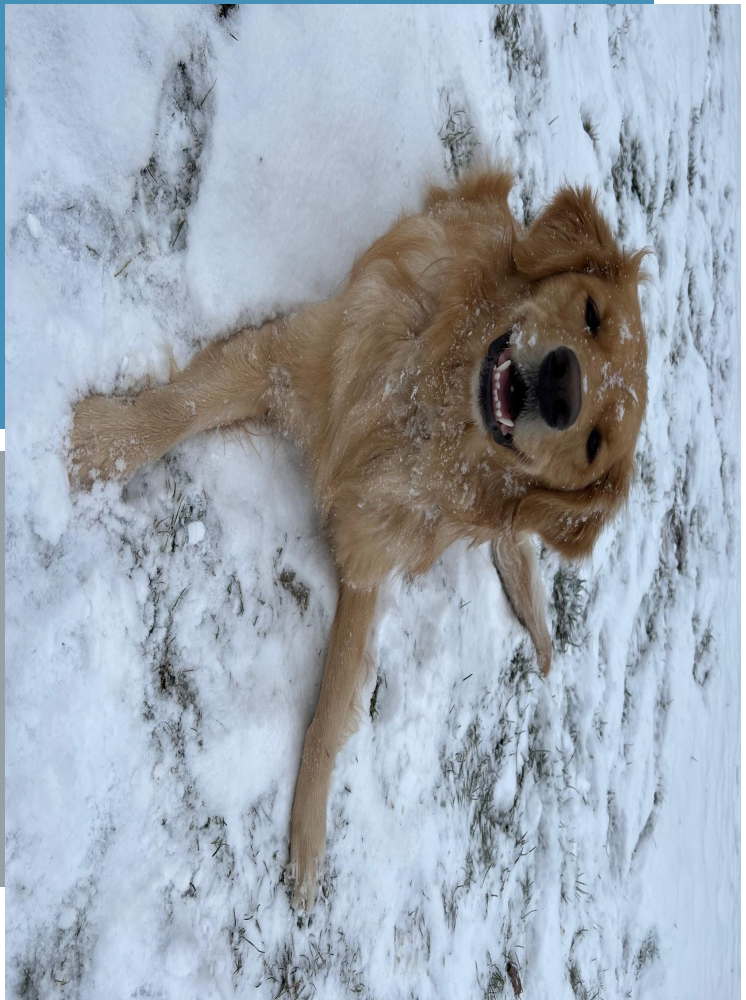
DEPLOYING NEW BETA-LACTAM / BETA-LACTAMASE INHIBITORS IN CLINICAL PRACTICE



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Director, Infectious Diseases Improvement & Clinical Research Innovation, UPMC

Clinical Assistant Professor of Medicine, University of Pittsburgh

@erinmccreary

DISCLOSURES AND ACKNOWLEDGEMENTS

Disclosures

- Advisory board: Shionogi, Entasis, AbbVie, Merck, Cidara, Ferring, LabSimply, MeMed, La Jolla
- Honorarium for symposium presentation: Shionogi

Acknowledgements

- Ryan K. Shields for being a stellar clinician-researcher and teacher, and who was pivotal in the comprehensive care of the patients presented today
- Sam Aitken, Yohei Doi, Jason Pogue, Pranita Tamma, and others for teaching me most of what I know about GNR

@erinmccreary
@OncIDPharmd

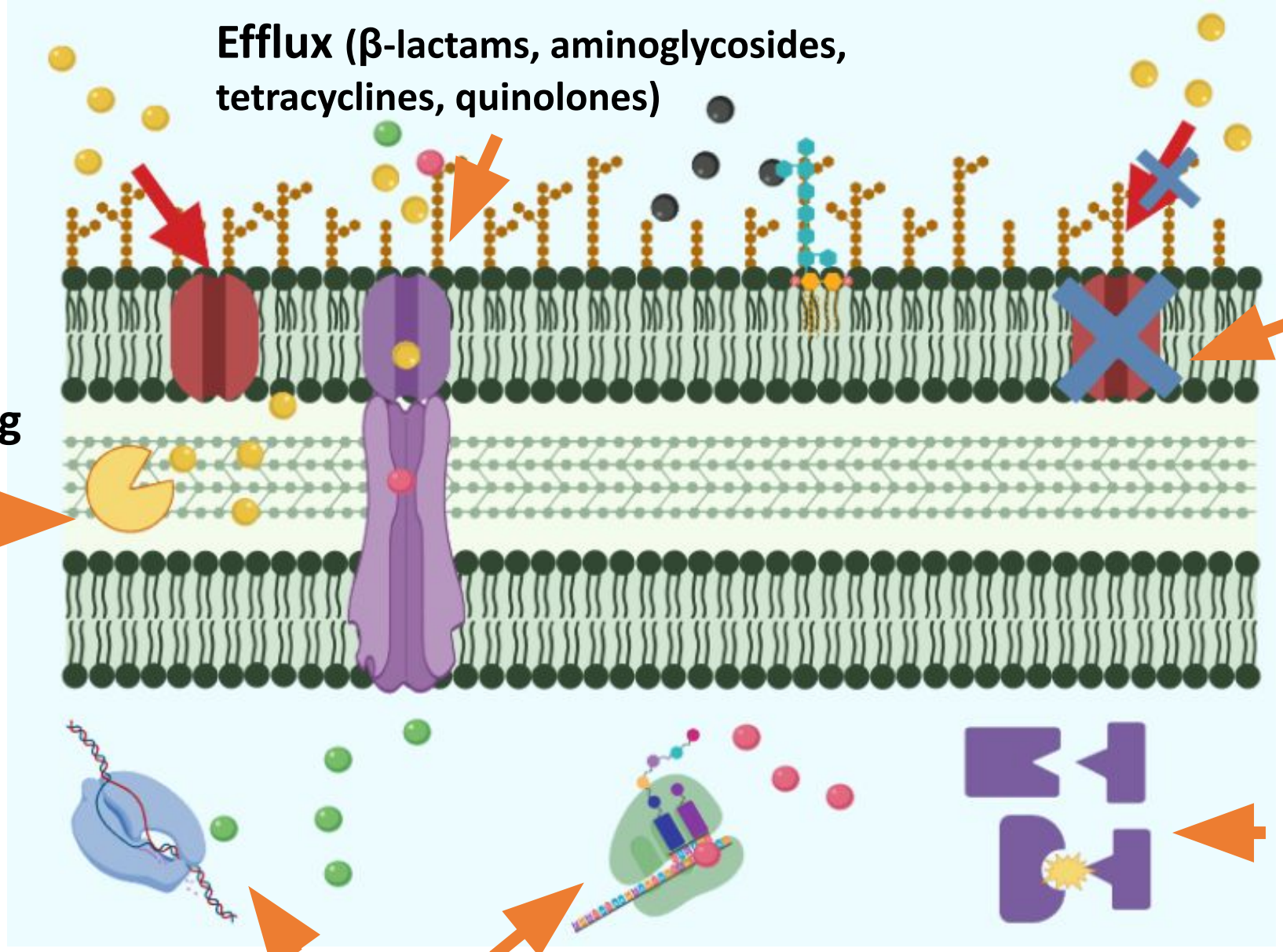


Image created by Samuel Aitken using BioRender.com

CASE I

- 62yo F w/ h/o gastric bypass s/p multiple procedures total gastrectomy, presents w/ back pain, chest pain, body aches. Denies dysuria or hematuria.
- Given 2g ceftriaxone in referring ED transfer to ICU facility due to sepsis 2/2 UTI
- Upon arrival: Tmax 103, tachypneic, WBC 18, lactate 2.1, BP 80/50
- CT PE, troponin, EKG all negative

Resident calls stewardship phone around 11pm

"How do I dose gentamicin for bed 1?"

ARE WE ASKING THE RIGHT QUESTION?

