bars) and sulbactam (gray bars) MIC distributions for 5,032 isolates of *Acinetobacter baumannii-calcoaceticus* complex (ABC) species collected globally from 2016 to 2021.

Karlowsky JA, et al. AAC 2022 10.1128/aac.00781-22



Primary efficacy endpoint achieved

SUL-DUR non-inferiority on 28-day all-cause mortality vs. colistin in CRABC m-MITT population



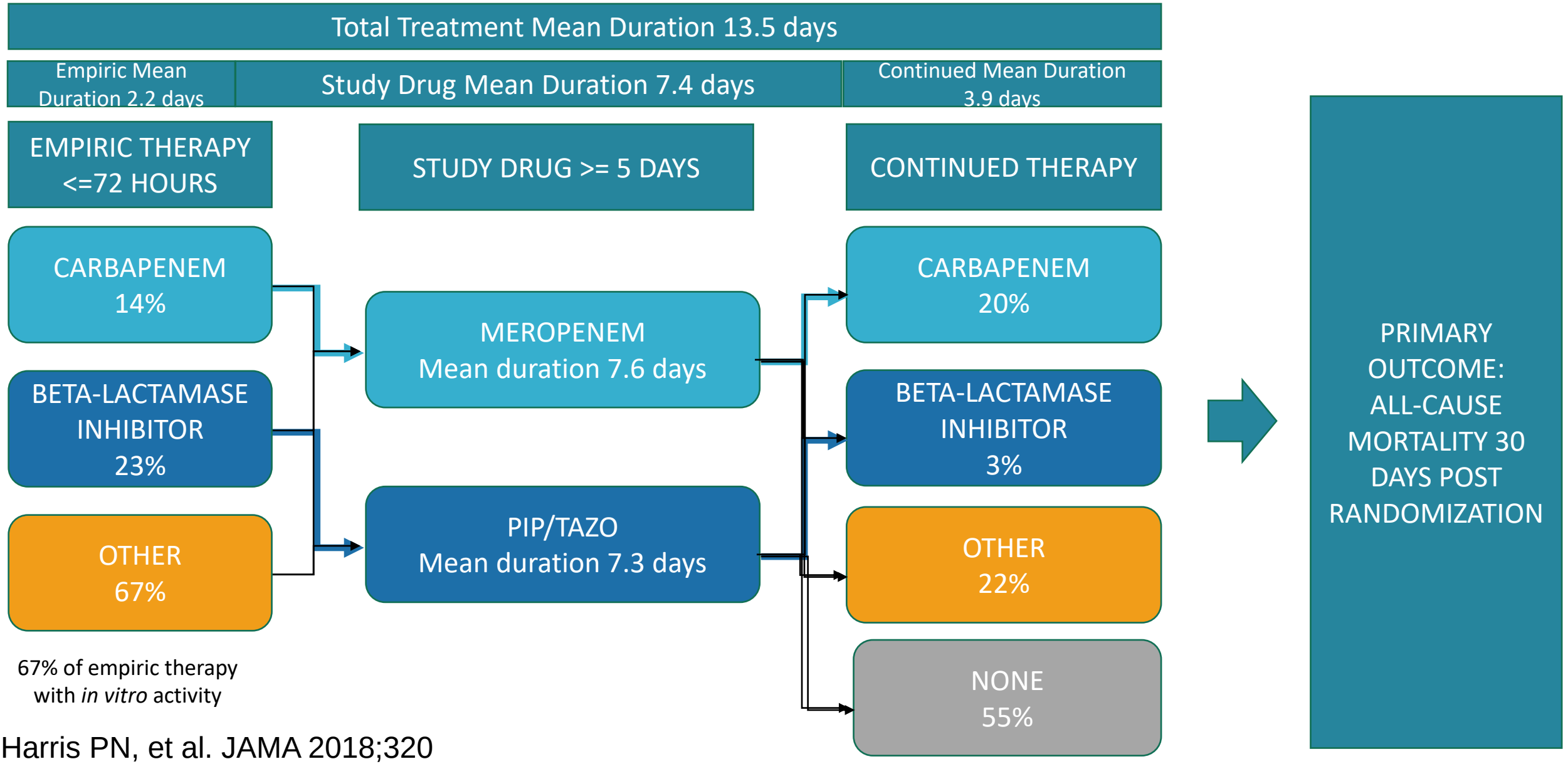
McLeod SM, et al. ID Week 2023

Key Points Review

- Interpret susceptibility results in context of potential resistance mechanisms
  - Situations to **avoid even when S** for severe infections
    - Likely ESBL: pip/tazo, cefepime
    - Likely Amp-C (HECK-Yes): ceftriaxone, pip/tazo
  - Situations to **consider even when R**
    - Likely NDM-1: ceftaz/avi + aztreonam
    - *Acinetobacter* (likely OXA): amp/sulbactam [or sulbactam/durlobactam]
- IDSA has new expert guidance on management of GNRs – use it!

