A PAIN IN THE ACINETOBACTER: MANAGING INFECTIONS CAUSED BY MULTIDRUG RESISTANT GRAM-NEGATIVE PATHOGENS

Bessma Hassani, PharmD, BCPS, BCIDP
Clinical Pharmacy Specialist – Infectious Diseases & Antimicrobial Stewardship
Long Island Jewish Valley Stream

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Northwell Health

DISCLOSURES

I have no financial interests or relationships to disclose.

AI was not utilized in the making of this presentation.

All references are cited using PMID (PubMed Identifier) number.

ABBREVIATIONS

Abbreviation	Antibiotic
FQ	Fluoroquinolone
TMP-SMX	Trimethoprim-sulfamethoxazole
AG	Aminoglycoside
Pip-tazo	Piperacillin-tazobactam
CAZ-AVI	Ceftazidime-avibactam
TOL-TAZ	Ceftolozane-tazobactam
MER-VAB	Meropenem-vaborbactam
IMI-REL	Imipenem-relebactam
FDC	Cefiderocol
AZT-AVI	Aztreonam-avibactam
SUL-DUR	Sulbactam-durlobactam
AMP-SUL	Ampicillin-sulbactam
Imipenem	Imipenem-cilastatin

Abbreviation	Definition
BL	Beta-lactam
TDM	Therapeutic drug monitoring
AST	Antimicrobial susceptibility testing
PBP	Penicillin binding protein
RCT	Randomized controlled trial
SOC	Standard-of-care
BAT	Best available therapy
PNA	Pneumonia
MDR	Multidrug resistant
MBL	Metallo-beta-lactamase
PCR	Polymerase chain reaction
ESBL	Extended-spectrum beta-lactamase

OBJECTIVES

1. Identify and explain the various mechanisms of antimicrobial resistance amongst gram-negative pathogens
2. Describe the differences in spectrum of activity between the novel antimicrobial agents
3. Construct a treatment plan for infections caused by multidrug resistant gram-negative pathogens

BACKGROUND & REVIEW OF GRAM-NEGATIVE RESISTANCE MECHANISMS

EPIDEMIOLOGY

Antimicrobial resistance (AMR) is a global public health crisis

- In 2021, an estimated 4.71 million deaths were associated with bacterial AMR
  - Low middle-income countries disproportionately affected

Multidrug resistant gram-negative bacteria (MDR-GNB) are a large part of this threat

- Leading cause of community and healthcare-associated infections in recent decades
- Until recently, new therapeutics for MDR-GNB were almost non-existent

Multiple factors have contributed to the expansion to MDR-GNB

- Misuse and overuse of antibiotics in both human and animal health
- Absence of clean water and sanitation
- Increasing complexity of medical care
- Inadequate infection prevention & control