18 months prior

URINE CULTURE

KLEBSIELLA PNEUMONIAE

	MIC (mcg/mL)	MIC Interpretation
Amikacin	32	Intermediate
Amp/Sulbactam	>16/8	Resistant
Ampicillin	>16	Resistant
Aztreonam	>16	Resistant
Cefazolin	>16	Resistant
When cefazolin is used for therapy of UNCOMPLICAT based on a dosage regimen of 1g every 12h.		
Cefepime	>16	Resistant
Ceftazidime	>16	Resistant
Ceftriaxone	>32	Resistant
Cefuroxime	>16	Resistant
When Cefuroxime is used for therapy of UNCOMPLICA		
Ciprofloxacin	>2	Resistant
Gentamicin	<=4	Sensitive
Meropenem	>8	Resistant
Nitrofurantoin	>64	Resistant
Piperacillin/Tazobactam	>64	Resistant
Sulfa/Trimethoprim	>2/38	Resistant
Tobramycin	>8	Resistant

WHAT INFORMATION DO I HAVE TO GUIDE EMPIRIC PRESCRIBING

Micro data

- KPC-producing *K. pneumoniae* in urine 18 months prior to admission
- Pan-susceptible *E. coli* and *K. oxytoca* in urine 16 months prior to admission; mostly susceptible *E. coli* 9 months prior to admission
- Multiple TPN port infections with CONS over time
- MRSA bacteremia 6 months prior to admission
- TODAY: Urine and blood cultures pending

Patient-specific data

- Frequent flyer, lots of antibiotic exposure
- History of CRE (but >1 year ago?)
- Sulfa allergy
- Received 2g CRO ~8 hours ago and clinically worse

THINGS GOING THROUGH MY HEAD

- I can't call anyone it's 11pm
- Is a culture from 18 months ago worth covering empirically?
- If the answer is yes, then the solution isn't gent
- I've worked here about a year and I don't think I've seen or heard anyone give a novel BLBLI before culture data returned? Have I?
- OMG am I really going to recommend…
- I am a pharmacist and my life's worth is drug dollars saved!!
- I am a pharmacist and my job is to provide exceptional patient care. Period.
- This patient is incredibly ill Erin don't blow this
- I am a good pharmacist who will monitor this patient every step over the next few days and I can stop or change antibiotics as easily as I can start them
- I'm gonna do it I'm gonna go for it Yes this is the right call You can do this Erin
- Lol I am going to tell the ICU to ADD vanco that's interesting what a night

RECOMMENDATION

#Sepsis 2/2 pyelonephritis - Rib, back, chest, pain with fever and foul smelling urine. Hypotensive and febrile to 103. Px exam revealed CVA tenderness, CT at OSH demonstrated pyelo of the right kidney. Leukocytosis of 28. Empirically started on ceftriaxone then continued to decompensate, required 4L of LR without BP response. Consistent with acute pyelonephritis likely with inadequately treated organisms.

- BCx, UCx, UA
- CT w/con showed pernephric fat stranding of right kidney
- Hx of nephrolithiasis
- BPs progressively decreased overnight, s/p 4L LR and added NE peripheral
- Discussed with AMP, broaded overnight to:
- Vanc 1250mg q12
- Meropenem/vaborbactam 4g q8h --> for carbapenamase klebsiella

Cr	
Cr	Cr
12/21/2019 6:43 AM EST	0.7
12/20/2019 3:41 AM EST	0.8
12/19/2019 3:46 AM EST	0.8
12/18/2019 11:20 AM EST	0.9
12/17/2019 8:08 PM EST	1.1
12/17/2019 2:44 PM EST	1.1

(beyond the scope of this talk but note the full dose recommendation despite the AKI)

TO QUOTE THE GREAT DR. ROBERT BONOMO

"If you can save a life, I think you should"

This susceptibility reported 2 days later

Last Update: [redacted]

Collected: [redacted]

Specimen Desc: Blood

BLOOD CULTURE

[redacted]

Special Request: None

Gram Stain: ANAEROBIC BOTTLE Gram Negative Rods; Results called to and read back by [redacted]

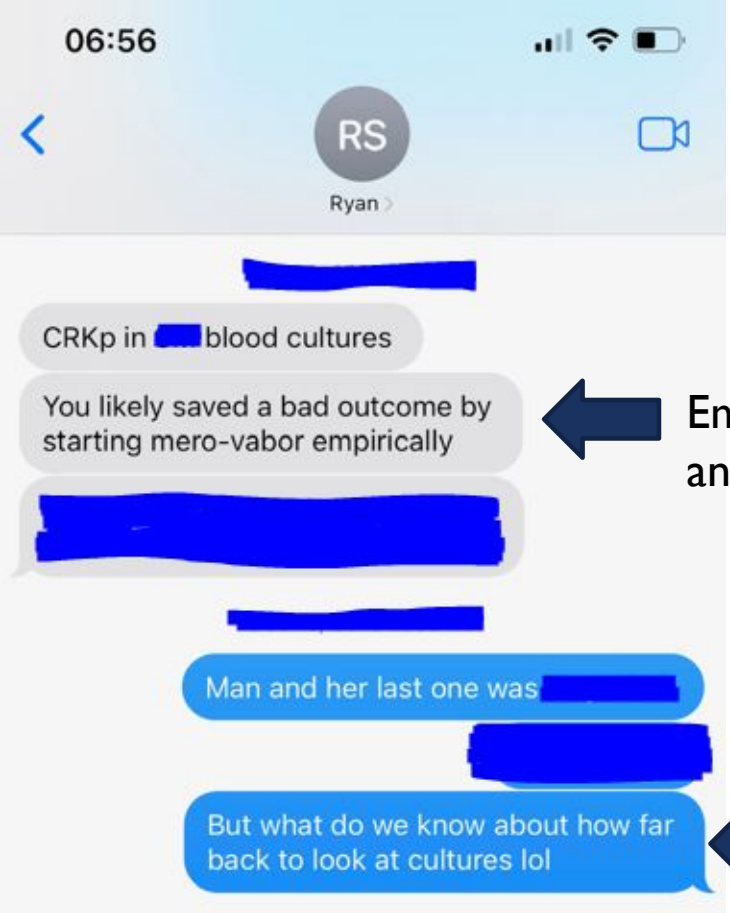
Culture: ANAEROBIC BOTTLE Klebsiella pneumoniae Extended spectrum beta lactamase produ
is a carbapenem resistant organism Confirmed as a carbapenemase producer
AEROBIC BOTTLE No Growth 5 Days

KLEBSIELLA PNEUMONIAE

	MIC (mcg/mL)	MIC Interpretation
Amikacin	<=16	Sensitive
Ciprofloxacin	>2	Resistant
Ertapenem	>1	Resistant
Gentamicin	4	Sensitive
Levofloxacin	>4	Resistant
Meropenem	8	Resistant
Sulfa/Trimethoprim	>2/38	Resistant
Tobramycin	>8	Resistant

WE LOVE A HAPPY ENDING

Patient discharged to a SNF on hospital day 5



Empiric escalation is good antimicrobial stewardship

Still a lot to learn!!

KLEBSIELLA PNEUMONIAE CARBAPENEMASE (KPC)

- We have options now!!!
- UTI FQ, TMP/SMX, nitrofurantoin, single-dose AG
- **Other infection sites ceftazidime-avibactam, meropenem-vaborbactam**
  - Comparative data suggest similar outcomes; more resistance development with CZA?
  - Imipenem-relebactam displays *in vitro* activity but no clinical data yet
    - Mutation selection *in vitro*?
  - Cefiderocol displays *in vitro* activity but limited clinical data is conflicting
  - Tigecycline/eravacycline reasonable for intraabdominal infections, bone/joint infections

Ackley R, et al. AAC. 2020.
Tamma PD et al. Clin Infect Dis. 2022.

THE PHENOTYPE GAME

Last Update: [redacted]

BLOOD CULTURE

Collected: [redacted]

Specimen Desc: Blood

[redacted] Special Request: None

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THE PHENOTYPE GAME

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Imipenem	1	Sensitive
Levofloxacin	>4	Resistant
Meropenem	<=1	Sensitive
Sulfa/Trimethoprim	>2/38	Resistant
Tobramycin	>8	Resistant

45yo F w/ extensive abdominal surgical history; recently admitted with klebsiella bacteremia s/p course of ceftazidime-avibactam. New cultures shown above.

Question 3: What Are Preferred Antibiotics for the Treatment of Infections Outside of the Urinary Tract Caused by CRE Resistant to Ertapenem but Susceptible to Meropenem, When Carbapenemase Testing Results Are Either Not Available or Negative?

Recommendation: Extended-infusion meropenem is the preferred treatment for infections outside of the urinary tract caused by CRE resistant to ertapenem (ie, ertapenem MICs $\geq$2 mcg/mL) but susceptible to meropenem (ie, meropenem MICs $\leq$1 mcg/mL), when carbapenemase testing results are either not available or negative.

Tamma PD et al. Clin Infect Dis. 2022.
Van Duin D, Arias CA, et al. CRACKLE-2. 2020.

IS PHENOTYPE ENOUGH?

