Pseudomonas aeruginosa: Declassified

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Disclosures

I attest that I have no relevant interests, financial or otherwise, pertaining to this presentation

At the conclusion of this presentation, the learner will be able to…

- Recognize risk factors for infection with *Pseudomonas aeruginosa*
- Explain the mechanism of action of antimicrobials targeting *P. aeruginosa*
- Interpret susceptibility and resistance patterns of *P. aeruginosa*
- Describe treatment options when resistance in *P. aeruginosa* is present

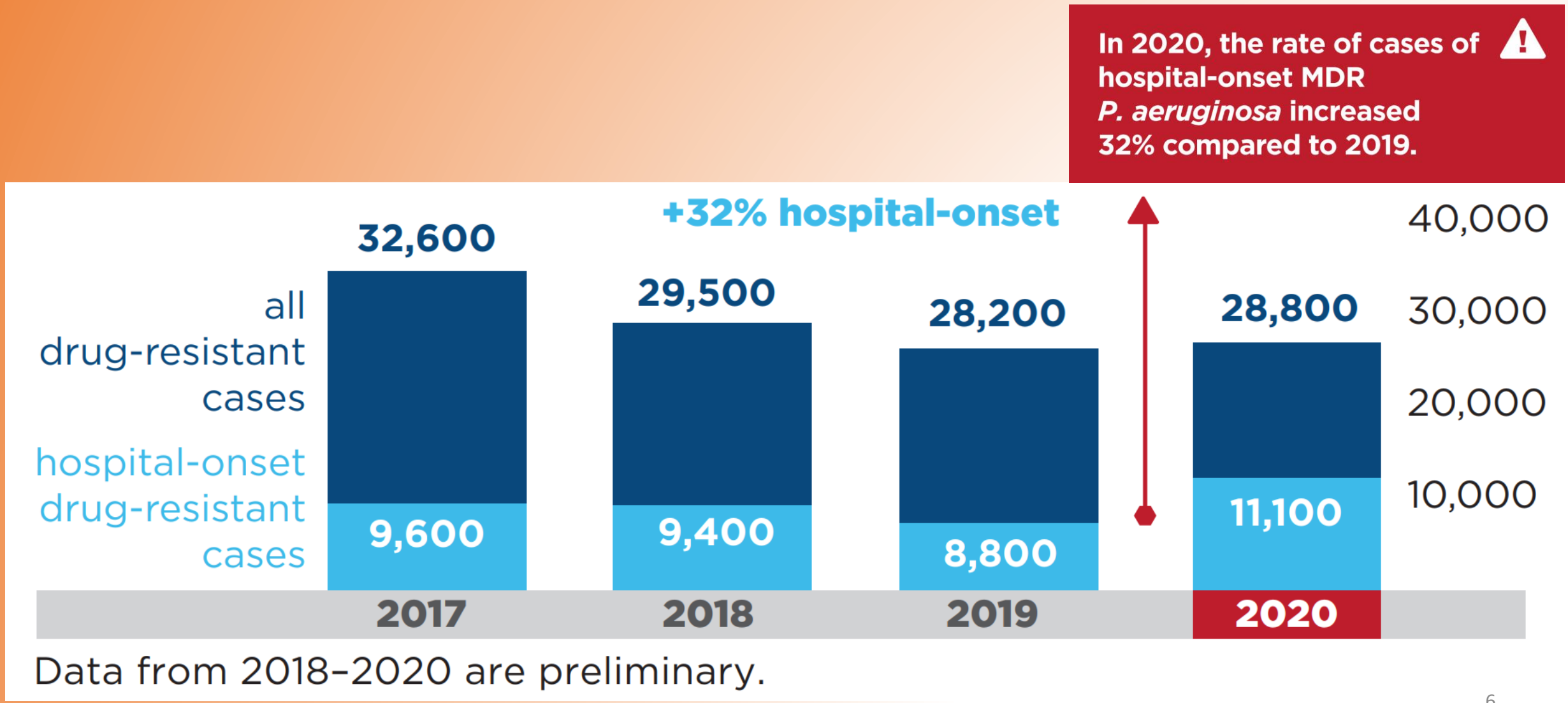
VC is an 81-year-old female presenting to the emergency department complaining of high-grade fevers and general malaise for the past four days

- PMH: Hypertension, hyperlipidemia, osteoporosis
- Social history: Drinks 1 glass of wine with dinner daily. Denies tobacco or illicit drug use. Retired elementary school teacher.
- VS: HR 106bpm | RR 22bpm | T 102.1°F | BP 87/53mmHg | SpO_2 98% RA
- WBC: 12.7cells/mm^3 | Lactic Acid: 2.4mmol/L

A sepsis alert is called for this patient. What is appropriate empiric therapy?

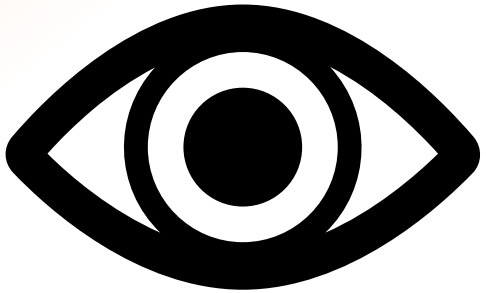
Multidrug-Resistant *Pseudomonas aeruginosa*. Centers for Disease Control and Prevention. 2019

MDR *P. aeruginosa* Cases 2017 – 2020



Outbreak of Extensively Drug-Resistant *Pseudomonas aeruginosa* Associated with Artificial Tears

- As of May 15, 2023, 81 patients across 18 states were infected with a rare strain of extensively drug-resistant (XDR) *Pseudomonas aeruginosa*
- Traced to several brands of artificial tears and eye ointments
  - Recalled in February of 2023



Centers for Disease Control and Prevention May 18, 2023; Accessed September 19, 2023

Background

What is *Pseudomonas aeruginosa* (*P. aeruginosa*)?

- Gram-negative, glucose-nonfermenting rod
- Lives in the soil and aquatic environments
- Antibiotic resistance is common
- Often implicated in nosocomial infections
- Common infection sites include the urinary tract, the bloodstream, the lungs, bones/joints, and skin/soft tissues

Bouglé et al. *Intensive Care Med*. 2022
Botelho et al. *Drug Resist Updat*. 2019
Pang et al. *Biotechnol Adv*. 2019
Maraolo et al. *Int J antimicrobe Agents*. 2020

Risk Factors

Who is at risk of *P. aeruginosa* urinary tract infection?

Patient Characteristics		*P. aeruginosa* UTI (N=525)	Non-*P. aeruginosa* UTI (N=2727)	P-Value
Sex Ratio (M/F)		2	0.9	<0.01
Age (year)		64.5 (17.3)	63.8 (16.6)	NS
SAPS II Score		57.6 (93.8)	53.9 (85.1)	NS
Duration of ICU stay before UTI (days)		23.5 (12.9)	15.2 (14.7)	<0.01
Duration of urinary catheterization before UTI (days)		22.2 (18.4)	14.2 (14.1)	0.01
Origin				
	No hospitalization before admission – n (%)	262 (50%)	1473 (55%)	-
	Medical surgical unit – n (%)	214 (41%)	1088 (40%)	NS
	ICU – n (%)	45 (9%)	139 (5%)	<0.05

NS: Not significant Data are presented as mean (standard deviation) unless otherwise noted

Venier et al. *Clin Microbiol Infect*. 2012

Who is at risk of *P. aeruginosa* urinary tract infection?

Patient Characteristics		*P. aeruginosa* UTI (N=525)	Non-*P. aeruginosa* UTI (N=2727)	P-Value
Antibiotic Exposure at ICU Admission		351 (67%)	1444 (54%)	<0.05
Trauma patient		62 (12%)	370 (13%)	NS
Type of diagnosis				
	Medical	358 (68%)	1940 (71%)	NS
	Surgical	166 (32%)	774 (29%)	
Immunodeficiency		458 (12%)	2383 (11%)	NS
Urinary catheterization before UTI		517 (98%)	2676 (98%)	NS

NS: Not significant

Data are presented as n (%) unless otherwise noted

Venier et al. *Clin Microbiol Infect*. 2012

Who is at risk of *P. aeruginosa* urinary tract infection?

- Presence of an indwelling urinary catheter
- Increased length of hospital stay
- Previous antibiotic therapy in preceding 30 days
- ICU admission

Hooton et al. *Clin Infect Dis*. 2010
Venier et al. *Clin Microbiol Infect*. 2012
Gomila A, et al. *Infect Drug Resist*. 2018;11:2571-2581.

Who is at risk of *P. aeruginosa* bacteremia?

Risk Factor	Bacteremia Due to *P. aeruginosa* (n=15)	Bacteremia NOT Due to *P. aeruginosa* (n=325)	Total Number (%)	P-value
Hospitalization Within Previous 4 Weeks	7 (46.6%)	63 (19.3)	70 (20.6)	0.01
Invasive Procedure Within Previous 4 Weeks	3 (20%)	9 (2.7%)	12 (3.5%)	0.01
Surgery Within Previous 4 Weeks	3 (20%)	3 (0.9%)	6 (1.%)	0.001
Community-Onset Bacteremia	5 (33.3%)	271 (83.3%)	276 (81.2%)	<0.001
Febrile Neutropenia	2 (13.3%)	4 (1.2%)	6 (1.8%)	0.02
Malignancy	8 (53.3%)	79 (24.3%)	87 (25.6%)	0.02

Data are presented as n (%) unless otherwise noted

Lee et al. *Am J Emerg Med*. 2012

Who is at risk of *P. aeruginosa* bacteremia?

- Presence of a central venous catheter
- Previous antibiotic therapy within the previous 30 days
- Previous bloodstream infection
- Malignancy
- Recent surgery or invasive procedure

Tumbarello et al. *Epidemiol Infect*. 2011
Lee et al. *Am J Emerg Med*. 2012

Who is at risk of *P. aeruginosa* nosocomial pneumonia?