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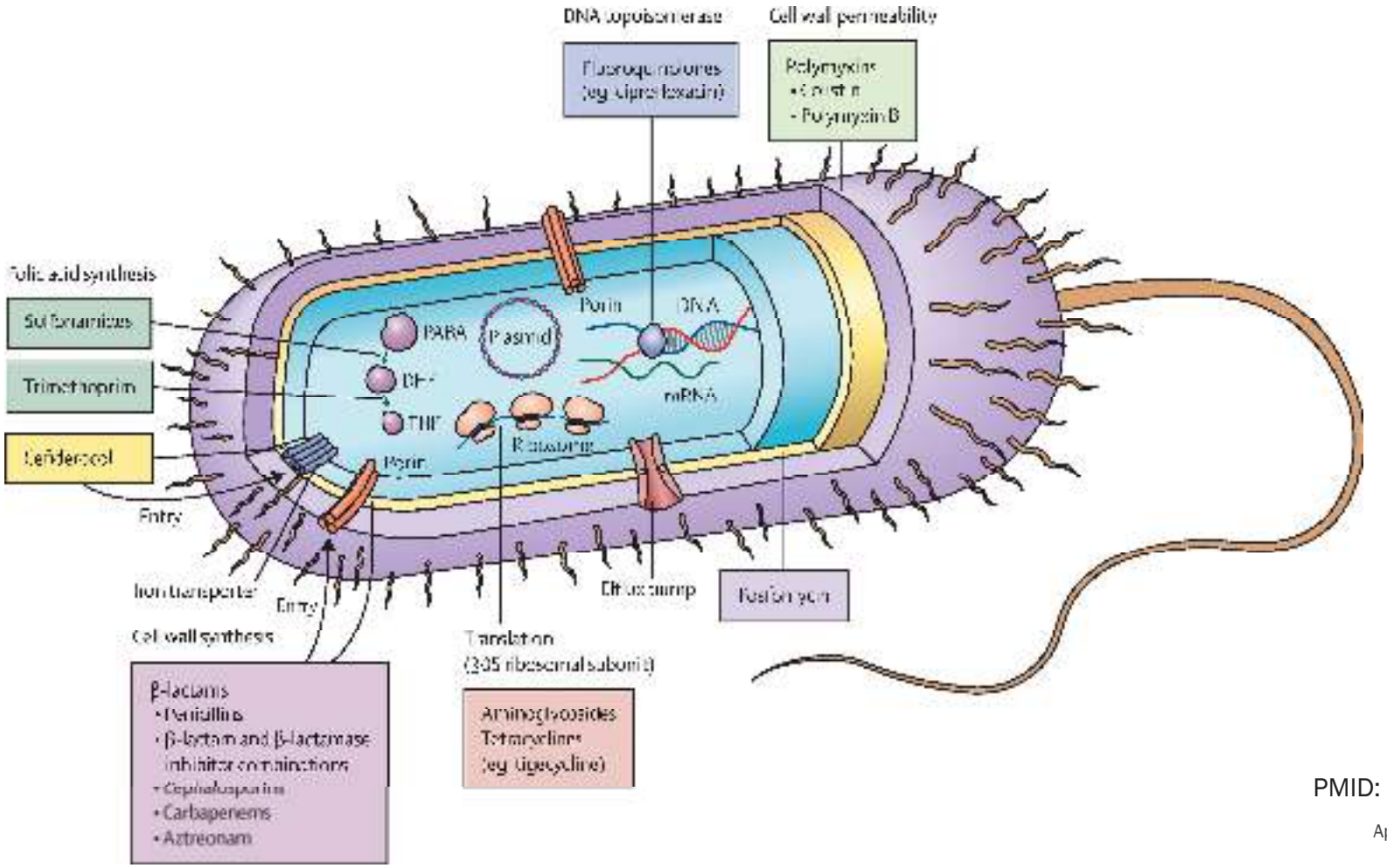
ANTIBIOTIC SITES OF ACTION



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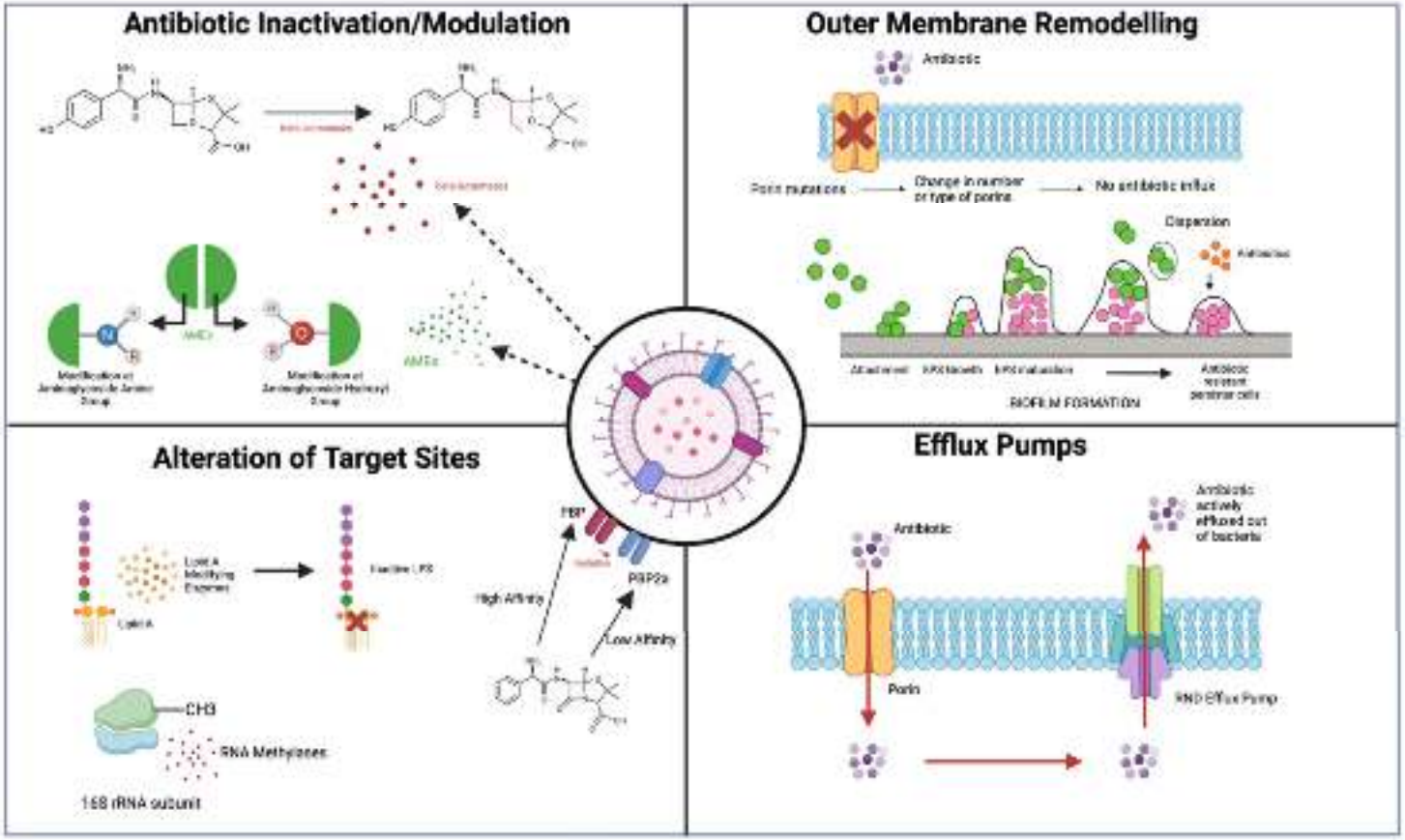
GRAM-NEGATIVE RESISTANCE MECHANISMS