KLEBSIELLA PNEUMONIAE

	MIC (mcg/mL)	MIC Interpretation
Amikacin	<=16	Sensitive
Ciprofloxacin	>2	Resistant
Gentamicin	<=1	Sensitive
Imipenem	1	Sensitive
Levofloxacin	>4	Resistant
Meropenem	<=1	Sensitive
Sulfa/Trimethoprim	>2/38	Resistant
Tobramycin	>8	Resistant

KLEBSIELLA PNEUMONIAE

	MIC (mcg/mL)	MIC Interpretation	
Amikacin	<=16	Sensitive	
CEFTAZIDIME/AVIBACTAM		>256	Resistant
Ciprofloxacin	>2	Resistant	
Gentamicin	2	Sensitive	
Imipenem	1	Sensitive	
Levofloxacin	>4	Resistant	
Meropenem	<=1	Sensitive	
Sulfa/Trimethoprim	>2/38	Resistant	
Tobramycin	>8	Resistant	

Upon additional testing, confirmed to harbor KPC-3 D179Y variant.
MVB MIC= 0.064 mg/L.

Taracila MA, et al AAC. 2022.
Shields RK, et al. OFID. 2017.

DO I NEED A BLI?

- This question is unanswered clinically but pretty settled *in vitro*
- I could have the genotype, phenotype, or both debate all day – in a perfect world we'd always have both
- The bug matters (e.g., K. pneumoniae vs E. aerogenes)
- Carbapenem treatment of ceftazidime-avibactam-resistant *K. pneumoniae* infections may select for carbapenem resistance
- In general, if you're using an antibiotic, you should confirm it is active

Hospital day when sample was cultured	Source	MIC (μg/ml)			Treatment course				KPC
		CAZ-AVI	MEM (Vitek)	MEM (BMD)	MEM	PMB	TGC	CAZ-AVI	
5	Pancreatic fluid	3	≥16	128	Days 5 to 38	Days 7 to 36			KPC-2
16	Pancreatic fluid	3	≥16	128			Days 24 to 60		KPC-2
49	BAL fluid	>256	2	2			Days 24 to 60	Days 37 to 60	KPC-2 D179Y
58	BAL fluid	>256	2	2					KPC-2 D179Y
59	Tracheal aspirate	>256	1.5	2					KPC-2 D179Y
68	Blood	12	≥16	≥128	Days 60 to 72	Days 57 to 72			KPC-2
72	Blood	12	≥16	≥128					KPC-2

Isolate	Starting KPC variant	Replicate no.	Meropenem MIC (μg/ml) at[a]: Baseline	Wk 1	Wk 2	Wk 3	Wk 4	Wk 5	Wk 6	Ending KPC variant	*ompK36* variant[b]	Ceftazidime-avibactam MIC (μg/ml) at end of protocol (change from baseline)[c]
1-B	D179Y, T243 M	1	0.5	8	8	16	16	32	64	D179Y, T243 M	Deletion	512 (↔)
		2	0.5	8	8	16	64	64	>64	T243A	IS5 ins	128 (↔)
		3	0.5	8	16	16	32	32	32	D179Y, T243 M	IS5 ins	512 (↔)

Giddins MJ, et al. AAC. 2017.
Shields RK, et al. AAC. 2017.

DO I NEED A BLI?

Question 5: What Are the Preferred Antibiotics for the Treatment of Infections Outside of the Urinary Tract Caused by CRE if Carbapenemase Production is Present?

Recommendation: Meropenem-vaborbactam, ceftazidime-avibactam, and imipenem-cilastatin-relebactam are preferred treatment options for KPC-producing infections outside of the urinary tract. Ceftazidime-avibactam in combination with aztreonam, or cefiderocol as monotherapy, are preferred treatment options for NDM and other metallo-β-lactamase-producing infections. Ceftazidime-avibactam is the preferred treatment option for OXA-48-like-producing infections.

Tamma PD, et al. CID. 2022.

IS PHENOTYPE ENOUGH?

Antimicrobial Susceptibility, Phenotypic Testing, and β-Lactamase Contents of KPC-Producing *Escherichia coli*

Patient	PTZ	CTX	CAZ	FEP	ATM	ERT	IPM	MEM	DOR
1	>128/4	32	>128	64	128	32	2	8	4
2	>128/4	32	>128	32	>128	4	4	4	4
3	128/4	4	32	**2**	128	0.5	**1**	**0.5**	**1**
4	128/4	16	>128	**8**	>128	1	**0.5**	**0.5**	**0.5**
5	>128/4	128	>128	64	>128	4	2	2	**1**
6	128/4	8	128	**4**	128	16	**1**	**1**	**1**
7	>128/4	32	128	16	>128	16	4	4	4
8	>128/4	32	>128	32	>128	4	4	2	4
9	>128/4	32	128	16	128	2	2	**1**	**1**
10	128/4	4	32	**4**	64	1	2	**0.5**	**1**
11	>128/4	128	>128	64	>128	8	8	4	4
12	128/4	64	>128	32	>128	8	4	2	2
13	128/4	16	128	**8**	>128	8	2	2	2

Kim YA, et al. CID. 2012.

KPC - negative

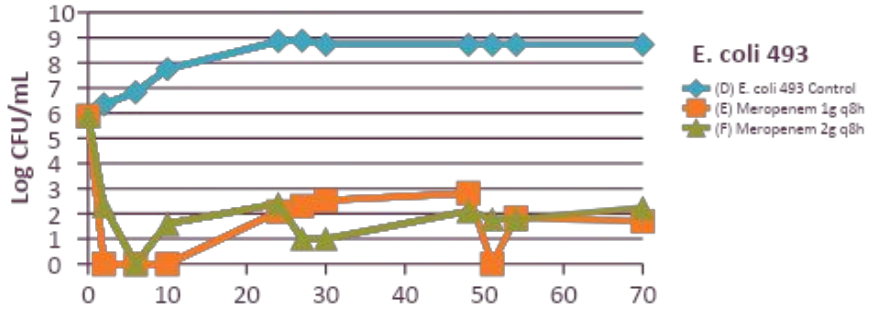
Exposures confirmed by UHPLC-MS

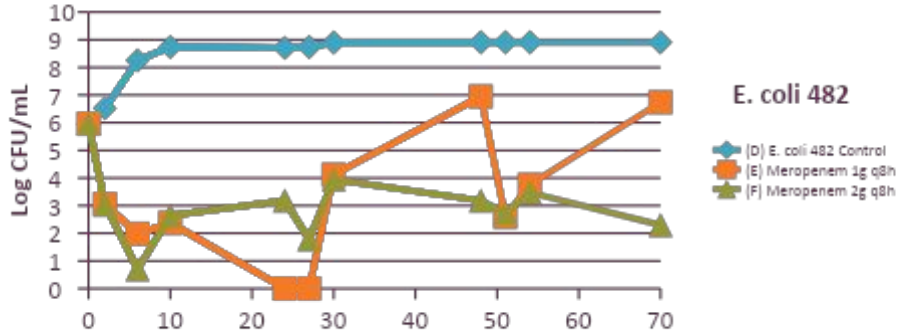
KPC - positive

@ryankshields

Meropenem MIC

1





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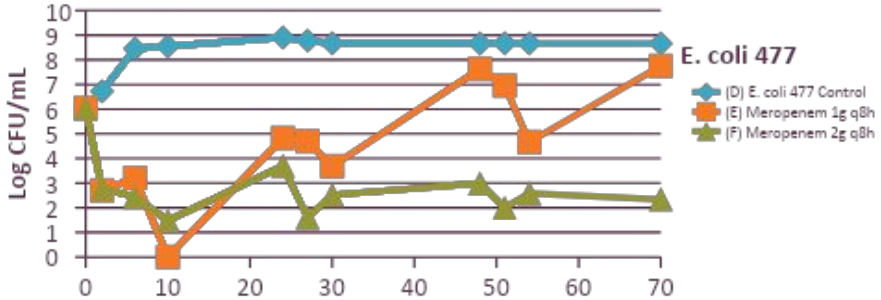