Additional Slides

MERINO I intervention was ***DEFINITIVE treatment***, after identification & susceptibility of infecting organism



Harris PN, et al. JAMA 2018;320

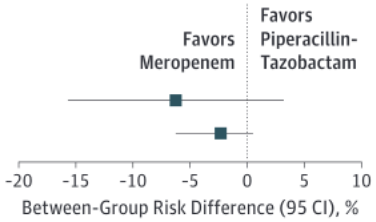
Outcomes favored meropenem; trial ***stopped early for potential harm***

So…carbapenems > pip/tazo for serious ESBL infections regardless of susceptibility

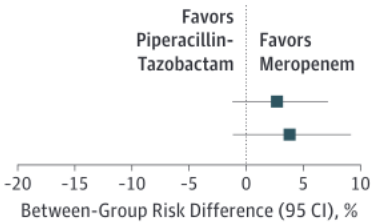
Group/ Subgroup	30-day mortality		p-value (noninferiority or interaction)
	Pip/tazo	Meropenem	
mITT	12.3%	3.7%	0.90
Source			
UTI	6.9%	3.1%	0.44
Non-UTI	18.8%	4.8%	
Empiric Abx			0.70
Adequate	14.3%	3.9%	
Inadequate	8.2%	3.1%	
Immuno-compromsed			0.27
Yes	19.6%	2.5%	
No	9.6%	4.0%	

Figure 2. Secondary Outcomes

Measure of Success	Patients Meeting End Point, No./Total No. (%)		Between-Group Difference (95% CI)
	Piperacillin-Tazobactam	Meropenem	
Clinical and microbiological success at day 4[a]	121/177 (68.4)	138/185 (74.6)	-6.2 (-15.5 to 3.1)
Microbiological success at day 4	169/174 (97.1)	184/185 (99.5)	-2.3 (-6.1 to 0.4)



Measure of Failure	Patients Meeting End Point, No./Total No. (%)		Between-Group Difference (95% CI)
	Piperacillin-Tazobactam	Meropenem	
Microbiological relapse	9/187 (4.8)	4/191 (2.1)	2.7 (-1.1 to 7.1)
Secondary infection with multiresistant organism or *Clostridium difficile*	15/187 (8.0)[b]	8/191 (4.2)[c]	3.8 (-1.1 to 9.1)



Harris PN, et al. JAMA 2018;320

UCSF's approach to reporting CTX-R *E. coli*, *Proteus mirabilis*, *K. pneumoniae*, *K. oxytoca* (putative ESBL producers w/o other intrinsic beta-lactamases)

Sample	CTX	CTZ	Micro report (non-ID)	Notation
Sterile site (blood, CSF, etc)	>1	>4	Ertapenem only	"Testing indicates potential extended spectrum beta lactamase (ESBL) production . Carbapenems are the drug of choice for treatment of severe ESBL infections.Contact id or id pharmacy for alternatives."
Non-sterile site other than urine (respiratory, non-sterile tissue, etc)	>1	>4	All sensitivities per normal cascade	"Testing indicates potential extended spectrum beta lactamase (ESBL) production . Carbapenems are the drug of choice for treatment of severe ESBL infections. For superficial infections (e.g. cellulitis) other drugs to which the organism is susceptible in vitro are effective."
Urine	>1	>4	All sensitivities per normal cascade	"Based on this organism's drug resistance profile, a carbapenem may be preferred for patients with pyelonephritis or urosepsis."

Potential AmpC-producing organisms vary in their risk of treatment-emergent resistance

Enterobacterales with inducible chromosomal AmpC		What about…?	
Significant risk of emergent resistance ("HECK-Yes")	**Low risk of emergent resistance**	**Organism**	**Rationale**
Enterobacter cloacae	*Serratia marcescens*	*E. coli**	Chromosomal AmpC but non-inducible
Klebsiella aerogenes	*Morganella morganii*	*Proteus spp*	*mirabilis, penneri* – no AmpC *vulgaris* - cefuroximase
Citrobacter freundii/ Citrobacter youngae	*Providencia spp*	*Citrobacter koseri*	Lacks chromosomal AmpC
Hafnia alvei		*Pseudomonas*	Inducible chromosomal AmpC – but not Enterobacterales (& multiple other resistance mechanisms)
Yersinia entercolitica			

*acquisition of plasmid-borne, high-expression AmpC can occur