Treatment *of Pseudomonas aeruginosa* Infections

Whitney Hartlage, PharmD

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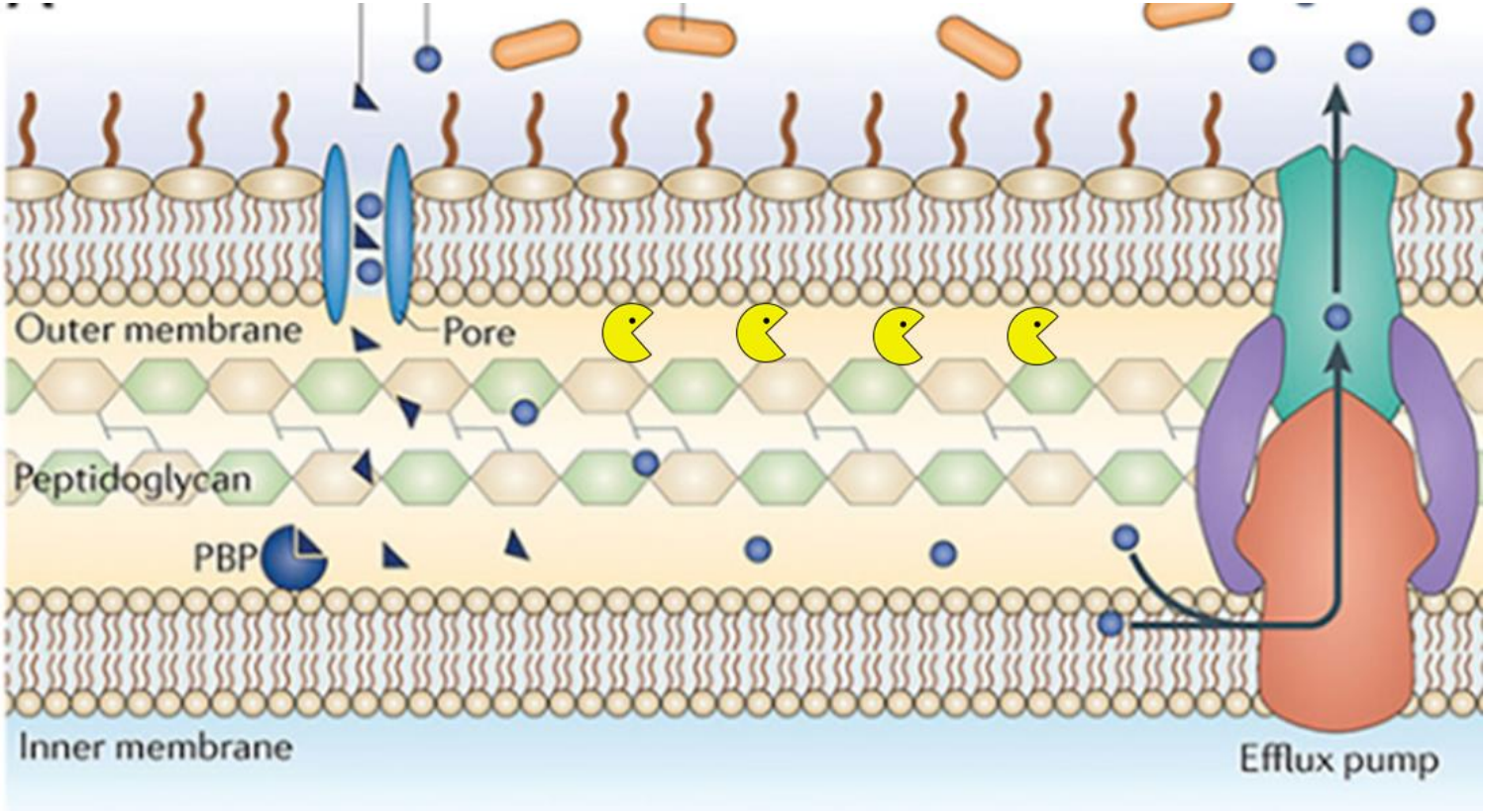
Disclosures

I have no financial relationships with an ineligible company relevant to this presentation to disclose.