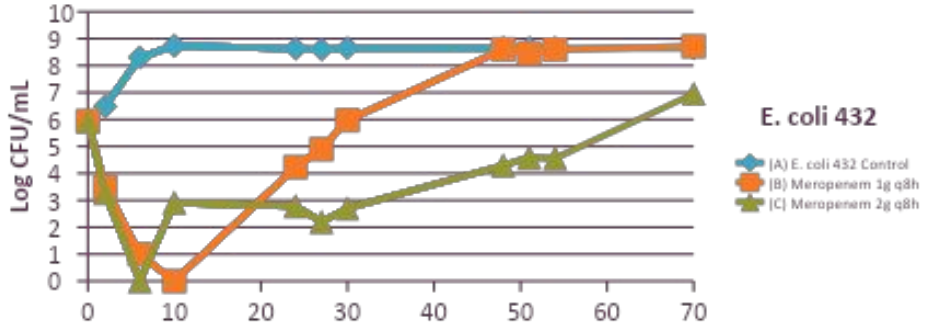

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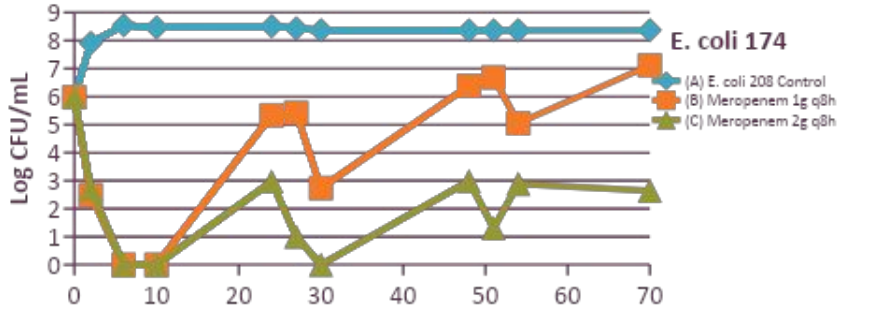

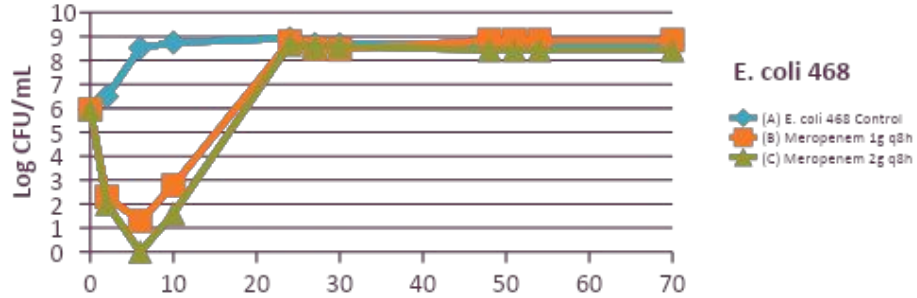

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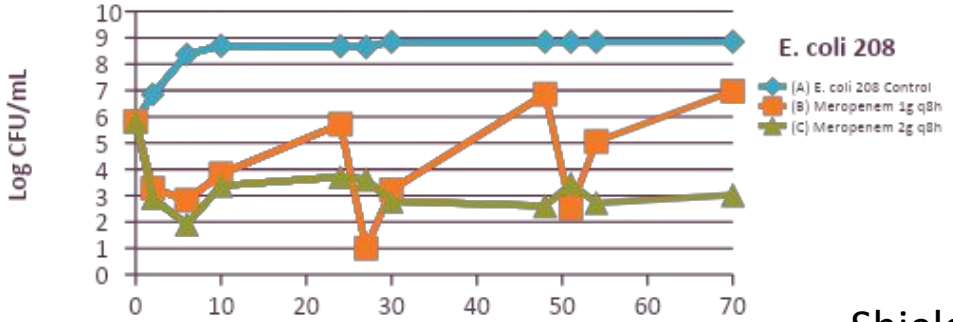

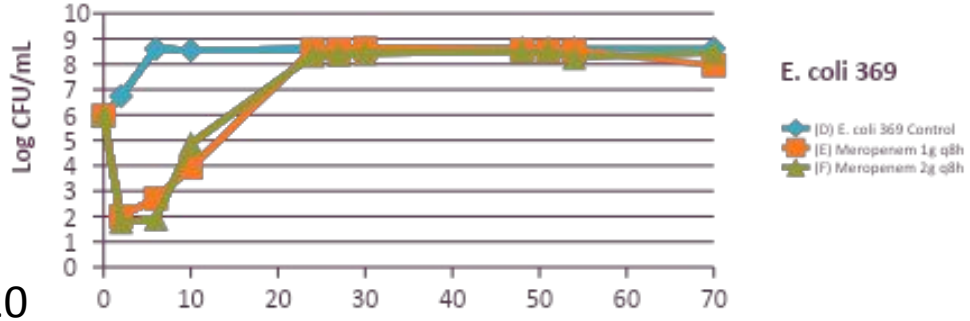

Shields RK, et al. ECCMID 2020

NON-CP-CRE IS ACTUALLY OUR BIGGER PROBLEM

74 yo M with necrotizing pancreatitis with a complicated intra-abdominal infection. OR cultures from an abdominal abscess grow **carbapenem-resistant *Enterobacter cloacae***

- PCR confirms carbapenemase negative (targets = KPC, OXA-48, NDM, VIM, IMP)

Meropenem and meropenem-vaborbactam MICs are the <u>same</u>. This is a dosing and breakpoint issue.

- MEM ≤ 4 (1g IV q8h over 30 minutes meropenem)
- MVB ≤ 4/8 (2g IV q8h over 3h meropenem)

Deploy CZA vs extended infusion mero?

Drug	Interpretation	MIC
Amikacin	<=16	Susceptible
Aztreonam	**>16**	**Resistant**
Cefepime	**>16**	**Resistant**
Ciprofloxacin	**1**	**Resistant**
Gentamicin	**8**	**Intermediate**
Meropenem	**4**	**Resistant**
Piperacillin-tazobactam	**>64**	**Resistant**
TMP/SMX	**>2/38**	**Resistant**
Ceftazidime-avibactam	1	Susceptible
Meropenem-vaborbactam	4	Susceptible

JUST AN AVERAGE AFTERNOON IN PITTSBURGH

67 yo with poor compliance to medical care presenting with a worsening right foot infection

- PMH: Severe PVD, CHF
  - Refused bilateral amputation
- Vitals: T=39.4, BP=80/46, WBC=15.6
- Blood cultures turn positive within 24 hours…

ENTEROBACTER CLOACAE COMPLEX

	MIC (mcg/mL)	MIC Interpretation	
Amikacin	16	Sensitive	
Aztreonam		Resistant	
CEFTAZIDIME/AVIBACTAM	>256	Resistant	
Cefepime	32	Resistant	
Ceftriaxone	32	Resistant	
Ciprofloxacin	1	Sensitive	
Gentamicin	4	Sensitive	
Imipenem	16	Resistant	
Meropenem	>=16	Resistant	
Meropenem/Vaborbactam	1.0	Sensitive	
Piperacillin/Tazobactam	>=128	Resistant	
Sulfa/Trimethoprim	>=320	Resistant	
Tobramycin	>=16	Resistant	

Lol wtf

BEFORE YOU BUST OUT BLBLIS… COMMON THINGS ARE COMMON

Order/Culture	Result
Blood Culture	**ANAEROBIC BOTTLE Escherichia coli This is a carbapenem resistant organism**

Susceptibility Results

	Tested	Interpretation	Result
	Amikacin	SS	<=16
	Amoxicillin/Clavulanate	SS	<=8/4
*	Ampicillin	R	>16
*	Ampicillin/Sulbactam	I	16/8
*	Aztreonam	R	>16
*	Cefazolin	R	>16
*	Cefepime	R	>16
*	Ceftazidime	R	16
*	Ceftriaxone	R	>32
*	Cefuroxime	R	>16
*	Ciprofloxacin	R	>2
*	Gentamicin	R	>8
*	Levofloxacin	R	>4
*	Meropenem	I	2
	Piperacillin/Tazobactam	SS	<=8
*	Tetracycline	R	>8
*	Tobramycin	R	>8
	Sulfa/Trimethoprim	SS	<=0.5/9.5
*	Ertapenem	R	>1
	Meropenem/Vaborbactam	SS	<=2

Stewardship collaboration with micro lab to rapidly update reporting

This patient matches the EZ Alert c

Medication:
Drug
MEROPENEM/VABORBACTAM 2G

ENTEROCOCCUS FAECALIS

	MIC (mcg/mL)	MIC Interpretation
Ampicillin	<=2	Sensitive
Daptomycin	1	Sensitive
Gentamicin Synergy		Resistant
Linezolid	2	Sensitive
Penicillin	2	Sensitive
Vancomycin	2	Sensitive