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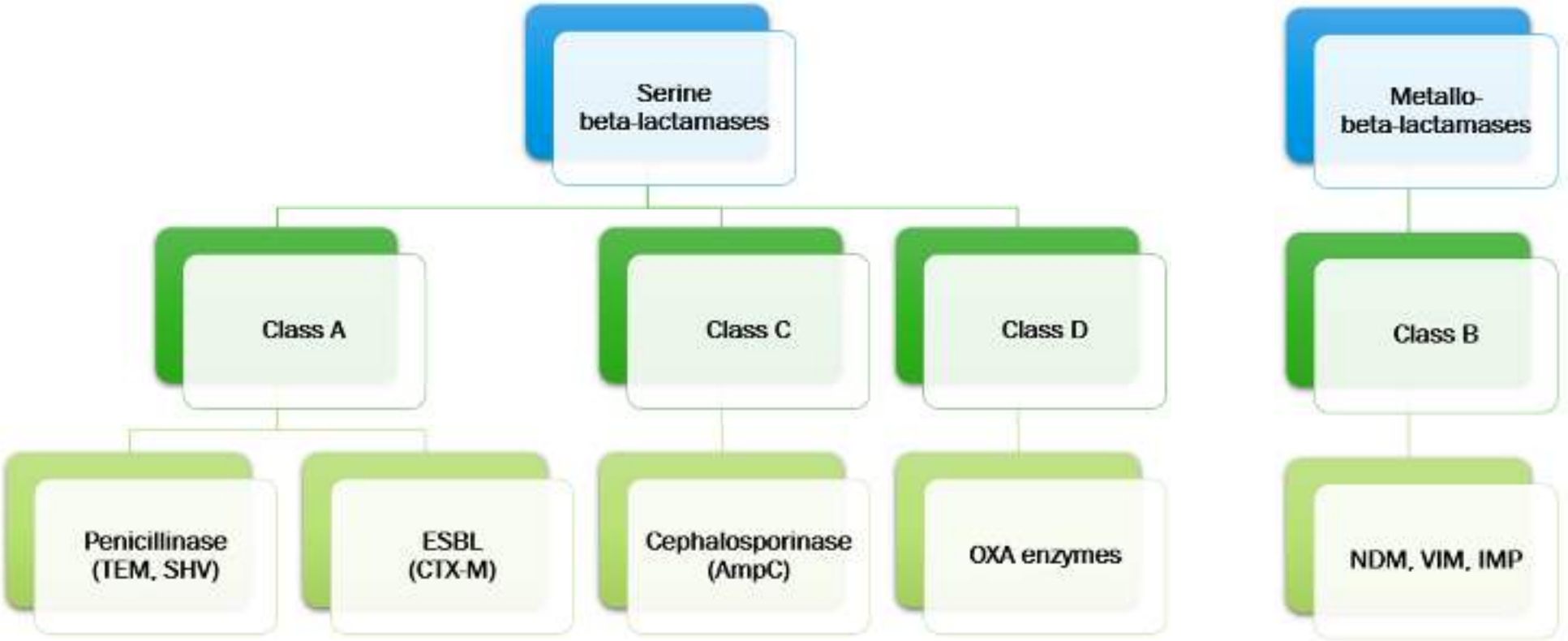
BETA-LACTAMASES – AMBLER CLASSIFICATION