None of the planners have relevant financial relationship(s) to disclose with ineligible companies whose primary business is producing, marketing, selling, re-selling, or distributing healthcare products used by or on patients

Visual of GNR Resistance



1) Reduction in membrane porins (decreased entry)
2) Upregulation of efflux pumps (increased exit)
3) Increased production of Pseudomonal AmpCs (beta-lactamases)
4) Target site modifications (eg, PBPs)

= beta-lactamase

Susceptible *P. aeruginosa* Infections

Clinical Case

- 65 yo male with metastatic colon cancer and a tunnel central venous catheter for chemotherapy
- Transfer from OSH – initially presented with fever, rigors, and has no localizing symptoms
  - Temp 39C, WBC 14, Scr 0.9, ANC 654
  - Hemodynamically stable
- Blood cx from OSH – *Pseudomonas aeruginosa*
  - No resistance markers detected, sensi pending
- OSH initiated empiric meropenem and tobramycin

Clinical Case

Would you continue combination therapy in this situation?

- Yes
- No

Clinical Case

What is the role of combination therapy for *P. aeruginosa*?

- Empiric; increase likelihood of at least 1 active agent
- Definitive therapy; attack *P. aeruginosa* from two different mechanisms
- Definitive therapy; decrease risk of resistance
- Definitive therapy; identified survival advantage

Combination Therapy for *P. aeruginosa* Bacteremia? Consider MDR History and Severity

- Role: empirically; increase likelihood of at least one active agent
  - History of MDR
  - Severe illness
- Let antibiogram guide empiric therapy
- Definitive therapy?
  - Synergy data (all in vitro) suggests maybe(?), BUT
  - Once in vitro activity demonstrated, no benefit with combo over mono has been demonstrated clinically with high-quality data and increases risk of harm

2025 Antibiogram at UW Medicine for *P. aeruginosa* (% susceptible)

	HMC	ML	NW
Cefepime	95	94	95
Ceftazidime	93	93	97
Meropenem	91	93	92
Pip/tazo	89	90	95

Tamma PD, et al. Clin Infect Dis. 2024.
Tamma PD. Et al. Clin Microbiol Rev. 2012.

Clinical Case

What is the role of combination therapy for *P. aeruginosa*?

- **Empiric; increase likelihood of at least 1 active agent**
- Definitive therapy; attack *P. aeruginosa* from two different mechanisms
- Definitive therapy; decrease risk of resistance
- Definitive therapy; identified survival advantage

Clinical Case

- Blood culture: *Pseudomonas aeruginosa*
- Sensi results now available from OSH (*they don't report MICs*)

Antibiotic	Interpretation
Aztreonam	**S**
Ceftazidime	**S**
Cefepime	**S**
Levofloxacin	**S**
Meropenem	**S**
Piperacillin/tazobactam	**S**
Tobramycin	**S**

Clinical Case

Bacteremia with susceptible *P. aeruginosa*

Which of the following would you select for this case?

- Continue meropenem 1g IV q8h + tobramycin 7mg/kg IV q24h
- Meropenem monotherapy at 1g IV q8h
- Ceftazidime monotherapy at 2g IV q8h
- Pip/tazo monotherapy at 3g IV q8h

Definitive IV Therapy for Susceptible *P. aeruginosa* Bacteremia: Ceftazidime or Piperacillin > Carbapenem

Factors to consider when selecting one agent over another

1) **Is there a beta-lactam more clinically effective than another?**
   - No difference with carbapenem vs pip/tazo vs ceftazidime[1]

2) **Is there a difference in treatment-emergent resistance from one beta-lactam to another?**
   - Isolation of *P. aeruginosa* with new resistance to antipseudomonal drugs more frequent with carbapenems (17.5%) vs ceftazidime (12.4%) and pip/tazo (8.4%), p=0.007[1]

3) **Difference in adverse events?**
   - No difference in renal failure, *C. difficile* infection, seizures[1]

4) **Are MIC values close to breakpoint?**
   - Use high-dose, extended-infusion regimens to optimize time > MIC[2]

1) Babich, et al. *Clin Infect Dis.* 2020.
2) Tamma PD, et al. Clin Infect Dis. 2024.

How does the MIC help you?