ESCHERICHIA COLI

	MIC (mcg/mL)	MIC Interpretation
Amikacin	<=16	Sensitive
Amox/K Clavulanate		No Interp. Avail.
Not reported. Previously reported as Sensitive		
Amp/Sulbactam		No Interp. Avail.
Not reported. Previously reported as Intermediate		
Ampicillin		No Interp. Avail.
Not reported. Previously reported as Resistant		
Aztreonam		No Interp. Avail.
Not reported. Previously reported as Resistant		
Cefazolin		No Interp. Avail.
Not reported. Previously reported as Resistant		
Cefepime		No Interp. Avail.
Not reported. Previously reported as Resistant		
Ceftazidime		No Interp. Avail.
Not reported. Previously reported as Resistant		
Ceftriaxone		No Interp. Avail.
Not reported. Previously reported as Resistant		
Cefuroxime		No Interp. Avail.
Not reported. Previously reported as Resistant		
Ciprofloxacin	>2	Resistant
Ertapenem	<=0.5	Sensitive
CORRECTED [redacted] at 1120: PREVIOUSLY REPORTED AS >1 R		
Gentamicin	<=2	Sensitive
CORRECTED [redacted] at 1120: PREVIOUSLY REPORTED AS >8 R		
Levofloxacin	>4	Resistant
Meropenem	<=1	Sensitive
CORRECTED [redacted] at 1120: PREVIOUSLY REPORTED AS 2 I		
Meropenem/Vaborbactam	<=2	Sensitive
Piperacillin/Tazobactam		No Interp. Avail.
Not reported. Previously reported as Sensitive		
Sulfa/Trimethoprim	<=0.5/9.5	Sensitive
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CORRECTED [redacted] at 1120: PREVIOUSLY REPORTED AS >8 R		

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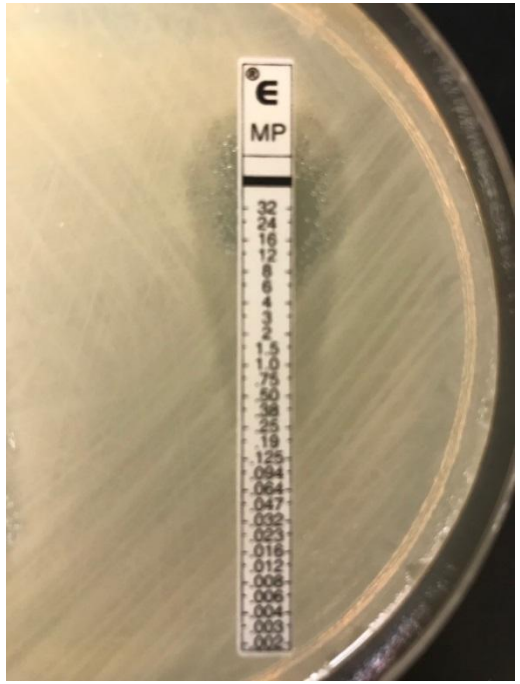
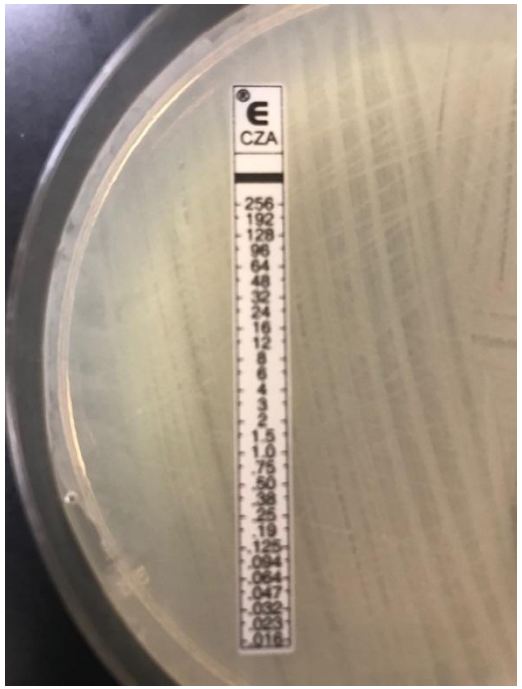
Back to this

REPEAT MIC RESULTS (ETEST)

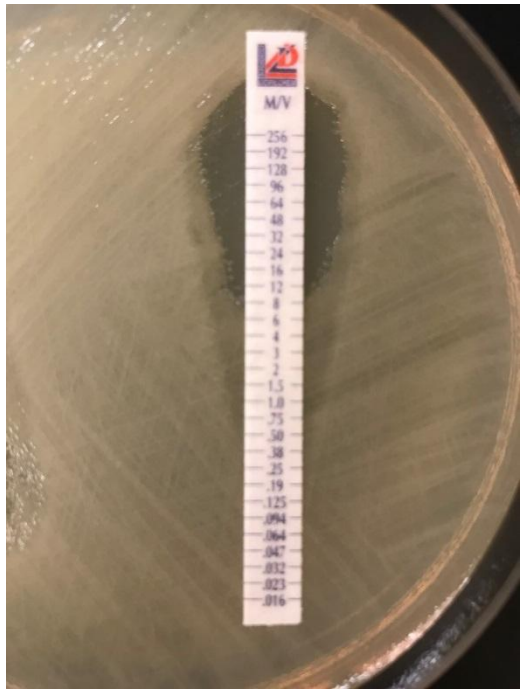
Meropenem >32



Ceftaz-avi >256



Mero-vabor = 12

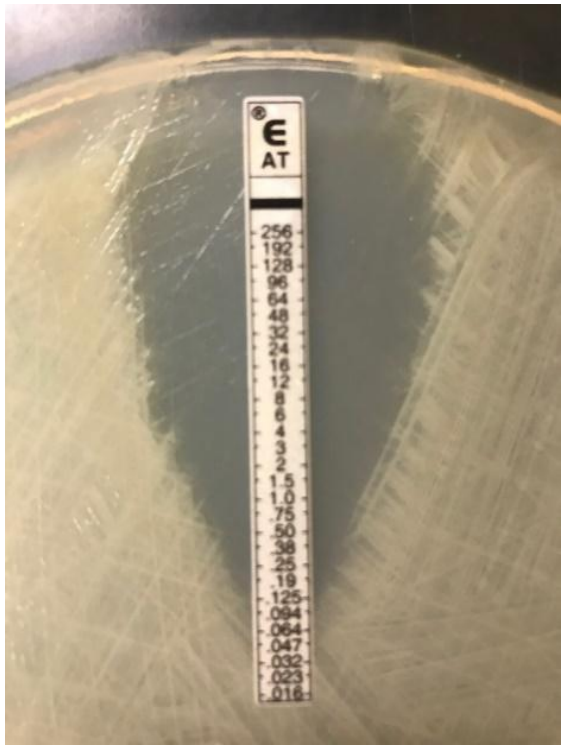


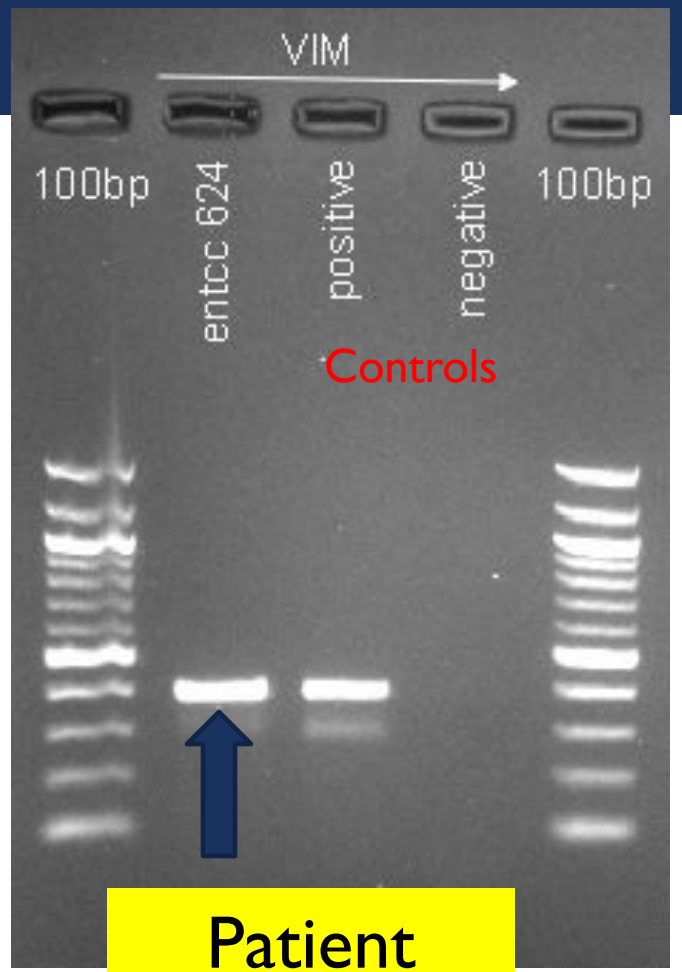
Originally reported MIC = 1

Meropenem-vaborbactam Etest read too early may overcall susceptibility

So, what is this?