Patient Characteristics	*P. aeruginosa* pneumonia (N=967)	Non-*P. aeruginosa* Pneumonia (N=2870)	P-value
Sex ratio (M/F)	2.1	2.3	NS
Age (years)	64.2 (16)	60.5 (18.2)	<0.01
SAPS II score	49.6 (17.8)	47.7 (18.3)	<0.01
Length of ICU stay before onset of pneumonia (days)	14.8 (12.9)	10.8 (11.7)	<0.01
Duration of mechanical ventilation before onset of pneumonia (days)	13.7 (12.3)	9.7 (9.4)	<0.01
Number of reintubations before onset of pneumonia	0.8 (1.6)	0.6 (1.0)	<0.01
Origin			
Number of hospitalizations before admission – n (%)	452 (47%)	1647 (57%)	-
Medical unit – n (%)	434 (45%)	1077 (38%)	<0.01
ICU – (%)	80 (8%)	144 (5%)	<0.01

Data are presented as mean (standard deviation) unless otherwise noted

Venier et al. *J Hosp Infect*. 2011

Who is at risk of *P. aeruginosa* nosocomial pneumonia?

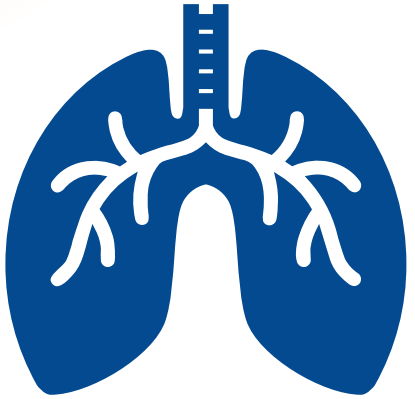
Patient Characteristics		Patient with *P. aeruginosa* pneumonia (N=967)	Patient with non-*P. aeruginosa* pneumonia (N=2870)	P-value
Antibiotics at admission		720 (75%)	1609 (57%)	<0.01
Traumatic patient		85 (9%)	533 (19%)	<0.01
Type of diagnosis				
	Medical	692 (72%)	1961 (68%)	NS
	Surgical	274 (28%)	897 (32%)	NS
Immunosuppression		145 (15%)	361 (13%)	0.04
Non-invasive ventilation before onset of pneumonia		179 (19%)	498 (18%)	NS
Mechanical ventilation before pneumonia		944 (98%)	2759 (96%)	0.03

NS: Not significant Data are presented as n (%) unless otherwise noted

Venier et al. *J Hosp Infect*. 2011

Who is at risk of *P. aeruginosa* nosocomial pneumonia?

- Intravenous antibiotics in the previous 90 days
- Septic shock at the onset of VAP
- ARDS preceding VAP
- Five or more days of hospitalization prior to VAP
- Acute renal replacement therapy prior to VAP
- Advanced age



VAP: Ventilator-acquired pneumonia; ARDS: Acute Respiratory Distress Syndrome

Kalol et al. *Clin Infect Dis*. 2016; Venier et al. *J Hosp Infect*. 2011

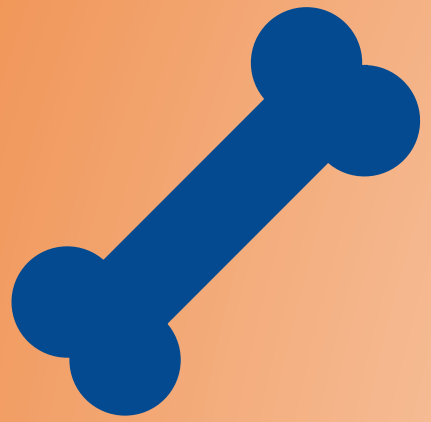
Who is at risk of *P. aeruginosa* Community-Acquired Pneumonia?

Prior isolation of *P. aeruginosa* from a respiratory culture

Recent hospitalization AND receipt of intravenous antibiotics in the past 90 days

Metlay et al. *Am J Respir Crit Care Med*. 2019

Who is at risk of *P. aeruginosa* diabetic foot infection?

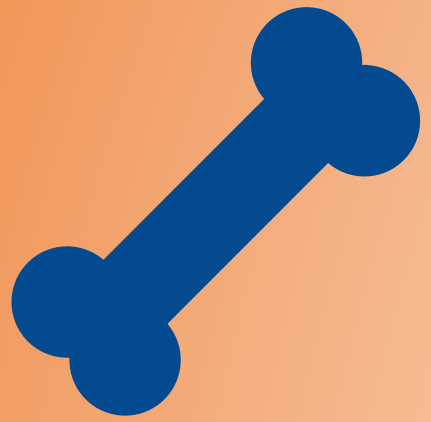


Risk Factor	Odds Ratio (95% CI)	P
Age > 65 years	5.94 (1.4, 25.28)	0.016
BMI > 35kg/m^2	7.53 (1.73, 32.81)	0.007
Former or current smoker	9.27 (1.06, 81.54)	0.045
History of a lower extremity bypass procedure	9.63 (1.52, 61.15)	0.016
Cardiovascular disease	5.28 (1.22, 22.86)	0.026
Severe infections	4.5 (0.97, 20.95)	0.055

BMI: Body Mass Index

Farhat et al. *Open Forum Infect. Dis*. 2017

Who is at risk of *P. aeruginosa* diabetic foot infection?



- High local prevalence of *P. aeruginosa* infection
- Warm climate
- Frequent exposure of the extremity to water
- Age >65 years
- BMI >35
- Current or prior smoking

Lipsky et al. *Clin Infect Dis*. 2012; Farhat et al. *Open Forum Infect. Dis*. 2017

Which of the following patients is at an increased risk of *Pseudomonas aeruginosa* being the causative organism of their pneumonia?

A. A 17-year-old male who develops patchy infiltrates one day after being intubated in the emergency department for a severe asthma exacerbation
B. A 67-year-old female with end-stage renal disease on dialysis three times weekly admitted for a traumatic hip fracture who develops a productive cough on hospital day 5 of her admission for total hip arthroplasty
C. A 58-year-old male admitted following a stroke who aspirates while eating and subsequently develops patchy infiltrates on imaging
D. A 31-year-old female who recently completed a course of oral amoxicillin/clavulanate for a sinus infection

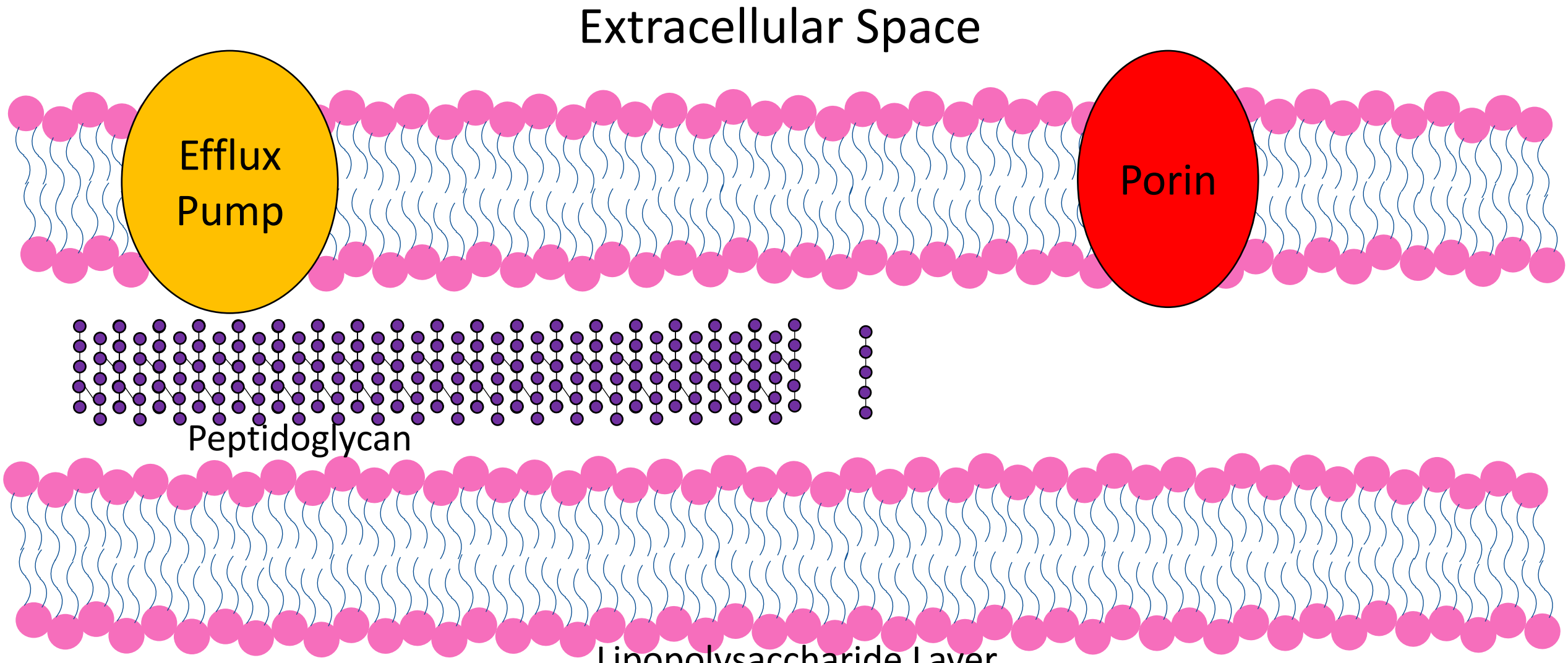
Knowledge Check: Objective 1

Antibiotic Mechanisms and Susceptibility

Antibiotics for *P. aeruginosa*

Fluoroquinolones	• Ciprofloxacin • Levofloxacin
Traditional Beta-Lactams	• Piperacillin/Tazobactam • Cefepime • Meropenem • Imipenem/Cilastatin • Aztreonam
Novel Beta Lactams	• Cefiderocol • Ceftolozane/Tazobactam • Imipenem/Cilastatin/Relebactam • Ceftazidime/Avibactam
Miscellaneous Agents	• Aminoglycosides • Polymyxins