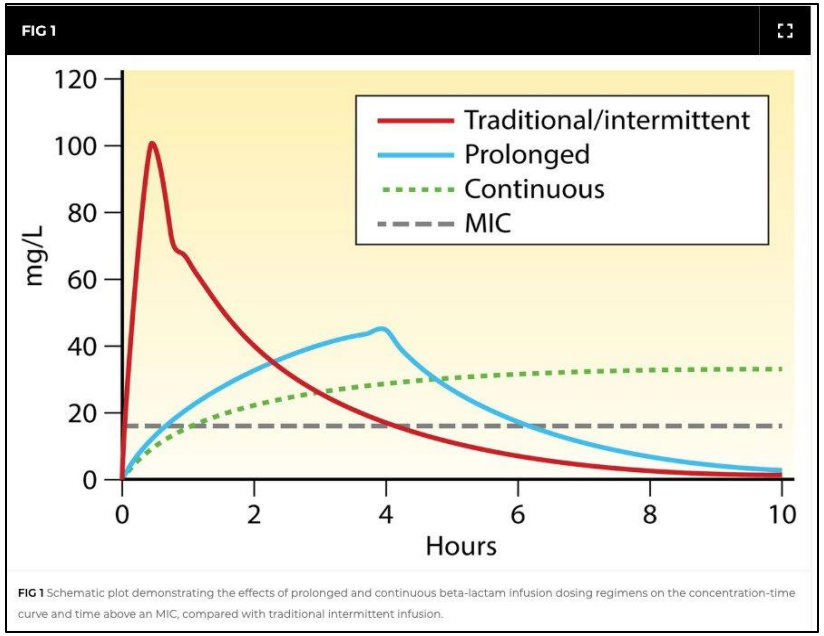
Antibiotic	MIC (mcg/ml)	Interpretation	Breakpoint MIC (mcg/ml) *P. aeruginosa*
Aztreonam	4	S	≤8
Ceftazidime	2	S	≤8
Cefepime	4	S	≤8
Levofloxacin	1	S	≤1
Meropenem	2	S	≤2
Piperacillin/tazobactam	16	S	≤16
Tobramycin	1	S	≤1

A quick reference guide of CLSI breakpoints was created by Antimicrobial Stewardship for the most common organisms and can be viewed here.
https://em100.edaptivedocs.net/GetDoc.aspx?doc=CLSI%20M100%20ED35:2025&scope=user

Prolonged Infusion Beta-Lactams in *P. aeruginosa* Infections Optimizes Time > MIC

- Recommended for "Difficult to treat *P. aeruginosa*"[1]

- International recommendations endorsed by ACCP, BSAC, CFF, ESCMID, IDSA, ASM, and SIDP recommend[2]:
  - "Prolonged infusion beta-lactams over standard infusion to reduce mortality and increase clinical cure among severely ill adult patients, particularly those with gram-negative infections – emphasizing the strongest evidence is for critically ill patients."



Slide credit: Frank Tverdek

ACCP: American College of Clinical Pharmacy; BSAC: British Society for Antimicrobial Therapy; ESCMID: European Society of Clinical Microbiology and Infectious Diseases; ASM: American Society for Microbiology; SIDP: Society of Infectious Diseases Pharmacist

1) Tamma PD, et al. Clin Infect Dis. 2024.
2) Hong LH, et al. Pharmacotherapy. 2023.

Clinical Case

Bacteremia with susceptible *P. aeruginosa*

Which of the following would you select for this case?

- Still continue meropenem 1g IV q8h + tobramycin 7mg/kg IV q24h – **susceptibilities are known, transition to monotherapy**
- Meropenem monotherapy at 1g IV q8h – **reach for other beta-lactams**
- **Ceftazidime monotherapy at 2g IV q8h**
- Pip/tazo monotherapy at 3g IV q8h – **dosing incorrect**

Same Clinical Case, Different Susceptibility Profile

- Blood culture: *Pseudomonas aeruginosa*
- Sensi results now available with MIC data*:*

Antibiotic	MIC (mcg/mL)	Interpretation
Aztreonam	**4**	**S**
Ceftazidime	**2**	**S**
Cefepime	**4**	**S**
Levofloxacin	**1**	**S**
Meropenem	**4**	**R**
Piperacillin/tazobactam	**16**	**S**
Tobramycin	**1**	**S**

Clinical Case

Bacteremia with meropenem resistance; pip/tazo, ceftazidime, and cefepime susceptible *P. aeruginosa*

Which of the following would you select for this case?