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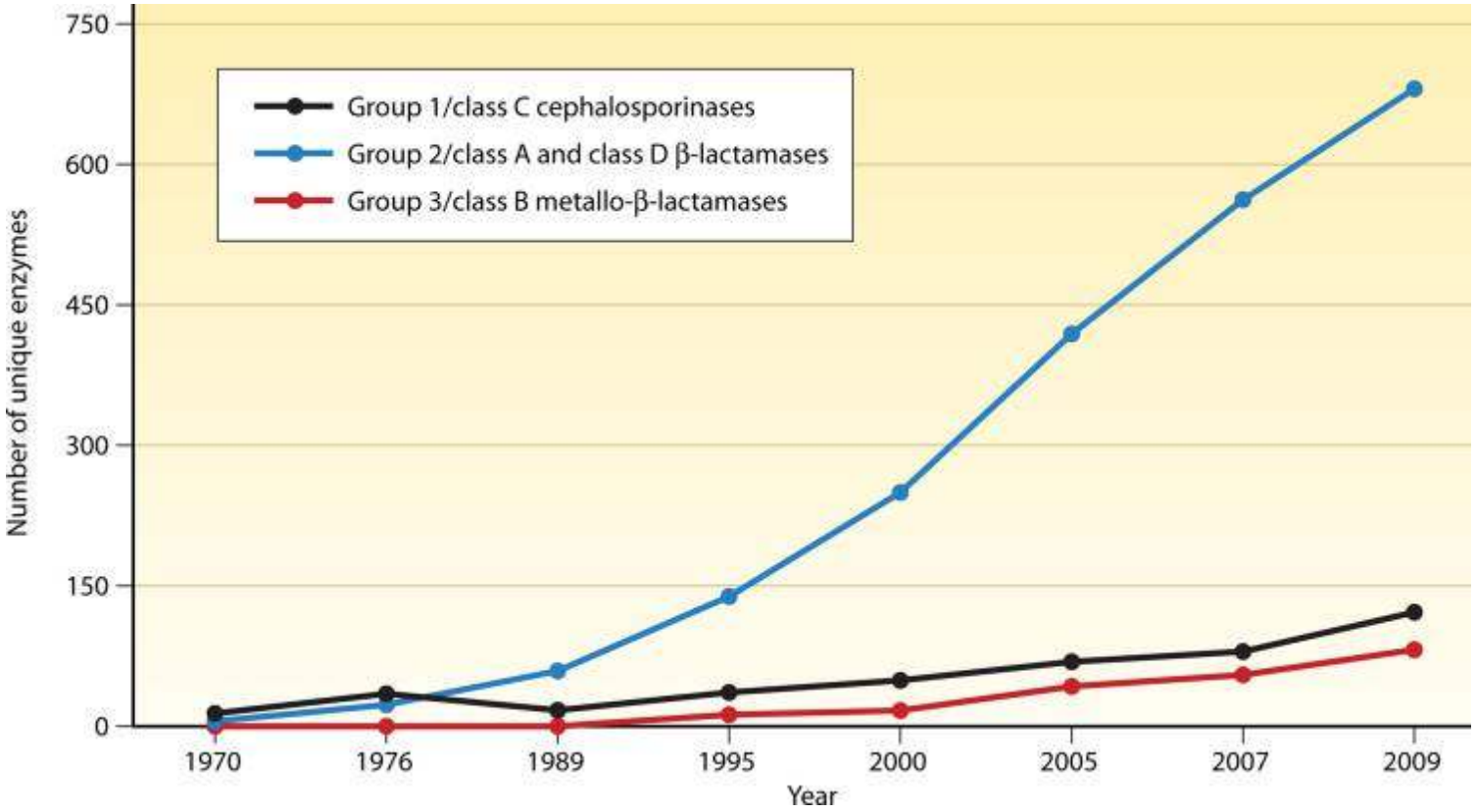