Pang et al. *Biotechnol Adv*. 2019

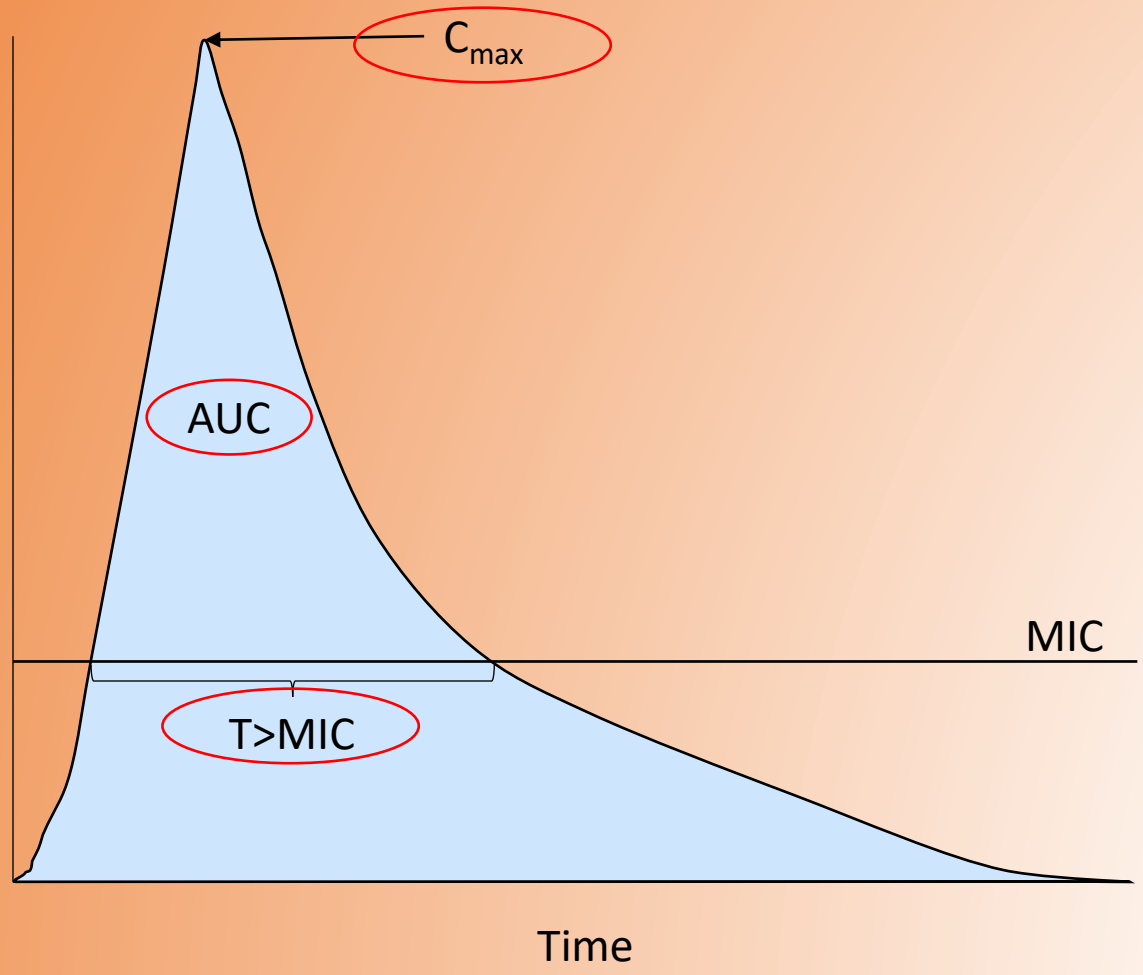

Extracellular Space
Efflux Pump
Porin
Peptidoglycan
Lipopolysaccharide Layer
Gram Negative Cell
Intracellular Space

What antibiotic kills bacteria by inhibiting Penicillin-Binding-Protein mediated peptidoglycan crosslinking?

A. Levofloxacin
B. Gentamicin
C. Cefepime
D. Colistin

Knowledge Check: Objective 2

Pharmacodynamic Targets of Antibiotics



Time Dependent

- Beta Lactams

Concentration Dependent

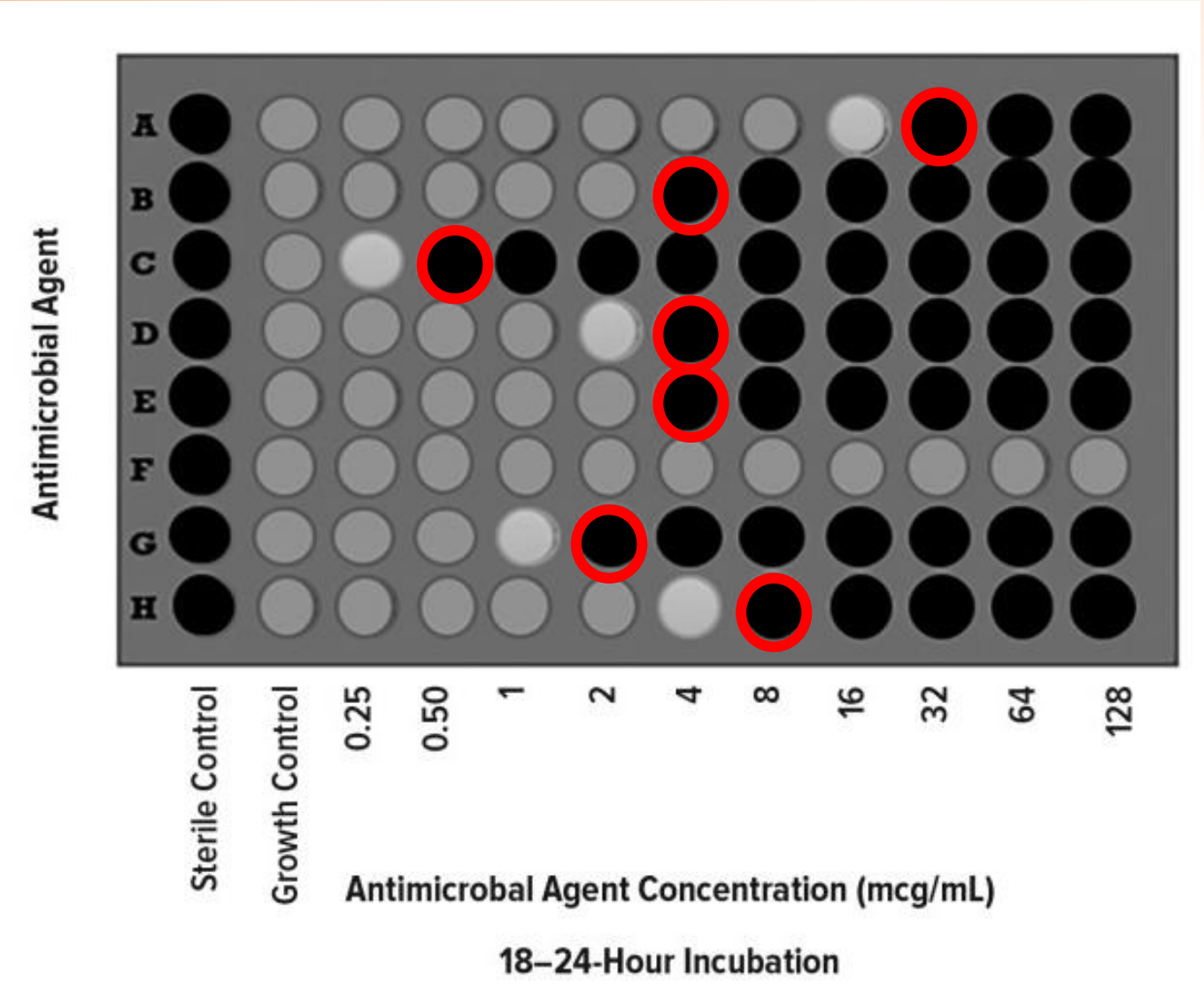
- Aminoglycosides
- Fluoroquinolones

Exposure Dependent

- Vancomycin

Dhaese et al. *Clin Pharmacokinet*. 2020

Susceptibility Testing



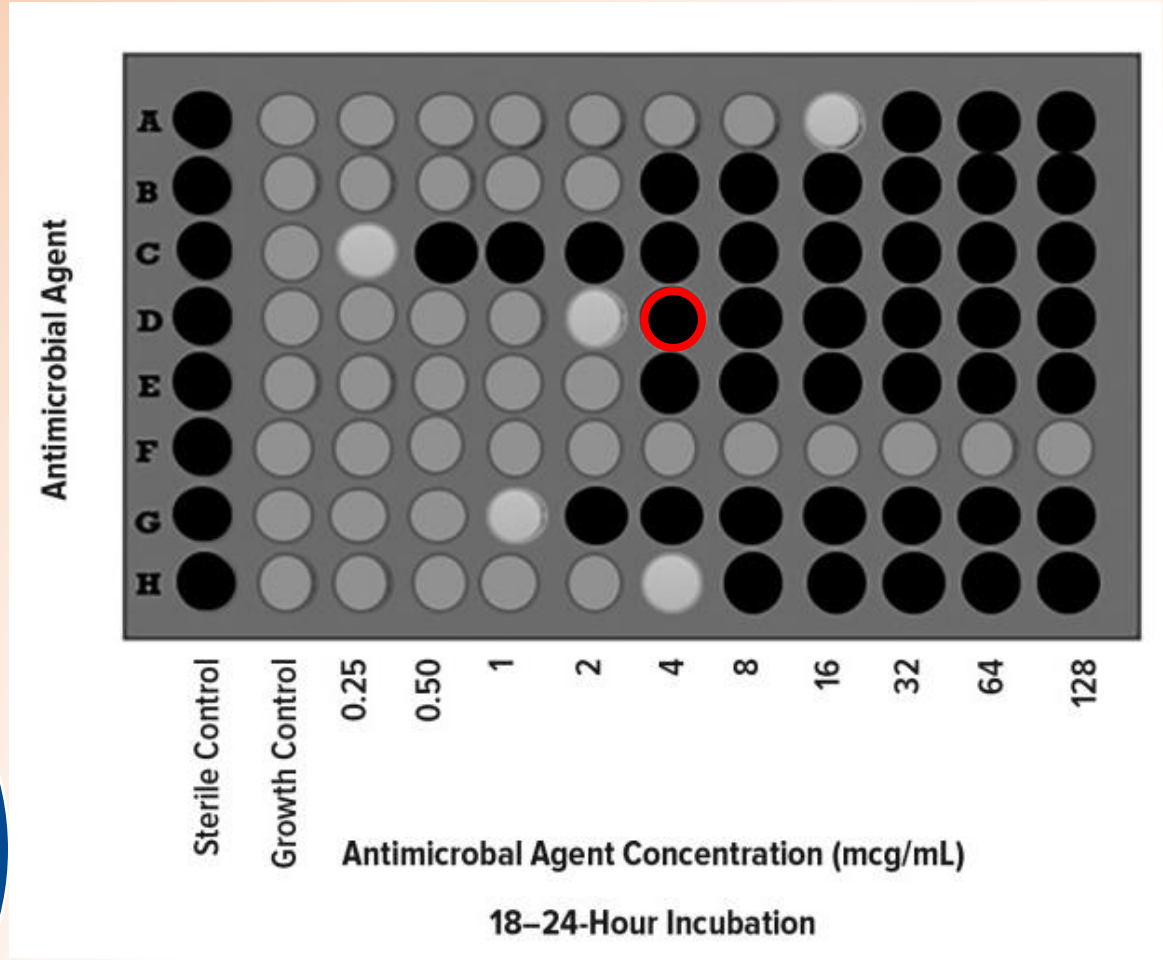
Giuliano et al. *P T*. 2019

Knowledge Check

The breakpoint of drug D against the cultured organism is 8mcg/mL

Is this organism sensitive to drug D?