- Switch to Tobramycin 7mg/kg IV q24h
- Switch to Ceftazidime 2g IV q8h, infused over 3 hr
- Switch to Pip/tazo 4.5g IV q6h, infused over 4 hr
- Switch to Ceftolozane-tazobactam 3g IV q8h, infused over 3 hr

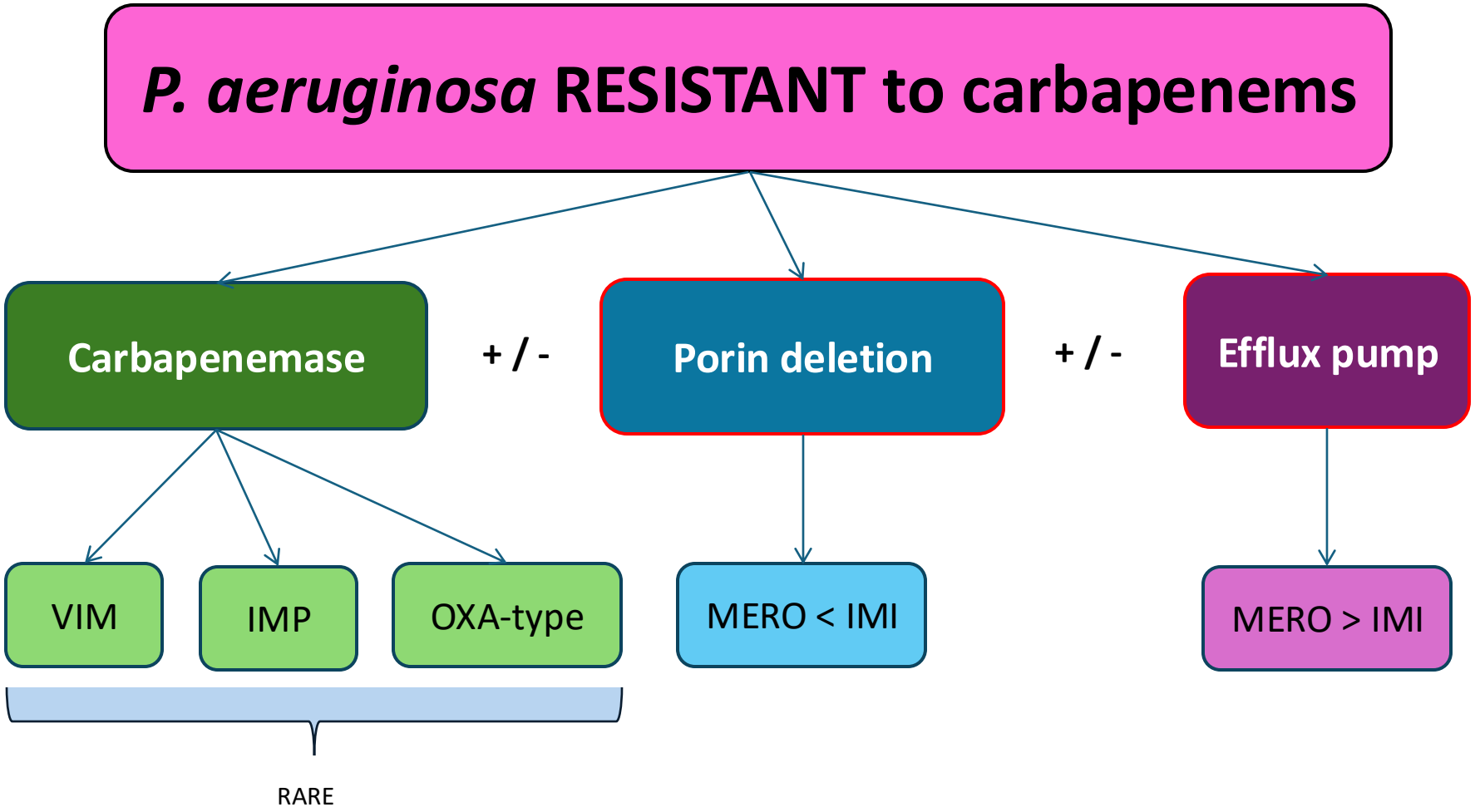
Clinical Case

***P. aeruginosa* with carbapenem resistance**

What is the most likely mechanism of resistance?

- Carbapenemase
- Porin deletion +/- efflux pump
- Both

Mechanism of Resistance



Slide credit: Frank Tverdek

Carbapenem-resistant *P. aeruginosa* isolates susceptible to other traditional β-lactam agents is common

- About 20-60% of carbapenem-resistant *P. aeruginosa*
- OprD porin facilitates carbapenem entry, but not other β-lactams
- Recommendation: if isolate is susceptible to non-carbapenem β-lactam (eg, cefepime), administer that agent as high-dose, extended infusion
  - Alternative: administer newer β-lactam agents (eg, ceftolozane-tazobactam)

Tamma PD, et al. Clin Infect Dis. 2024.