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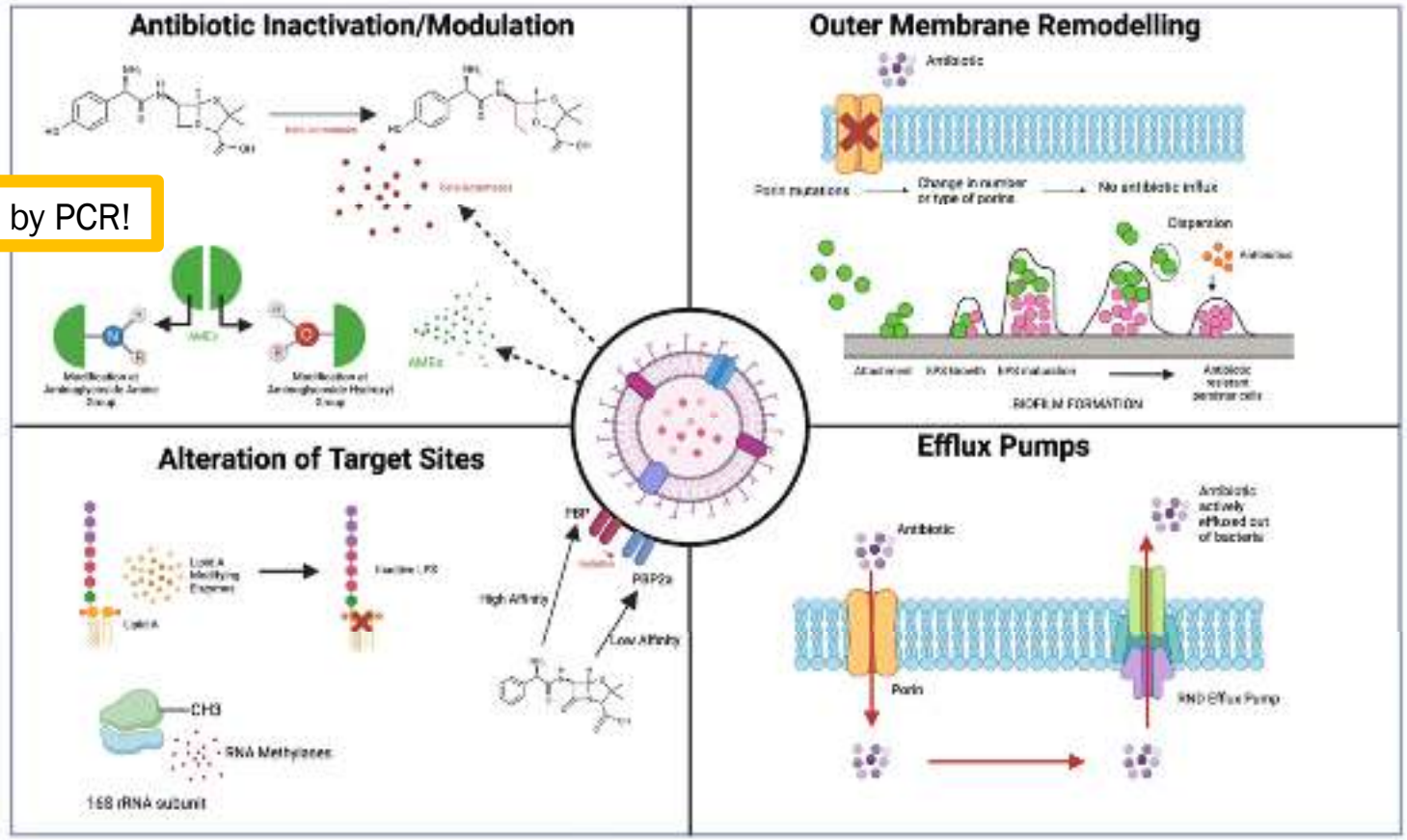
GRAM-NEGATIVE RESISTANCE MECHANISMS

★ Detected by PCR!