Yes! The MIC of 4mcg/mL falls below 8mcg/mL



Updated CLSI Breakpoints for *Pseudomonas aeruginosa*

Not Listed:
Meropenem/Vaborbactam
Ertapenem

Antimicrobial Agent	Interpretive Categories and MIC Breakpoints (mcg/mL) (Prev. Recommendation)		
	Sensitive	Intermediate	Resistant
Piperacillin/Tazobactam	≤16/4	**32/4 (32-64/4)**	**≥64/4 (≥128)**
Ceftazidime/Avibactam	≤8/4	-	≥16/4
Ceftolozane/Tazobactam	≤4/4	8/4	≥16/4
Imipenem/Relebactam	≤2/4	4/4	≥8/4
Ceftazidime	≤8	16	≥32
Cefepime	≤8	16	≥32
Cefiderocol	≤4	8	≥16
Aztreonam	≤8	16	≥32
Imipenem	≤2	4	≥8
Meropenem	≤2	4	≥8

2023 Performance Standards for Antimicrobial Susceptibility Testing, 33rd Edition, Clinical and Laboratory Sciences Institute. 2023

Updated CLSI Breakpoints for *Pseudomonas aeruginosa* (cont)

Antimicrobial Agent	Interpretive Categories and MIC Breakpoints (mcg/mL)		
	Sensitive	**Intermediate**	**Resistant**
Tobramycin	**≤1 (≤4)**	**2 (8)**	**≥4 (≥16)**
Amikacin (Urine only)	≤16	32	≥64
Gentamicin	-	-	-
Ciprofloxacin	≤0.5	1	≥2
Levofloxacin	≤1	2	≥4

2023 Performance Standards for Antimicrobial Susceptibility Testing, 33rd Edition, Clinical and Laboratory Sciences Institute. 2023

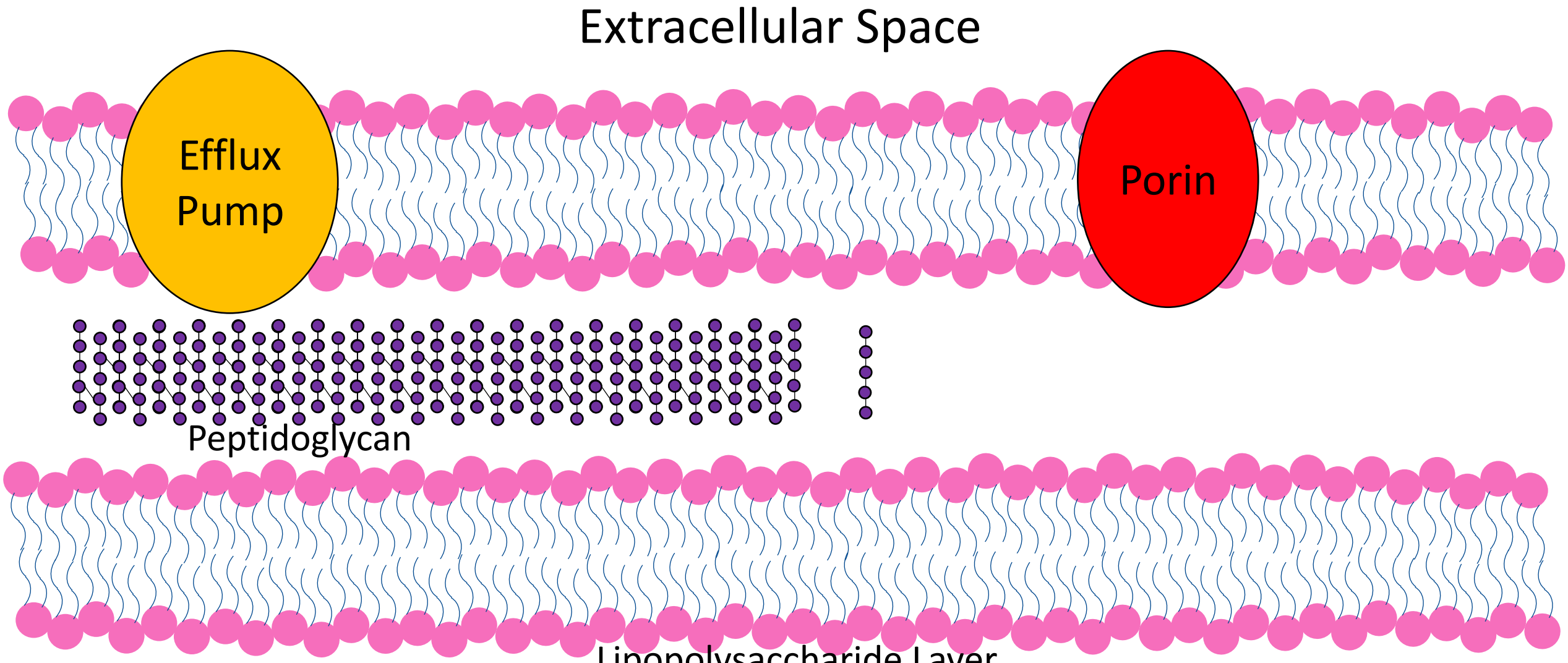
Based on the following culture and sensitivity report, this isolate of *P. aeruginosa* is susceptible to which antibiotic?

A. Piperacillin/Tazobactam
B. Cefepime
C. Aztreonam
D. Meropenem

Pseudomonas aeruginosa		
Antibiotic	**MIC**	**Breakpoint**
Piperacillin/Tazobactam	32	≤16
Cefepime	2	≤8
Ceftazidime	64	≤8
Aztreonam	16	≤8
Meropenem	4	≤2

Knowledge Check: Objective 3

Resistance Among *P. aeruginosa*


Extracellular Space
Efflux Pump
Porin
Peptidoglycan
Lipopolysaccharide Layer
Gram Negative Cell
Intracellular Space

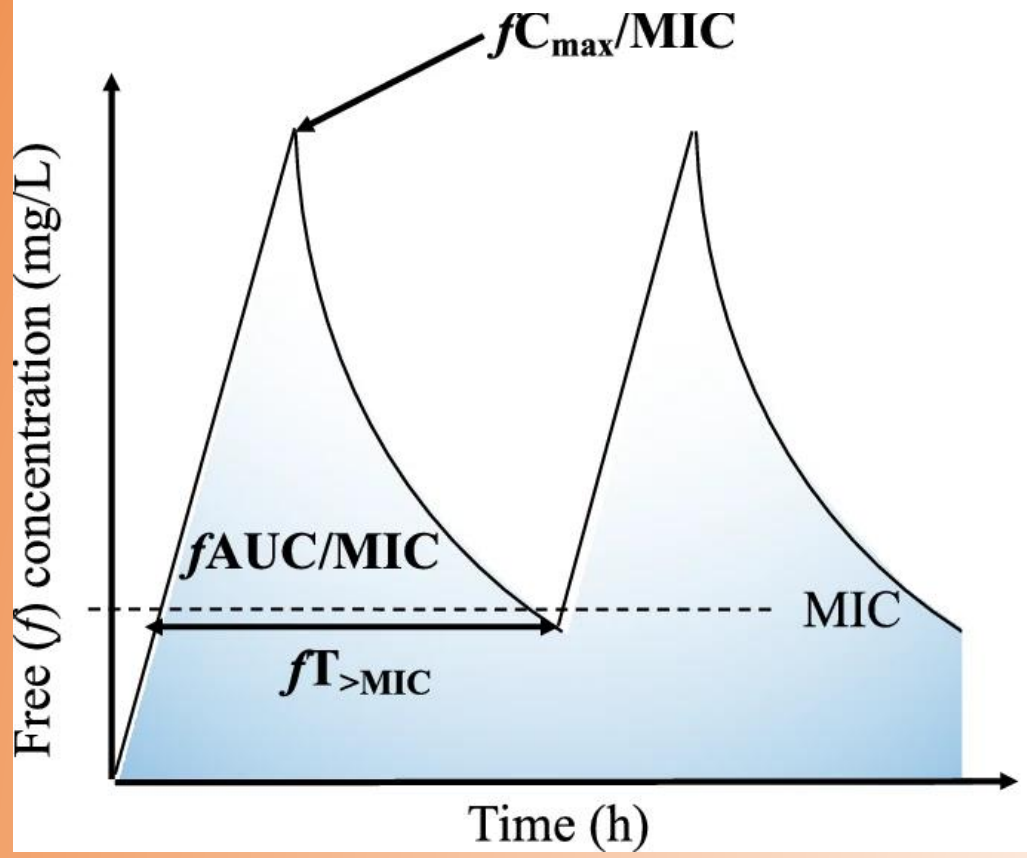
Strategies for Overcoming Resistance

- Increased Time Above MIC for Beta Lactams
- Combination Therapy
- Novel Agents
  - ***Ceftolozane/Tazobactam***
  - ***Cefiderocol***
  - Ceftazidime/Avibactam
  - Imipenem/Cilastatin/Relebactam