Clinical Case

Bacteremia with meropenem resistance; pip/tazo, ceftazidime, and cefepime susceptible *P. aeruginosa*

Which of the following would you select for this case?

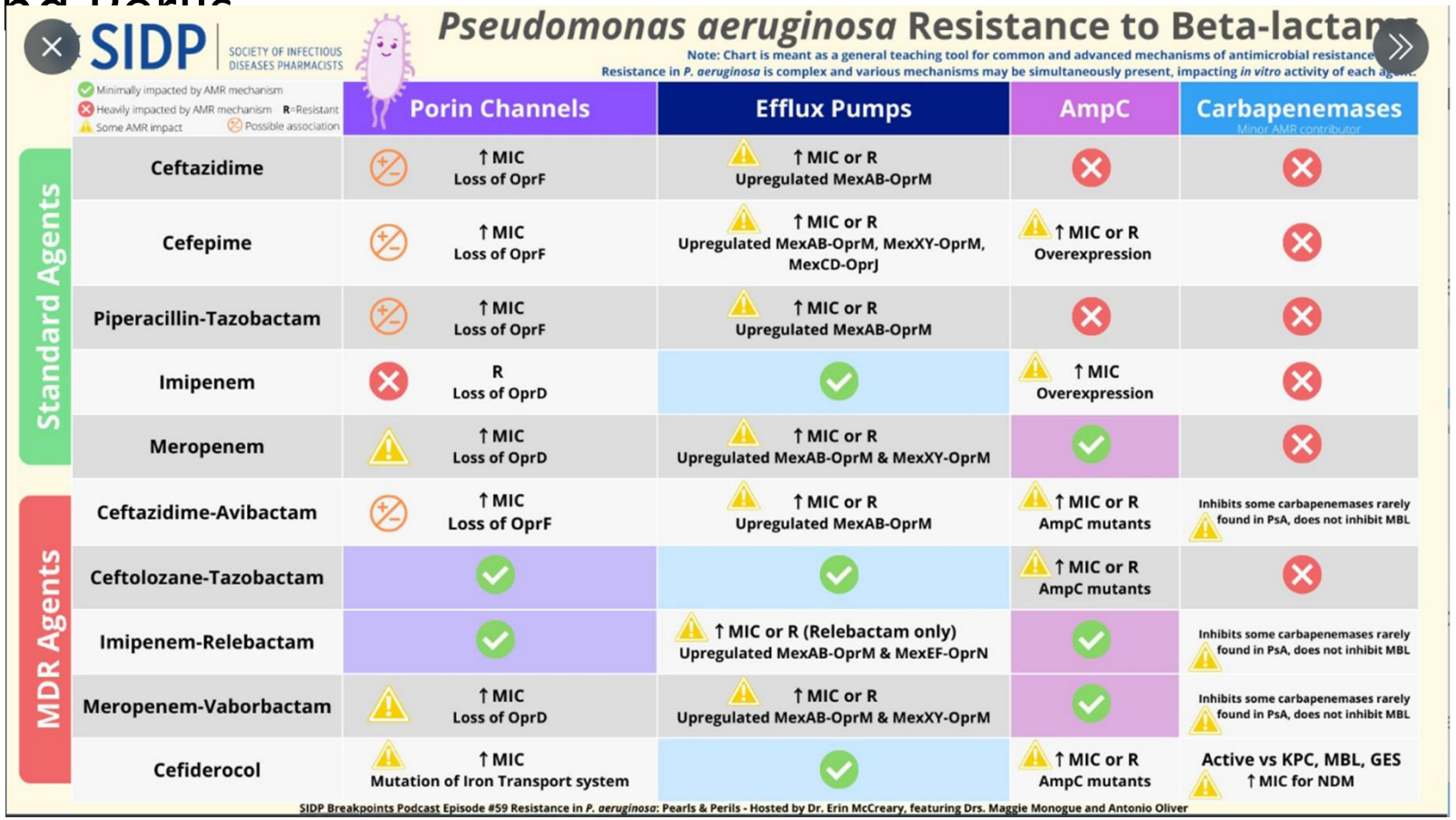
- Tobramycin 7mg/kg IV q24h – **not recommended**
- **Switch to Ceftazidime 2g IV q8h, infused over 3 hr**
- Switch to Pip/tazo 4.5g IV q6h, infused over 4 hr – **MIC near breakpoint (16)**
- Switch to Ceftolozane-tazobactam 3g IV q8h, infused over 3 hr – **Alternative**