- ***bla*$_{VIM}$ detected**
- Negative for KPC, NDM, IMP
- Aztreonam MIC = 0.125 µg/mL!!!!
  - Why reported resistant?





Patient isolate

METALLO-BETA-LACTAMASE-PRODUCING CRE

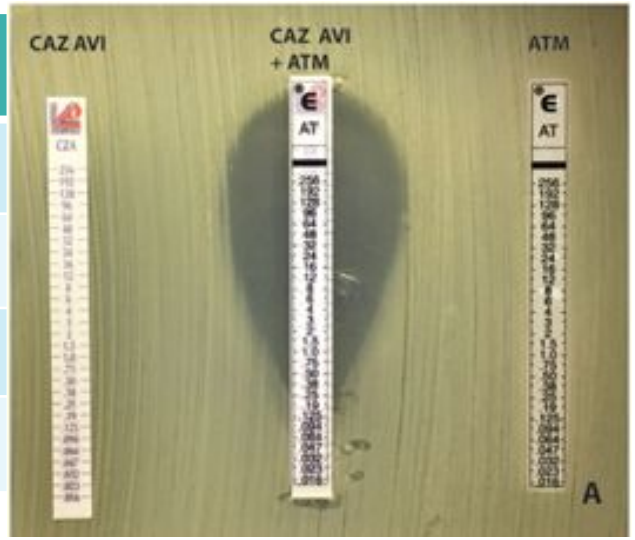
Clinical Infectious Diseases
MAJOR ARTICLE

Efficacy of Ceftazidime-avibactam Plus Aztreonam in Patients With Bloodstream Infections Caused by Metallo-β-lactamase–Producing Enterobacterales

Marco Falcone,[1] George L. Daikos,[2] Giusy Tiseo,[1] Dimitrios Bassoulis,[2] Cesira Giordano,[3] Valentina Galfo,[1] Alessandro Leonildi,[3] Enrico Tagliaferri,[1] Simona Barnini,[3] Spartaco Sani,[4] Alessio Farcomeni,[5] Lorenzo Ghiadoni,[6] and Francesco Menichetti[1]

- 107 MBL-producing bloodstream infections; treatment with ≥1 antimicrobial showing in vitro activity for at least 48 hours
- Mortality
  - **19.2%** CZA-ATM vs **59.3%** Colistin-containing vs **26.1%** Non-colistin therapy

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 (each 1 point increment)	1.21 (1.1–1.32)	<.001
CZA+ATM (vs OAA)	**0.17 (.07–.41)**	**<.001**



Falcone M, et al. *Clin Infect Dis.* 2020 May 19;ciaa586.
Davido B, et al. Antimicrob Agents Chemother. 2017.

BUT WE CAN'T ASSUME ANYTHING

- 106/459 isolates have ATM-AVI MICs 2-32
  - 76 isolates randomly screened, 72 had insertions!!
- Two common 4-AA insertions in PBP3 decrease the activity of aztreonam-avibactam
  - YRIN or YRIK at position 333 (Ambler numbering)
- **Recommend susceptibility testing of combinations whenever possible – don't assume they are active**

J Antimicrob Chemother 2020; **75**: 1650–1651
doi:10.1093/jac/dkaa021
Advance Access publication 10 February 2020

High prevalence of *Escherichia coli* clinical isolates in India harbouring four amino acid inserts in PBP3 adversely impacting activity of aztreonam/avibactam

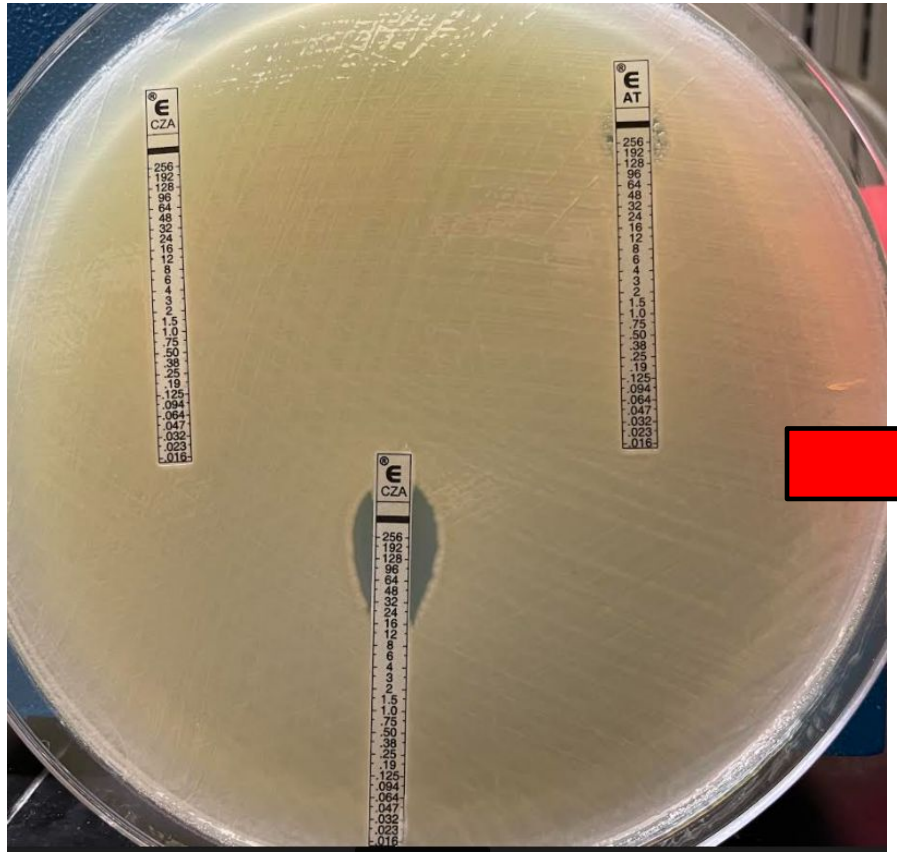
Hariharan Periasamy, Prashant Joshi, Snehal Palwe, Rahul Shrivastava, Sachin Bhagwat* and Mahesh Patel

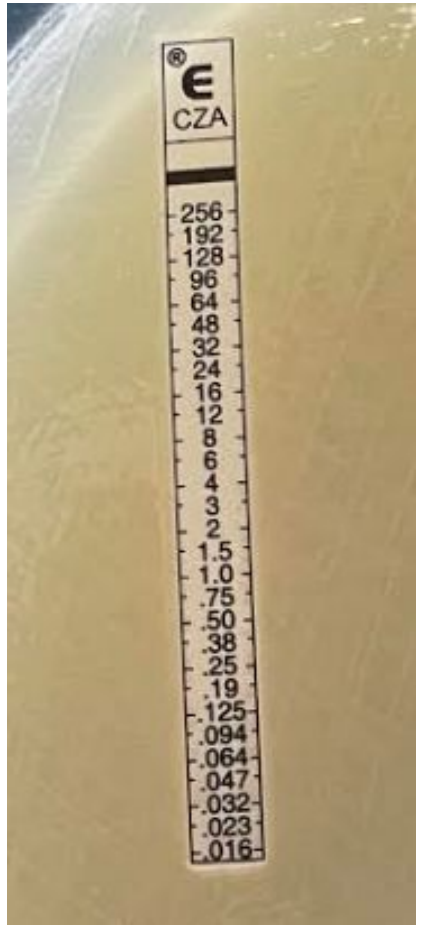
WE ALSO BREED THIS…. (#H2P)

61 y/o male with **NDM-5** *E. coli* bacteremia (YRIN insertion)

CAZ-AVI + ATM MIC increased from 16 to >256 after therapy

WGS of both isolates revealed an additional mutation in PBP3 (A417V)