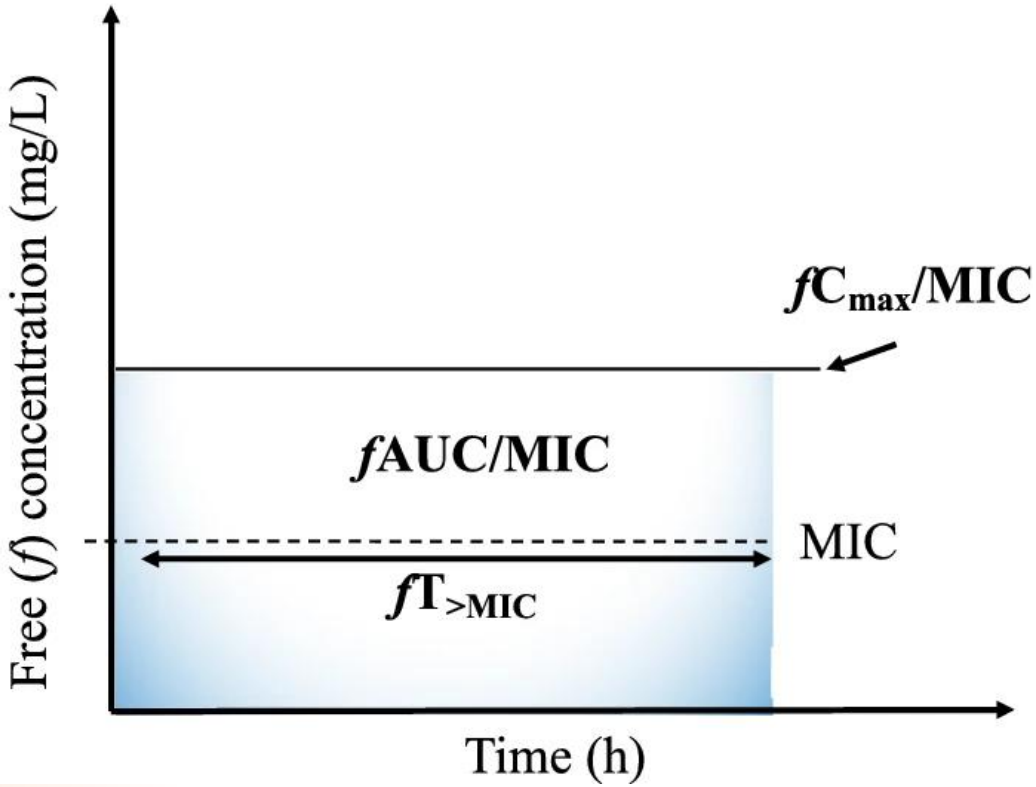
Pang et al. *Biotechnol Adv*. 2019

How Do We Increase Time Above MIC?

Concentration versus time for intermittent infusion

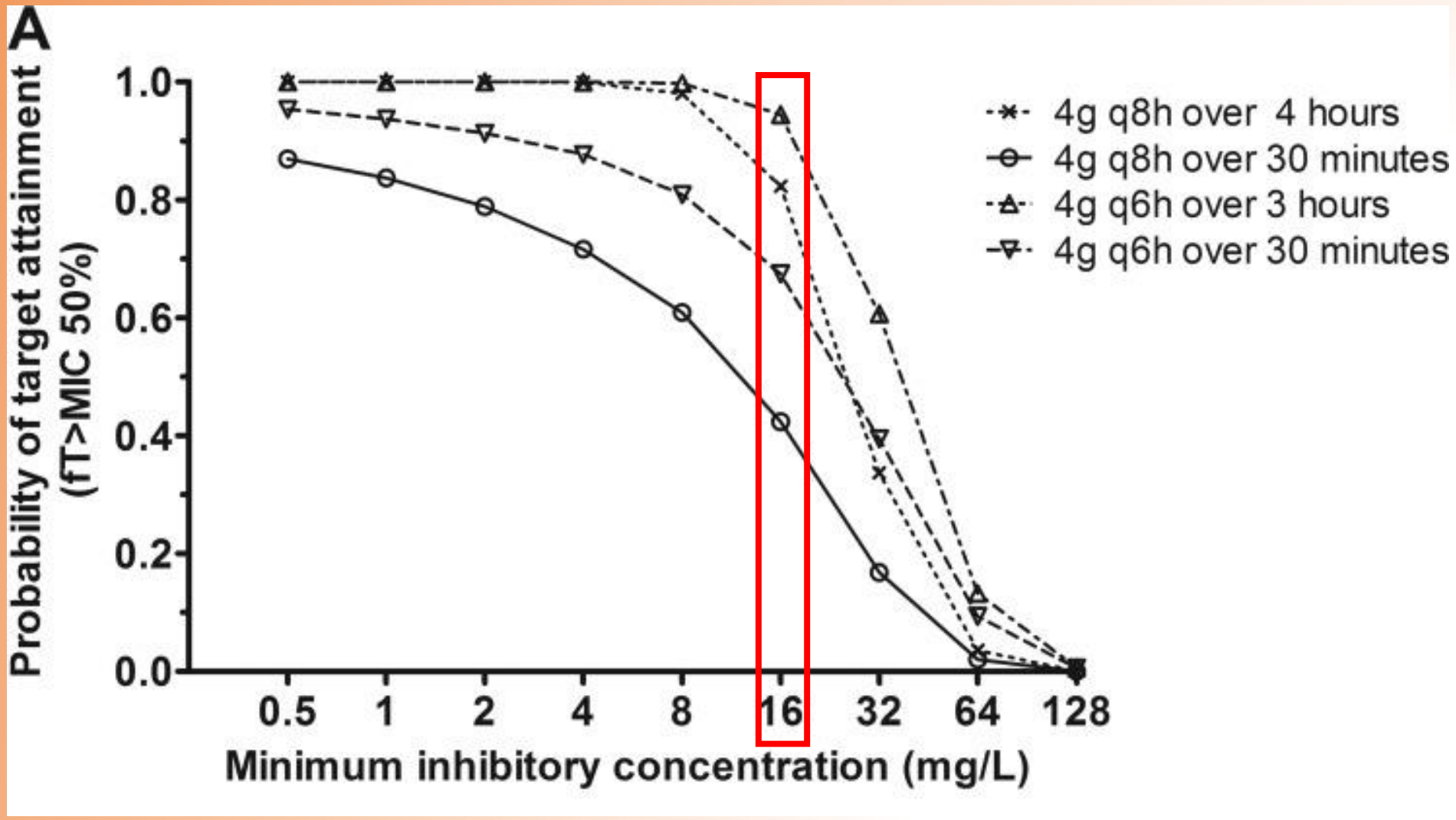


Concentration versus time for continuous infusion



Dhaese et al. *Clin Pharmacokinet*. 2020

Extended Infusion Beta Lactams



Felton et al. *Antimicrob Agents Chemother*. 2012

Outcomes with Prolonged Infusion Beta-Lactams

Outcome	Relative Risk	95% Confidence Interval
Severely Ill		
Mortality	0.86	0.72, 1.02
Clinical Cure	1.1	1.03, 1.19
Microbiological Cure	1.21	1.08, 1.35
Non-Severely Ill		
Mortality	1.06	0.52, 2.18
Clinical Cure	1	0.95, 1.06
Microbiological Cure	1.06	0.99, 1.15

Hong et al. *Pharmacotherapy*. 2023

Recommendations

Extended infusion beta lactams should be preferred over intermittent dosing for severely ill patients, especially with gram negative infections

The panel cannot recommend extended infusion beta lactams over intermittent dosing in non-severely ill patients due to lack of benefit

Hong et al. *Pharmacotherapy*. 2023

Combination Therapy

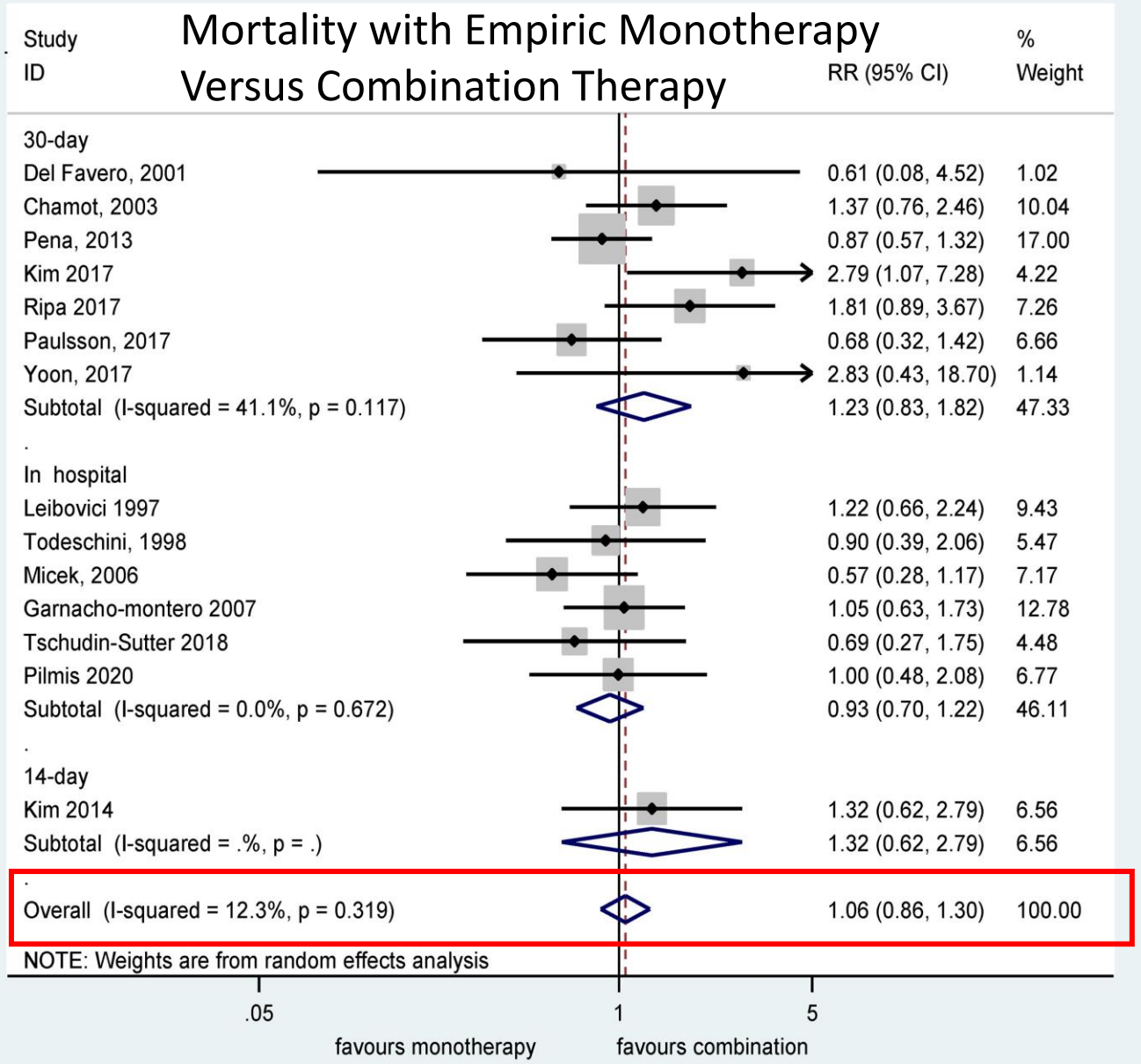
- Typically an anti-pseudomonal beta-lactam and another agent
- Proposed synergistic activity of combination therapy
- Possible accelerated microbial clearance and reduced mortality