Resistance phenotype	Suggested therapy	Rationale
Pan susceptible Pseudomonas	Cystitis: • Tobramycin IV x once • Ceftazidime or Cefepime • Cipro or Levo as oral option Outside of urinary tract: • Ceftazidime or Cefepime (prolonged infusion if feasible) • Cipro or Levo as oral option	Carbapenem leads to more resistance
R to meropenem or imipenem, but S to ceftazidime or cefepime	Use cephalosporin prolonged infusion	Most common carbapenem resistance mechanisms (porin/efflux) do not affect cephalosporins
DTR (or concern MDRO)	Ceftolozane-tazobactam	Bulky side chain of ceftolozane-tazobactam more likely to be effective

Slide credit: Jeannie Chan

Helpful Resources

- SIDP Breakpoints Podcast: Resistance in Pseudomonas aeruginosa: Pearls and Perils



Thank you!

- Whithart@uw.edu

Antimicrobial Agent	Disk Content	Interpretive Categories and Zone Diameter Breakpoints, Nearest Whole mm			Interpretive Categories and MIC Breakpoints, µg/mL		
		S	I	R	S	I	R
PENICILLINS							
Piperacillin*	100 µg	≥ 22	18–21^	≤ 17	≤ 16	32^	≥ 64
β-LACTAM COMBINATION AGENTS							
(7) Organisms that test susceptible to the β-lactam agent alone are also considered susceptible to t organisms that test susceptible to the β-lactam combination agent cannot be assumed to be suscep organisms that test intermediate or resistant to the β-lactam agent alone may be susceptible to the							
Piperacillin-tazobactam	100/10 µg	≥ 22	18–21	≤ 17	≤ 16/4	32/4	≥ 64/4
Ceftazidime-avibactam	30/20 µg	≥ 21	–	≤ 20	≤ 8/4	–	≥ 16/4
Ceftolozane-tazobactam	30/10 µg	≥ 21	17–20^	≤ 16	≤ 4/4	8/4^	≥ 16/4
Imipenem-relebactam	10/25 µg	≥ 23	20–22^	≤ 19	≤ 2/4	4/4^	≥ 8/4
Ticarcillin-clavulanate*	75/10 µg	≥ 24	16–23^	≤ 15	≤ 16/2	32/2–64/2^	≥ 128/2
CEPHEMS (PARENTERAL) (Including cephalosporins I, II, III, and IV. Please refer to Glossary I.)							
Ceftazidime	30 µg	≥ 18	15–17^	≤ 14	≤ 8	16^	≥ 32
Cefepime	30 µg	≥ 18	15–17^	≤ 14	≤ 8	16^	≥ 32
Cefiderocol	30 µg	≥ 18	13–17^	≤ 12	≤ 4	8^	≥ 16

Antimicrobial Agent	Disk Content	Interpretive Categories and Zone Diameter Breakpoints, Nearest Whole mm			Interpretive Categories and MIC Breakpoints, µg/mL		
		S	I	R	S	I	R
MONOBACTAMS							
Aztreonam	30 µg	≥ 22	16–21^	≤ 15	≤ 8	16^	≥ 32
CARBAPENEMS							
Doripenem*	10 µg	≥ 19	16–18^	≤ 15	≤ 2	4^	≥ 8
Imipenem	10 µg	≥ 19	16–18^	≤ 15	≤ 2	4^	≥ 8
Meropenem	10 µg	≥ 19	16–18^	≤ 15	≤ 2	4^	≥ 8

Antimicrobial Agent	Disk Content	Interpretive Categories and Zone Diameter Breakpoints, Nearest Whole mm			Interpretive Categories and MIC Breakpoints, µg/mL		
		S	I	R	S	I	R
FLUOROQUINOLONES							
Ciprofloxacin	5 µg	≥ 25	19–24^	≤ 18	≤ 0.5	1^	≥ 2
Levofloxacin	5 µg	≥ 22	15–21^	≤ 14	≤ 1	2^	≥ 4

Symbols: ^, designation for agents that have the potential to concentrate in the urine; *, designation for “Other” agents that are not included in Tables 1 but have established clinical breakpoints.