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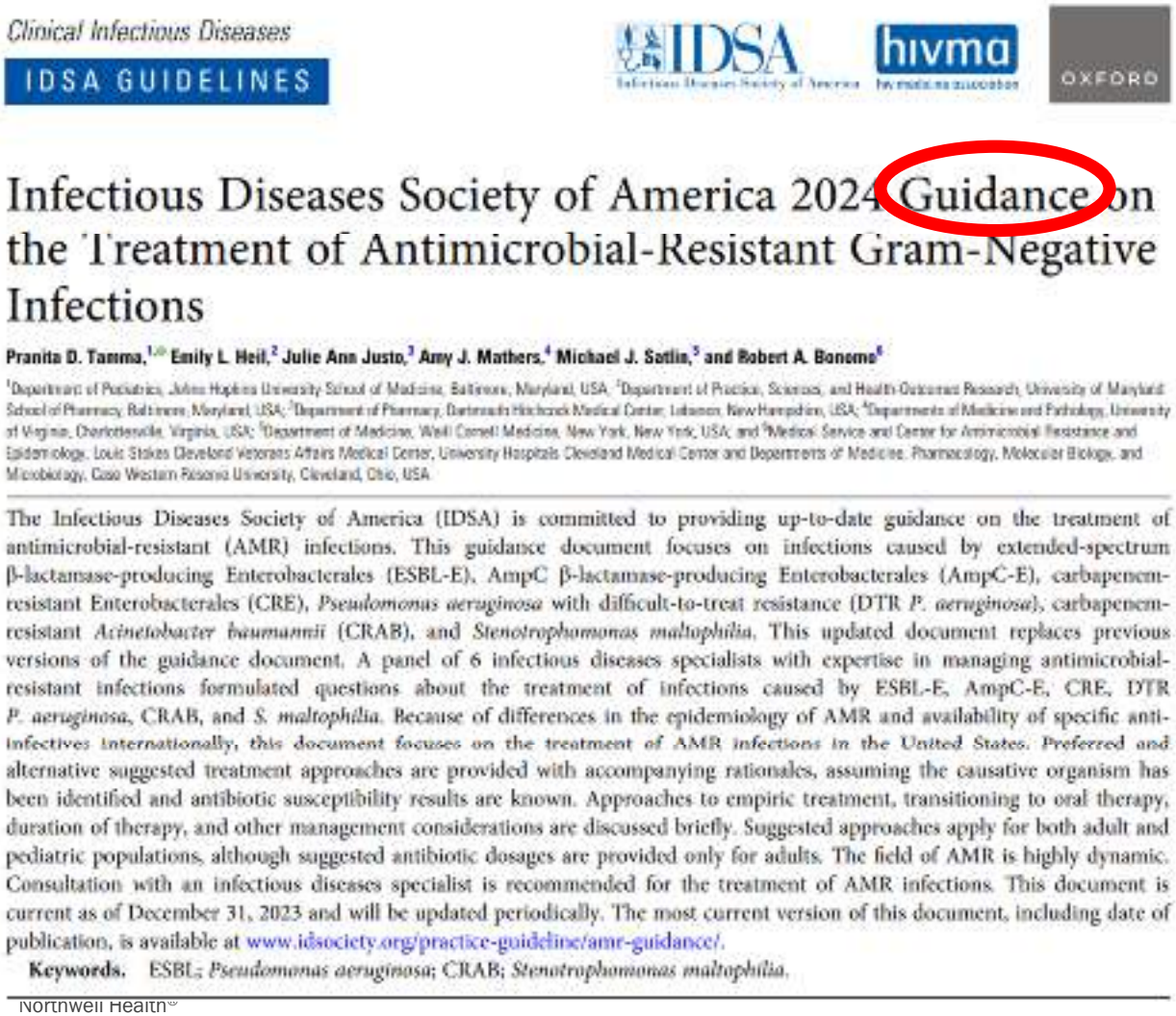

Clinical Infectious Diseases

IDSA GUIDELINES

Infectious Diseases Society of America 2024 Guidance on the Treatment of Antimicrobial-Resistant Gram-Negative Infections

Pranita D. Tamma,[1,a] Emily L. Heil,[2] Julie Ann Justo,[3] Amy J. Mathers,[4] Michael J. Satlin,[5] and Robert A. Bonomo[6]

[1]Department of Pediatrics, Johns Hopkins University School of Medicine, Baltimore, Maryland, USA, [2]Department of Practice, Sciences, and Health Outcomes Research, University of Maryland School of Pharmacy, Baltimore, Maryland, USA, [3]Department of Pharmacy, Dartmouth Hitchcock Medical Center, Lebanon, New Hampshire, USA, [4]Departments of Medicine and Pathology, University of Virginia, Charlottesville, Virginia, USA, [5]Department of Medicine, Weill Cornell Medicine, New York, New York, USA, and [6]Medical Service and Center for Antimicrobial Resistance and Epidemiology, Louis Stokes Cleveland Veterans Affairs Medical Center, University Hospitals Cleveland Medical Center and Departments of Medicine, Pharmacology, Molecular Biology, and Microbiology, Case Western Reserve University, Cleveland, Ohio, USA