Onorato et al. *Int J Antimicrob Agents*. 2022

Combination Therapy

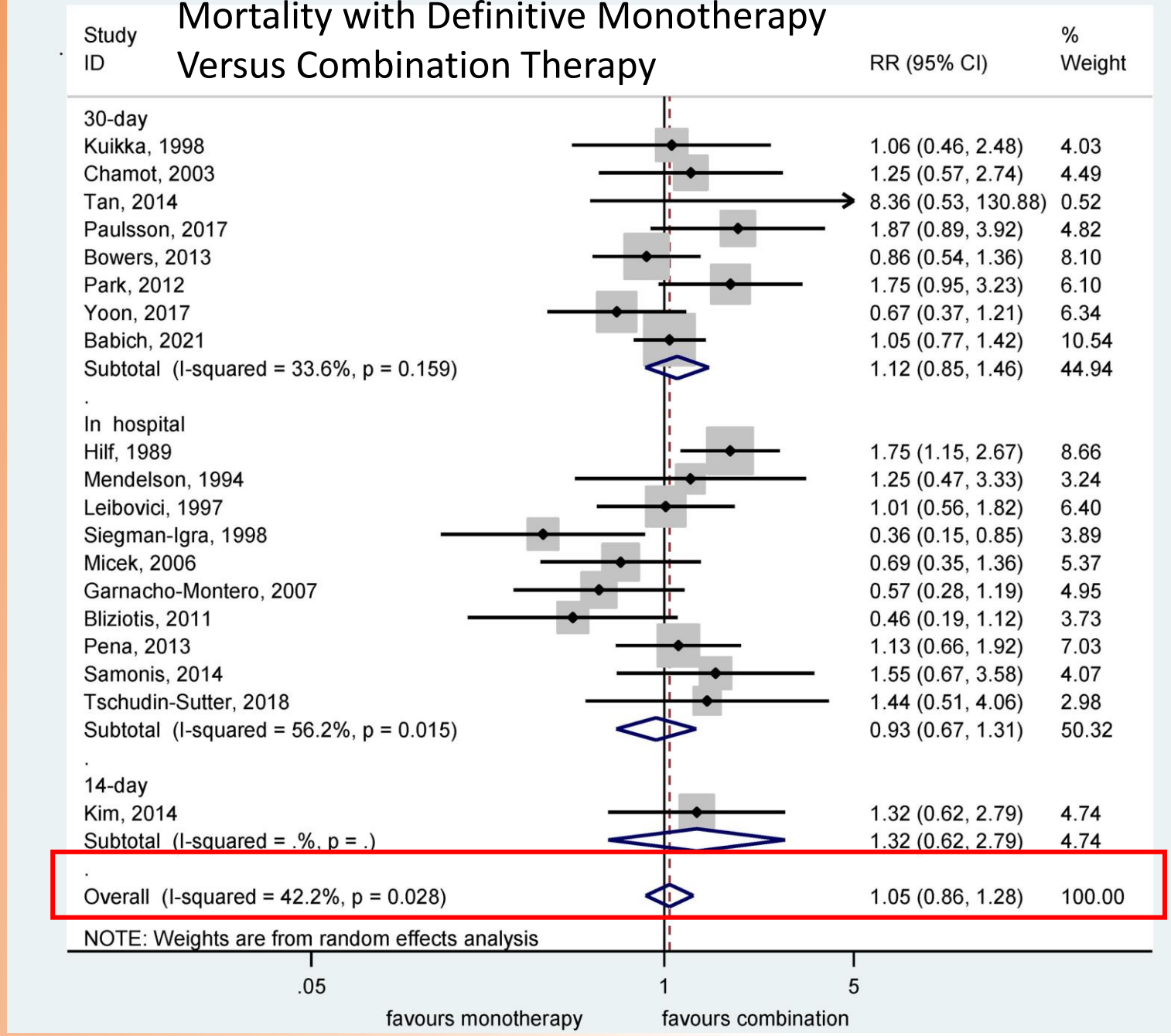
- Meta-analysis assessing combination versus monotherapy for *P. aeruginosa* bloodstream infection or pneumonia

- 35 studies were included in the analysis



Onorato et al. *Int J Antimicrob Agents*. 2022

Mortality with Definitive Monotherapy Versus Combination Therapy



Onorato et al. *Int J Antimicrob Agents*. 2022

Recommendations from the IDSA Pneumonia Guidelines

For patients who are in septic shock or at high risk for death when susceptibility results are known, **combination therapy** with 2 antibiotics to which the isolate is susceptible **is recommended**

For patients who are NOT in septic shock or at high risk for death when susceptibility results are known, **monotherapy** with an antibiotic to which the isolate is susceptible **is recommended**

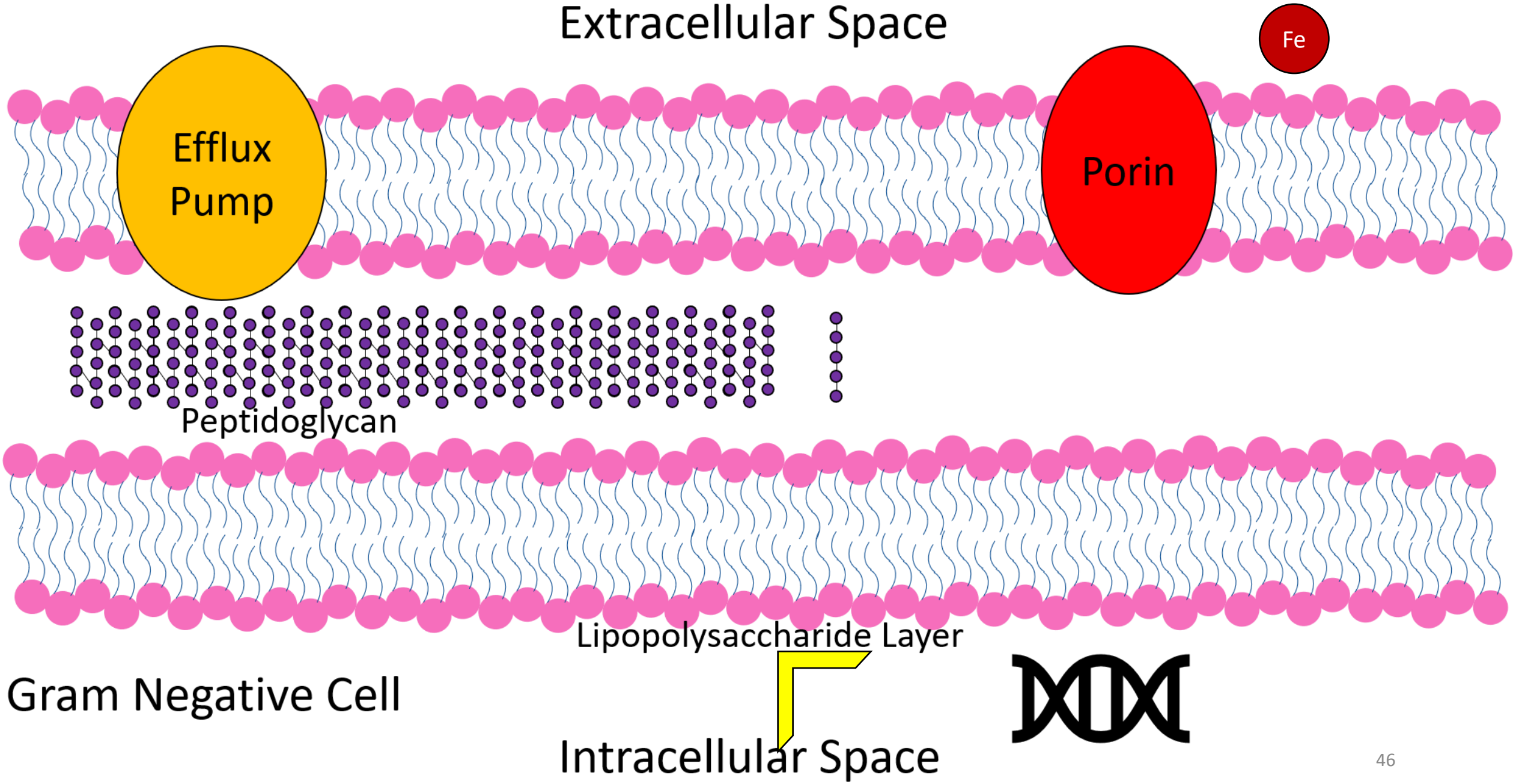
Kalil et al. *Clin Infect Dis*. 2016

Novel Agents

Cefiderocol

Ceftolozane/Tazobactam

Cefiderocol


Extracellular Space
Fe
Efflux Pump
Porin
Peptidoglycan
Lipopolysaccharide Layer
Gram Negative Cell
Intracellular Space