METALLO-BETA-LACTAMASE SUMMARY

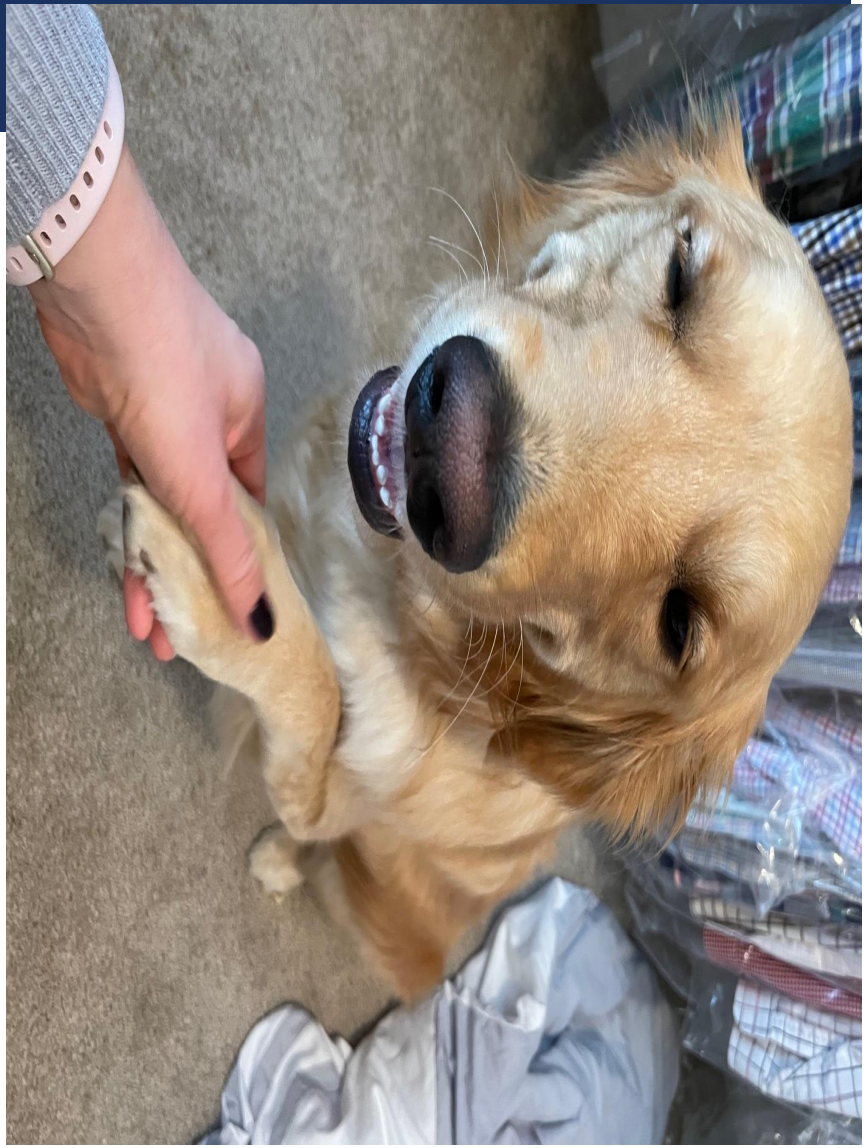
Aztreonam alone *might* work	Watch those automated panels; genotypic testing
Ceftazidime-avibactam plus aztreonam has some clinical data to support use (prolong those infusions!!)	Confirm susceptibility, especially for NDM I-R-ATM and MVB-ATM may also display *in vitro* synergy; no clinical data
Cefiderocol is a reasonable option	CREDIBLE-CR Clinical Cure: **75%** (12/16) FDC vs **29%** (2/7) BAT Higher MICs for NDMs
Non-β-lactam options, if *in vitro* susceptible (TMP/SMX, FQs, tetracyclines, etc)	
New BLIs on the horizon	

REACHING OUT AND RECOMMENDING SYNERGY

Hi friend!
Curious on your thoughts for this Steno. Critically ill patient who has been hospitalized for many months initially with Steno ?VAP vs colonization but now Steno CLABSI. Plan will be to remove his PICC.

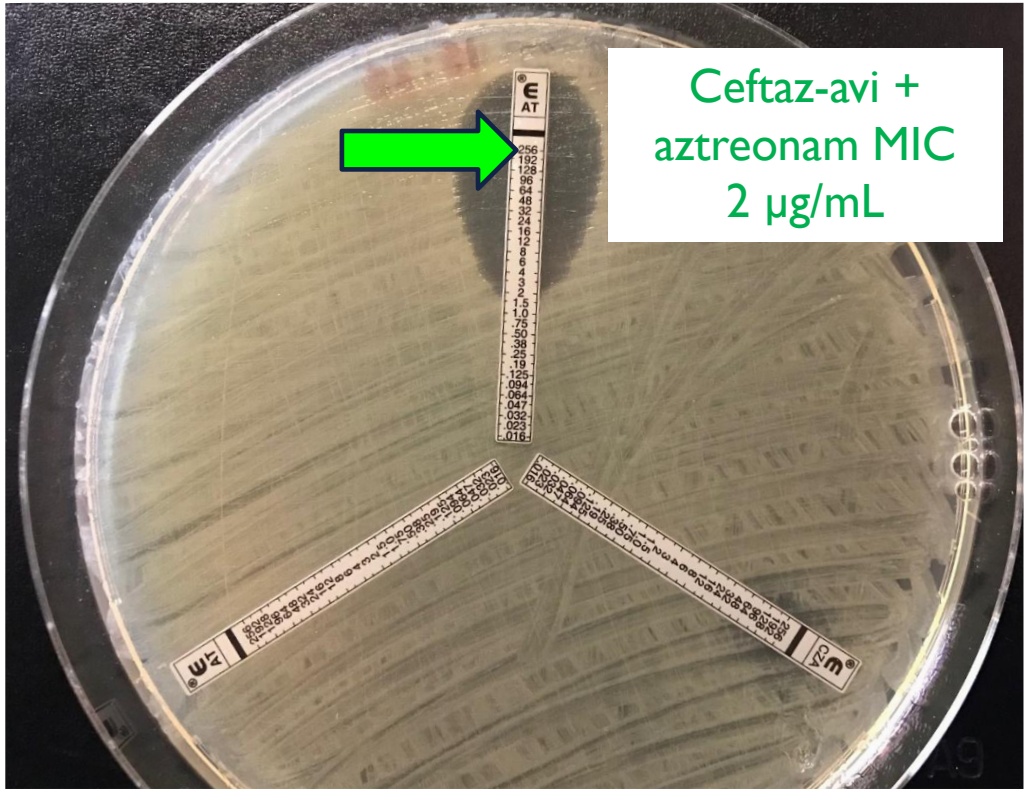
We were planning high-dose mino + Levo for now. I was going to request cefiderocol MICs, but don't love the idea given low albumin and high-protein binding.

Wasn't sure when to pull the trigger on ceftaz/avi + aztreo



STENOTROPHOMONAS MALTOPHILIA

Aztreonam MIC
>256 µg/mL



Ceftaz-avi MIC
256 µg/mL

OTHER FUN NON-FERMENTERS

TABLE 1 Activities of β-lactam–β-lactamase inhibitor antimicrobial agents and comparators against bacterial strains

Species or group (no. of isolates)	Antimicrobial agent	MIC (μg/ml) Range	MIC_{50}	MIC_{90}	% Susceptible[a]
Achromobacter (100)	Ceftazidime	1 to >32	8	32	71
	Ceftazidime-avibactam	1 to >32	8	32	78
	Ceftolozane-tazobactam	≤0.5 to >32	>32	>32	1
	Meropenem	≤0.5 to >32	1	>32	72
	Meropenem-vaborbactam	≤0.5 to 32	≤0.5	8	86
	Piperacillin-tazobactam	≤2 to >128	≤2	128	87
Burkholderia cepacia complex (150)	Ceftazidime	≤0.5 to >32	4	8	91
	Ceftazidime-avibactam	≤0.5 to >32	4	4	97
	Ceftolozane-tazobactam	≤0.5 to >32	1	8	89
	Meropenem	≤0.5 to >32	2	4	90
	Meropenem-vaborbactam	≤0.5 to >32	1	2	97
	Piperacillin-tazobactam	≤2 to >128	4	64	85
Burkholderia gladioli (50)	Ceftazidime	4 to >32	16	32	20
	Ceftazidime-avibactam	2 to >32	16	16	24
	Ceftolozane-tazobactam	2 to >32	16	32	12
	Meropenem	≤0.5 to 4	1	2	100
	Meropenem-vaborbactam	≤0.5 to 4	1	2	100
	Piperacillin-tazobactam	≤2 to 4	≤2	≤2	100
Stenotrophomonas maltophilia (100)	Ceftazidime	≤0.5 to >32	32	>32	34
	Ceftazidime-avibactam	≤0.5 to >32	16	>32	40
	Ceftolozane-tazobactam	≤0.5 to >32	32	>32	27
	Meropenem	≤0.5 to >32	>32	>32	11
	Meropenem-vaborbactam	≤0.5 to >32	>32	>32	12
	Piperacillin-tazobactam	≤2 to >128	128	>128	18
Pandoraea (20)	Ceftazidime	>32	>32	>32	0
	Ceftazidime-avibactam	>32	>32	>32	0
	Ceftolozane-tazobactam	>32	>32	>32	0
	Meropenem	32 to >32	>32	>32	0
	Meropenem-vaborbactam	32 to >32	>32	>32	0
	Piperacillin-tazobactam	8 to >128	64	>128	5