The Infectious Diseases Society of America (IDSA) is committed to providing up-to-date guidance on the treatment of antimicrobial-resistant (AMR) infections. This guidance document focuses on infections caused by extended-spectrum β-lactamase-producing Enterobacterales (ESBL-E), AmpC β-lactamase-producing Enterobacterales (AmpC-E), carbapenem-resistant Enterobacterales (CRE), *Pseudomonas aeruginosa* with difficult-to-treat resistance (DTR *P. aeruginosa*), carbapenem-resistant *Acinetobacter baumannii* (CRAB), and *Stenotrophomonas maltophilia*. This updated document replaces previous versions of the guidance document. A panel of 6 infectious diseases specialists with expertise in managing antimicrobial-resistant infections formulated questions about the treatment of infections caused by ESBL-E, AmpC-E, CRE, DTR *P. aeruginosa*, CRAB, and *S. maltophilia*. Because of differences in the epidemiology of AMR and availability of specific anti-infectives internationally, this document focuses on the treatment of AMR infections in the United States. Preferred and alternative suggested treatment approaches are provided with accompanying rationales, assuming the causative organism has been identified and antibiotic susceptibility results are known. Approaches to empiric treatment, transitioning to oral therapy, duration of therapy, and other management considerations are discussed briefly. Suggested approaches apply for both adult and pediatric populations, although suggested antibiotic dosages are provided only for adults. The field of AMR is highly dynamic. Consultation with an infectious diseases specialist is recommended for the treatment of AMR infections. This document is current as of December 31, 2023 and will be updated periodically. The most current version of this document, including date of publication, is available at www.idsociety.org/practice-guideline/amr-guidance/.

Keywords. ESBL; *Pseudomonas aeruginosa*; CRAB; *Stenotrophomonas maltophilia*.

What is a guidance document?

- Presented in the form of answers to clinical questions
- Does not provide a comprehensive review
  - GRADE methodology not used
- Has descriptions of:
  - Clinical trials
  - Resistance mechanisms
  - Susceptibility testing
- Applies to both adults and pediatrics

Grading of Recommendations, Assessment, Development, and Evaluations

ESBL-PRODUCING ENTEROBACTERALES

CASE 1



LK is a 31F with no PMH who presents to the hospital with a wound after falling into a pit 5 days ago. Pt hit her left lower extremity on a rock and developed an open wound with deep lacerations. Pt notes worsening pain, erythema, and warmth around the wound over the last 2 days. On day of admission, her temperature at home was 101.7F. Debridement of the wound was performed in the ED and cultures were sent. Patient received ceftriaxone and vancomycin in the ED. 2 hours after debridement she became hypotensive, unresponsive to fluids and requiring pressors, and was escalated to piperacillin-tazobactam. Wound culture resulted today showing many ESBL *Klebsiella pneumoniae* (susceptibilities pending). Which of the following would be the best treatment approach for LK?

a) Ertapenem 1g q24h

b) Piperacillin-tazobactam 4.5g q6h

c) Ceftazidime-avibactam 2.5g q8h

d) Meropenem 1g q8h

Respond at
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Poll Everywhere

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Ceftazidime-avibactam 2.5g q8h

Meropenem 1g q8h

Edit

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ESBL BACKGROUND

ESBL enzymes do not inactivate non-beta-lactam antibiotics	• e.g. fluoroquinolones, aminoglycosides, TMP-SMX • Resistance would be due to other mechanisms
Any gram-negative organism can harbor ESBL genes	• Most prevalent organisms are *E. coli, K. pneumoniae, K. oxytoca*, and *P. mirabilis*
CTX-M enzymes are the most common ESBL in the US	• Particularly CTX-M-15 • Variants of TEM & SHV may be ESBL
Routine testing for ESBL is not always available	• Typically done by PCR • Can utilize ceftriaxone resistance as a proxy