Cefiderocol in Pneumonia (APEKS-NP)

Cefiderocol versus high-dose, extended-infusion meropenem for the treatment of Gram-negative nosocomial pneumonia (APEKS-NP)	
Study Design	Multicenter, randomized, controlled, double-blind, parallel study
Population	Patients with gram negative nosocomial pneumonia
Intervention	Cefiderocol versus extended infusion meropenem
Primary Outcome	All-cause mortality at day 14
Secondary Outcomes	• 28-day all-cause mortality • Clinical response • Microbiological response
Population	Patients with gram negative nosocomial pneumonia
Intervention	Cefiderocol versus extended infusion meropenem

Wunderink et al. *Lancet Infect Dis*. 2021

Cefiderocol in Pneumonia (APEKS-NP) - Results

Outcome	Cefiderocol	Meropenem	Difference (95% CI)
Mortality	18/145 (12.4)	17/146 (11.6)	0.8 (-6.7, 8.2)
P aeruginosa	2/24 (8.3)	3/23 (13)	-4.7 (-22.4,12.9)
Clinical Cure	94/145 (64.8)	98/147 (66.7)	-1.8 (-12.7, 9)
P aeruginosa	16/24 (66.7)	17/24 (70.8)	-4.2 (-30.4, 22)
Microbiological Cure	59/145 (40.7)	61/147 (41.5)	-0.8 (-12.1, 10.5)
P aeruginosa	9/24 (37.5)	11/24 (45.8)	-8.3 (-36.1, 19.5)

Data are presented as n (%) unless otherwise noted

Wunderink et al. *Lancet Infect Dis*. 2021

Cefiderocol in Pneumonia (APEKS-NP) - Results

Outcome	Cefiderocol	Meropenem	Difference (95% CI)
Mortality			8.2)
P aeru			,12.9)
Clinical Cu			7, 9)
P aeru			4, 22)
Microbiol			, 10.5)
P aeruginosa	9/24 (37.5%)	11/24 (45.8%)	-8.3 (-36.1, 19.5)

Data are presented as n (%) unless otherwise noted

Summary:
Outcomes with cefiderocol in nosocomial pneumonia were not significantly different from those with meropenem

Wunderink et al. *Lancet Infect Dis*. 2021

Cefiderocol in UTI

Cefiderocol versus imipenem-cilastatin for the treatment of complicated urinary tract infections caused by Gram-negative uropathogens	
Study Design	Phase 2, multicenter, randomized, double-blind, non-inferiority trial
Population	Adults (18 and older) with complicated urinary tract infection with or without pyelonephritis
Intervention	Cefiderocol 2g IV versus imipenem-cilastatin 1g IV q8h
Primary Outcome	Composite of clinical and microbiological response at test of cure
Secondary Outcomes	• Microbiological response • Clinical response

Portsmouth et al. *Lancet Infect Dis*. 2018

Cefiderocol in UTI

Study Endpoint	Cefiderocol (%)	Imipenem/Cilastatin (%)	Treatment Difference (95% Confidence Interval)
Composite response at TOC	183/252 (72.6%)	65/119 (54.6%)	18.6 (8.2, 28.9)
P aeruginosa	8/18 (44.4%)	3/5 (60%)	-
Microbiologic response at TOC	184/252 (73%)	67/119 (56.3%)	17.3 (6.9, 27.6)
Clinical Response at TOC	226/252 (89.7%)	104/119 (87.4%)	2.4 (-4.7, 9.4)

Data are presented as n (%) unless otherwise noted

Portsmouth et al. *Lancet Infect Dis*. 2018

Cefiderocol in UTI

Study Endpoint		Cefiderocol (%)	Imipenem/Cilastatin (%)	Treatment Difference (95% Confidence Interval)
Composite response a TOC				.6 (8.2, 28.9)
	P aeruginosa			-
Microbiologic respons at TOC				.3 (6.9, 27.6)
Clinical Response at TOC		226/252 (89.7%)	104/119 (87.4%)	2.4 (-4.7, 9.4)

Data are presented as n (%) unless otherwise noted

Summary:
Cefiderocol significantly improved microbiologic response in patients with urinary tract infections versus imipenem-cilastatin

Portsmouth et al. *Lancet Infect Dis*. 2018

Cefiderocol for Any Severe Infection

Efficacy and safety of cefiderocol or best available therapy for the treatment of serious infections caused by carbapenem-resistant Gram-negative bacteria (CREDIBLE-CR)	
Study Design	Randomized, open-label, descriptive study
Population	Adult patients with HAP/VAP, bloodstream infection, cUTI, or sepsis due to carbapenem resistant organisms
Intervention	Cefiderocol 2g IV q8h versus standard of care per provider discretion (up to 3 drugs maximum)
Primary Outcome	Clinical cure for HAP/VAP, bloodstream infection, or sepsis Microbiological eradication for urinary tract infection
Secondary Outcomes	All-cause mortality Treatment-emergent adverse events

Bassetti et al. *Lancet Infect Dis*. 2021

Cefiderocol for Any Severe Infection

Endpoint	Cefiderocol (n=101)	SOC (n=49)
14-Day Mortality	19 (19%)	6 (12%)
Pneumonia	11 (24%)	3 (14%)
Bloodstream Infection	5 (17%)	1 (6%)
Urinary Tract Infection	3 (12%)	2 (20%)
28-Day Mortality	25 (25%)	9 (18%)
Pneumonia	14 (31%)	4 (18%)
Bloodstream Infection	7 (23%)	2 (18%)
Urinary Tract Infection	4 (15%)	2 (20%)
Mortality at End of Study	34 (34%)	9 (18%)
Pneumonia	19 (42%)	4 (18%)
Bloodstream Infection	11 (37%)	3 (18%)
Urinary Tract Infection	4 (15%)	2 (20%)
Pseudomonas aeruginosa	2/11 (18%)	2/12 (18%)

Data are presented as n (%) unless otherwise noted

Bassetti et al. *Lancet Infect Dis*. 2021

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Pseudomonas aeruginosa	2/11 (18%)	2/11 (18%)

Cefiderocol seemed to **improve mortality** only in patients with a **cUTI**, not pneumonia or bloodstream infections, potentially due to **confounding variables**.

Data are presented as n (%) unless otherwise noted

Bassetti et al. *Lancet Infect Dis*. 2021

Ceftolozane/Tazobactam

Advantages of Ceftolozane/Tazobactam

- Novel cephalosporin with significant anti-*Pseudomonas* activity
- Bulky side chain prevents efflux
- More stable to degradation by AmpC
- Its entry into the bacterial cell is independent of porin function
- Higher affinity for essential PBPs without upregulating AmpC

Giacobbe et al. *Expert Rev Anti Infect Ther*. 2018

The Evidence for Ceftolozane/Tazobactam

ASPECT-cIAI				
Arm	**Drug**	**Dose**	**Cure Rate**	**% Difference (95% Confidence Interval**
Active	Ceftolozane/Tazobactam + Metronidazole	1000/500mg q8h + 500mg q8h	323/389 (83%)	-4.2 (-8.9, 0.5)
Comparator	Meropenem	1000mg q8h	364/417 (87.3%)	

ASPECT-cUTI			
Drug	**Dose**	**Cure Rate**	**% Difference (95% Confidence Interval)**
Ceftolozane/Tazobactam	1000/500mg q8h	306/398 (76.9%)	8.5 (2.3, 14.6)
Levofloxacin	750mg daily	275/402 (68.4%)	

IAI: Intra-abdominal infection; UTI: Urinary tract infection
Data are presented as n (%) unless otherwise noted

Solomkin et al. *Clin Infect Dis*. 2015
Wagenlehner et al. *Lancet*. 2015

The Evidence for Ceftolozane/Tazobactam

ASPECT-cIAI				
				% Difference (95%
Levofloxacin	750mg daily	275/402 (68.4%)		

IAI: Intra-abdominal infection; UTI: Urinary tract infection
Data are presented as n (%) unless otherwise noted

Summary:

- Ceftolozane-tazobactam achieved a significantly higher cure rate than levofloxacin in urinary tract infections
- The cure rate achieved by ceftolozane-tazobactam with metronidazole was not significantly different from that achieved by meropenem in intra-abdominal infections

Solomkin et al. *Clin Infect Dis*. 2015
Wagenlehner et al. *Lancet*. 2015

IDSA Recommendations for DTR- *P. aeruginosa*

Traditional, non-carbapenem beta lactams are preferred over carbapenems when sensitivities allow to avoid overuse

DTR: Difficult-to-Treat Resistance

Tamma et al. *Clin Infect Dis*. 2023

IDSA Recommendations for DTR- *P. aeruginosa*

Traditional, non-carbapenem beta lactams are preferred over carbapenems when sensitivities allow to avoid overuse

Ceftolozane/Tazobactam, Ceftazidime/Avibactam, Imipenem/Cilastatin/Relebactam, and Cefiderocol are preferred for DTR-*P. aeruginosa* urinary tract infections

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The same agents are preferred for infections outside the urinary tract, except for cefiderocol

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- Cefiderocol is preferred if DTR-*P. aeruginosa* produces metallo-beta-lactamases

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IDSA Recommendations for DTR- *P. aeruginosa*