[a]Susceptibility based on CLSI breakpoints established for *Pseudomonas aeruginosa* as follows: ceftazidime, ≤8 μg/ml; ceftazidime-avibactam, ≤8 μg/ml; ceftolozane-tazobactam, ≤4 μg/ml; meropenem, ≤4 μg/ml; meropenem-vaborbactam, ≤4 μg/ml; piperacillin-tazobactam, ≤16 μg/ml.

Caverly LJ, et al. AAC. 2020.

THERE'S ALWAYS THOSE UNIQUE TIMES FOR BLBLIS, TOO!

Pt was to be changed from ceftazidime-avibactam to ceftolozane-tazobactam on [redacted] but received the ceftazidime-avibactam and then developed an erythematous rash over her face and neck. No respiratory distress or mouth swelling. The infusion was stopped. Today she reports improvement in the facial rash. Still with urticarial rash on upper legs. Nonpruritic. No other fevers, chills, or NS. Has ongoing drainage into pouch from the subincisional collection.

Agree with graded challenge to ceftolozane-tazobactam. If tolerates then can give 3gm IV q8h. If there is another drug reaction then options to treat this CRO-Pseudomonas are very limited. Aminoglycoside therapy typically not considered as first line agent or for monotherapy; pt would also be at risk for nephrotoxicity and ototoxicity. Risks may outweigh the benefits of treatment as pt is otherwise clinically improving. If pt does tolerate ceftolozane-tazobactam then would be ideal to treat for a short course since the subincisional collection is continuing to drain through the skin, and to avoid the risk of developing further antibiotic resistance.

Subincisional abscess with drainage through skin
Presence of CRO-Pseudomonas
Levofloxacin allergy
Ceftazidime-avibactam allergy

cefTAZidime-avibactam	ceftolozane-tazobactam
	3 gm IV
	3 gm IV
	3 gm IV
	3 gm IV
	3 gm IV
	3 gm IV
	300 mg IV Push
2.5 gm IV	

CEFTOLOZANE/TAZOBACTAM AND IMIPENEM/RELEBACTAM

55 y/o female with NICM s/p LVAD with recurrent driveline infections and bacteremia due to MDR *P. aeruginosa* following exposures to β-lactams

PSEUDOMONAS AERUGINOSA

	MIC (mcg/mL)	MIC Interpretation
Amikacin	<=16	Sensitive
Aztreonam	>16	Resistant
Cefepime	>16	Resistant
Ceftazidime	>16	Resistant
Ciprofloxacin	<=1	Sensitive
Gentamicin	4	Sensitive
Levofloxacin	0.5	Sensitive
Meropenem	<=1	Sensitive
Piperacillin/Tazobactam	>64	Resistant
Tobramycin	<=1	Sensitive

Lots of prior exposures

Meropenem x 8 days

PSEUDOMONAS AERUGINOSA

	MIC (mcg/mL)	MIC Interpretation	
Amikacin	<=16	Sensitive	
Aztreonam	16	Intermediate	
CEFTOLOZANE-TAZOBACTAM	2		Sensitive
Cefepime	16	Intermediate	
Ceftazidime	16	Intermediate	
Ciprofloxacin	2	Intermediate	
Gentamicin	4	Sensitive	
Levofloxacin	4	Intermediate	
Meropenem	>8	Resistant	
Piperacillin/Tazobactam	64	Intermediate	
Tobramycin	<=1	Sensitive	

TOL-TAZ x 8 weeks

PSEUDOMONAS AERUGINOSA

	MIC (mcg/mL)	MIC Interpretation	KB Interpretation
Amikacin	32	Intermediate	
Aztreonam	>16	Resistant	
CEFTAZIDIME/AVIBACTAM	>256		Resistant
CEFTOLOZANE-TAZOBACTAM	>256		Resistant
Cefepime	16	Intermediate	
Ceftazidime	>16	Resistant	
Ciprofloxacin	>2	Resistant	
Gentamicin	>8	Resistant	
IMIPENEM RELEBACTAM			Sensitive
Levofloxacin	>4	Resistant	
Meropenem	>8	Resistant	
Piperacillin/Tazobactam	16	Sensitive	
Tobramycin	4	Sensitive	

Rubio AM, et al. AAC. 2021.
Slide adapted from Ryan Shields

PSEUDO RESISTANCE IS WILD

SIDP | SOCIETY OF INFECTIOUS DISEASES PHARMACISTS

Pseudomonas aeruginosa Resistance to Beta-lactams

Note: Chart is meant as a general teaching tool for common and advanced mechanisms of antimicrobial resistance (AMR).
Resistance in *P. aeruginosa* is complex and various mechanisms may be simultaneously present, impacting *in vitro* activity of each agent.

Minimally impacted by AMR mechanism
Heavily impacted by AMR mechanism R=Resistant
Some AMR impact
Possible association

		Porin Channels	Efflux Pumps	AmpC	Carbapenemases (Minor AMR contributor)
Standard Agents	Ceftazidime	↑ MIC Loss of OprF	↑ MIC or R Upregulated MexAB-OprM		
	Cefepime	↑ MIC Loss of OprF	↑ MIC or R Upregulated MexAB-OprM, MexXY-OprM, MexCD-OprJ	↑ MIC or R Overexpression	
	Piperacillin-Tazobactam	↑ MIC Loss of OprF	↑ MIC or R Upregulated MexAB-OprM		
	Imipenem	R Loss of OprD		↑ MIC Overexpression	
	Meropenem	↑ MIC Loss of OprD	↑ MIC or R Upregulated MexAB-OprM & MexXY-OprM		
MDR Agents	Ceftazidime-Avibactam	↑ MIC Loss of OprF	↑ MIC or R Upregulated MexAB-OprM	↑ MIC or R AmpC mutants	Inhibits some carbapenemases rarely found in PsA, does not inhibit MBL
	Ceftolozane-Tazobactam			↑ MIC or R AmpC mutants	
	Imipenem-Relebactam		↑ MIC or R (Relebactam only) Upregulated MexAB-OprM & MexEF-OprN		Inhibits some carbapenemases rarely found in PsA, does not inhibit MBL
	Meropenem-Vaborbactam	↑ MIC Loss of OprD	↑ MIC or R Upregulated MexAB-OprM & MexXY-OprM		Inhibits some carbapenemases rarely found in PsA, does not inhibit MBL
	Cefiderocol	↑ MIC Mutation of Iron Transport system		↑ MIC or R AmpC mutants	Active vs KPC, MBL, GES ↑ MIC for NDM

SIDP Breakpoints Podcast Episode #59 Resistance in *P. aeruginosa*: Pearls & Perils - Hosted by Dr. Erin McCreary, featuring Drs. Maggie Monogue and Antonio Oliver

Check out Ryan Shields tomorrow at 10:05am!

PSEUDOMONAS SUMMARY

- Ceftolozane-tazobactam (C/T) vs. ceftazidime-avibactam (CZA) vs. imipenem-relebactam (I-R) decision should be based on local epidemiology
  - No comparative effectiveness data (but look out for it! )
  - Give over 3h infusion (except imipenem)

- C/T and I-R have comparative clinical data to support they are more effective and less toxic than polymyxins or aminoglycosides; outcomes are better if started earlier

- Cefiderocol an option if all 3 BLBLIs are resistant

USING OLDER, MORE TOXIC DRUGS MAKES US SAD

THERE'S STILL A LOT TO LEARN

BLBLIs have saved lives, are cost effective when you look at the comprehensive care picture, and we're very happy about that