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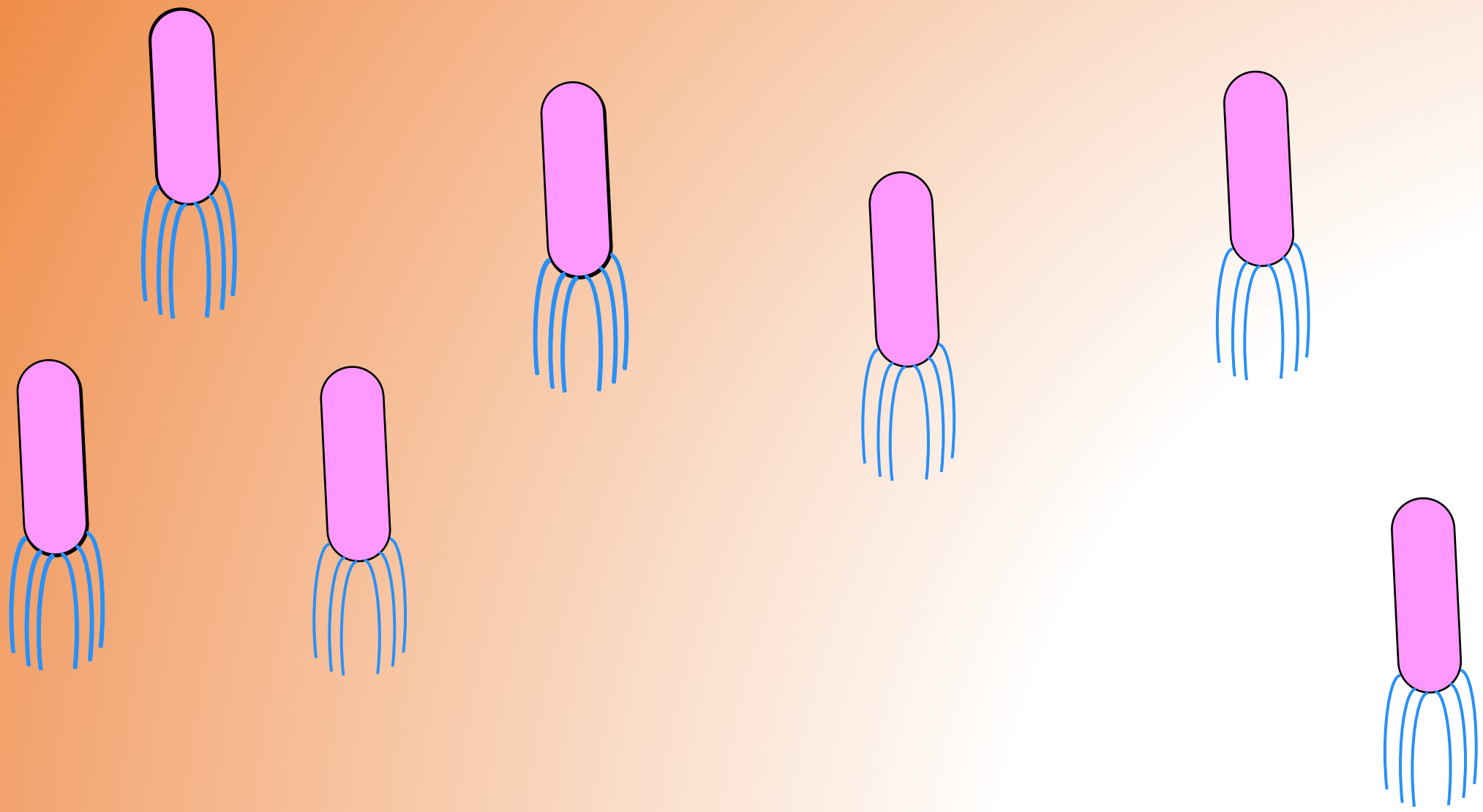
- The same agents are preferred for infections outside the urinary tract, except for cefiderocol
- Cefiderocol is preferred if DTR-*P. aeruginosa* produces metallo-beta-lactamases
- Combination therapy is not recommended for DTR-*P. aeruginosa* if susceptibility to novel agents is confirmed

DTR: Difficult-to-Treat Resistance

Tamma et al. *Clin Infect Dis*. 2023

Preventing Resistance



Shorter Durations of Therapy for HAP/VAP

Short-course versus prolonged-course antibiotic therapy for hospital-acquired pneumonia in critically ill adults	
Study Design	Systematic review and meta analysis
Population	Patients hospitalized with HAP/VAP
Intervention	Short course of therapy (8 days or shorter)
Primary Outcome	• 28 day mortality • Recurrence of pneumonia • 28-day antibiotic-free
Secondary Outcomes	• Duration of ICU and hospital stay • Duration of hospital stay • Duration of mechanical ventilation • Mechanical ventilation free days • Mortality attributable

Pugh et al. *Cochrane Database Syst Rev.* 2015

Shorter Durations of Therapy for HAP/VAP (cont)

Outcome	Odds Ratio	95% Confidence Interval
28-Day Mortality	1.18	(0.77, 1.8)
Pneumonia Recurrence	1.41	(0.94, 2.12)
28-Day Antibiotic Free Days	4.02	(2.26, 5.78)
Subsequent Infection with Resistant Organism	0.44	(0.21, 0.95)

Pugh et al. *Cochrane Database Syst Rev.* 2015

Shorter Durations of Therapy for HAP/VAP (cont)

Outcome	Odds Ratio	95% Confidence Interval
28-D		
Pne		
28-D		
Sub		

Summary:
A shorter duration of antibiotic therapy achieved similar rates of mortality and recurrence with lower incidence of resistant infections

Pugh et al. *Cochrane Database Syst Rev.* 2015

Recommendations from the IDSA for HAP/VAP

Patients being treated for HAP/VAP should receive a 7 day course of therapy rather than a longer duration

Kalil et al. *Clin Infect Dis*. 2016

Shorter Durations in Bacteremia

Short-course versus prolonged-course antibiotic therapy for hospital-acquired pneumonia in critically ill adults	
Study Design	International, multicenter, retrospective review spanning 2009-2015
Population	Adults (18 years and older) hospitalized with *P. aeruginosa* bacteremia
Comparison	Compared 6-10 days of antibiotic therapy versus 11-15 days
Primary Outcome	Composite of 30-day mortality and persistence/recurrence of bacteremia

Babich et al. *Infect Dis Ther*. 2022

Outcomes of 7 Versus 14 Days of Therapy for Gram Negative Bacteremia

Outcome	Short Treatment (N = 273)	Long Treatment (N = 384)	All Cohort (N=657)	P-Value
30-Day Mortality	25 (9.2%)	41 (10.7%)	66 (10%)	0.523
Days of Hospital Stay – entire cohort, N=544 (Median, 25-75%)	13 (9-21)	15 (11-26)	15 (10-23)	0.002
Recurrent/Persistent Bacteremia	8/264 (3%)	21/375 (5.6%)	29/639 (4.5%)	0.124
Adverse Events				
C. difficile infection	3 (1%)	1 (0.3%)	---	0.322
Drug Discontinuation Due To Adverse Events	0	10 (2.8%)	10 (1.6%)	0.006

Data are presented as n (%) unless otherwise noted

Babich et al. *Infect Dis Ther*. 2022

Outcomes of 7 Versus 14 Days of Therapy for Gram Negative Bacteremia

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Days of Hospital (Median, 25-75%				0.002
Recurrent/Persist				0.124
Adverse Events				
C. difficile in				0.322
Drug Discontinuation Due To Adverse Events	0	10 (2.8%)	10 (1.6%)	0.006

Data are presented as n (%) unless otherwise noted

Summary:
A shorter course of antibiotic therapy was associated with shorter length of stay and lower discontinuation rates with no difference in mortality

Babich et al. *Infect Dis Ther*. 2022

Future Directions

- Vaccines
- Novel Antibiotics
- Monoclonal Antibodies
- Immune Globulins
- Novel Diagnostics
- Bacteriophage Therapy
- Quorum Sensing Inhibition
- Inhaled Antibiotics

Clinicaltrials.gov. Accessed October 1, 2023

Bringing it All Together

PT is a 67 year old male presenting to the emergency department complaining of fever and a painful sore on his heel

- PMH: Diabetes mellitus, hypertension, hyperlipidemia
- Social history: Smoker (1.5ppd x 55 years), denies EtOH or illicit drug use, endorses taking Epsom salt baths nightly for muscle pain
- VS: HR 96 | RR 22 | T 100.7 | BP 116/59 | SpO_2 97% RA
- HbA1c: 9.6%, BMP within normal limits, WBC 14.7
- Physical exam reveals an ulcer on the right heel with tendons visible as well as eschar and surrounding erythema. Otherwise unremarkable

What empiric antibiotic therapy would be most appropriate for this patient?

What risk factors does this patient have for diabetic foot infection due to *Pseudomonas*?

- Smoking
- Frequent exposure of the extremity to water

Orthopedic surgery is consulted, and the patient is taken to the OR for debridement

What empiric antibiotic therapy would be most appropriate to add to vancomycin for this patient?

A. Ertapenem
B. Meropenem/vaborbactam
C. Piperacillin/tazobactam
D. Gentamicin

Knowledge Check: Objective 3

PT’s wound cultures following surgical debridement show no growth, indicating clear margins, and PT is discharged to a skilled nursing facility to recover

Unfortunately, PT is not compliant with his home insulin on discharge and returns to the ICU several weeks later for DKA

- On hospital day 3, PT develops shortness of breath, fever (102.1) and leukocytosis (WBC 15.2)
- Chest X-Ray: focal consolidation of the right upper lobe
- Sputum cultures are collected an the patient is started empirically on vancomycin and piperacillin/tazobactam

The sputum culture results, indicating resistance to current therapy. What would be an appropriate alternative antibiotic for PT?

A. Ceftolozane/Tazobactam
B. Meropenem/Vaborbactam
C. Extended Infusion Piperacillin/Tazobactam
D. Add Gentamicin for Dual Coverage

Pseudomonas aeruginosa		
Antibiotic	MIC	Breakpoint
Piperacillin/Tazobactam	128	≤16
Cefepime	32	≤8
Ceftazidime	64	≤8
Aztreonam	16	≤8
Ceftolozane/Tazobactam	1	≤4
Meropenem	4	≤2

Knowledge Check: Objective 4

As he receives his 7-day course of ceftolozane/tazobactam, PT passes his spontaneous breathing trial, is extubated, and makes a full recovery

Key Takeaways

- *P. aeruginosa* is a ubiquitous organism that can cause serious infections
- Patients who are older, have recently been hospitalized, are immunosuppressed, or have received recent IV antibiotics are at risk
- *P. aeruginosa* has a wide variety of resistance mechanisms, but current and emerging therapies give us ways to treat these infections

Pseudomonas aeruginosa: Declassified

William Norton Jr, PharmD

PGY1 Pharmacy Resident, Henrico Doctors' Hospital

November 8, 2023