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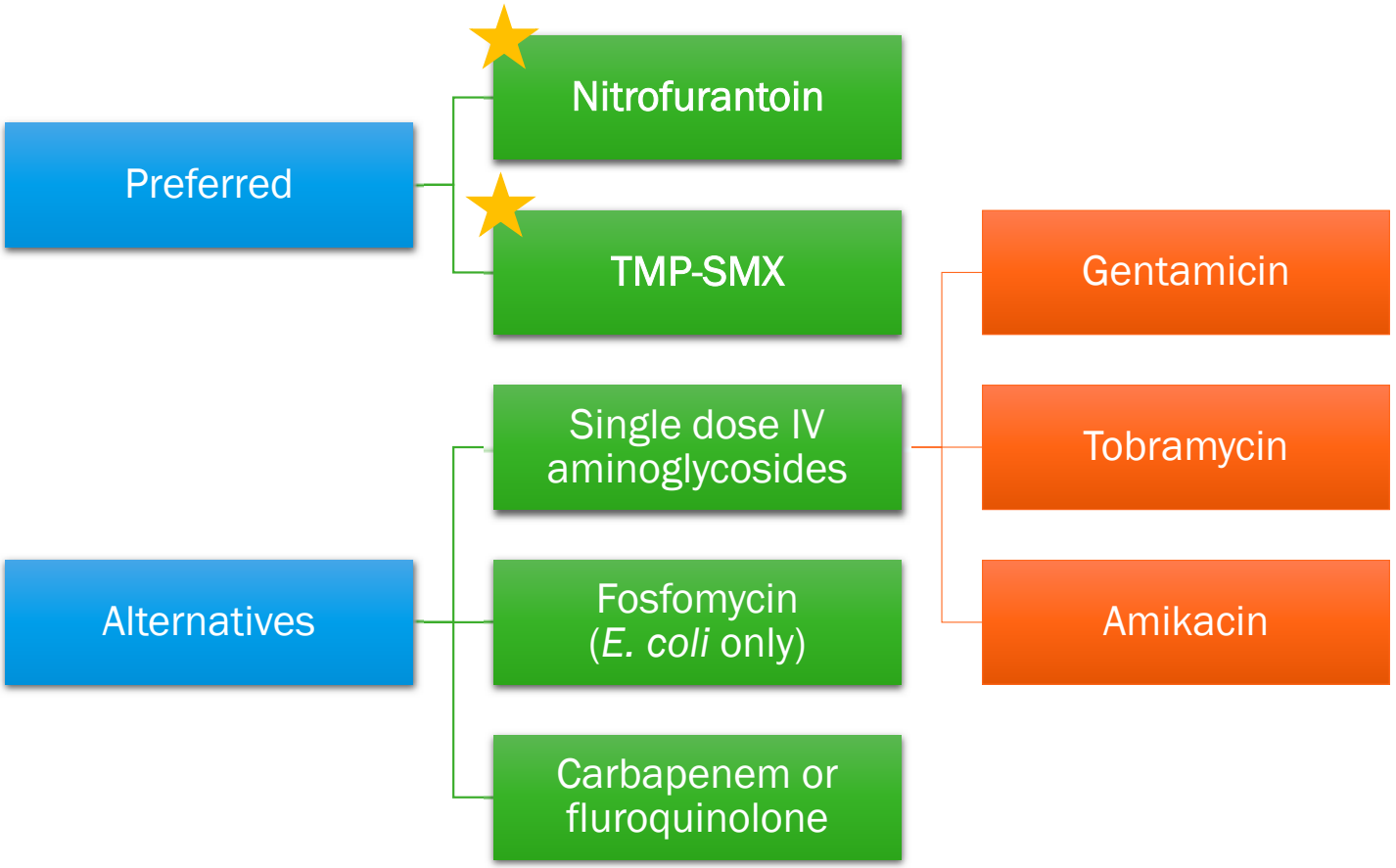
ESBL CYSTITIS TREATMENT



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NITROFURANTOIN (CYSTITIS ONLY)

Nitrofurantoin Targets	
ESBL	
AmpC	
CRE	
DTR-PsAg	
CRAB	
Steno	

Dosing

- Monohydrate/macrocrystals (Macrobid): 100mg PO q12h
- Macrocrystals (Macrodantin): 100mg PO q6h
- Avoid if CrCl < 30 mL/min

Important considerations

- Does not cover:
  - *Morganella morganii*
  - *Proteus* sp.
  - *Providencia* sp.
  - *Serratia marcescens*
- Requires renal function to reach site of infection
- Pulmonary toxicity (chronic use)

FOSFOMYCIN (CYSTITIS ONLY)

Fosfomycin Targets	
ESBL	*E. coli* only
AmpC	
CRE	*E. coli* only
DTR-PsAg	
CRAB	
Steno	

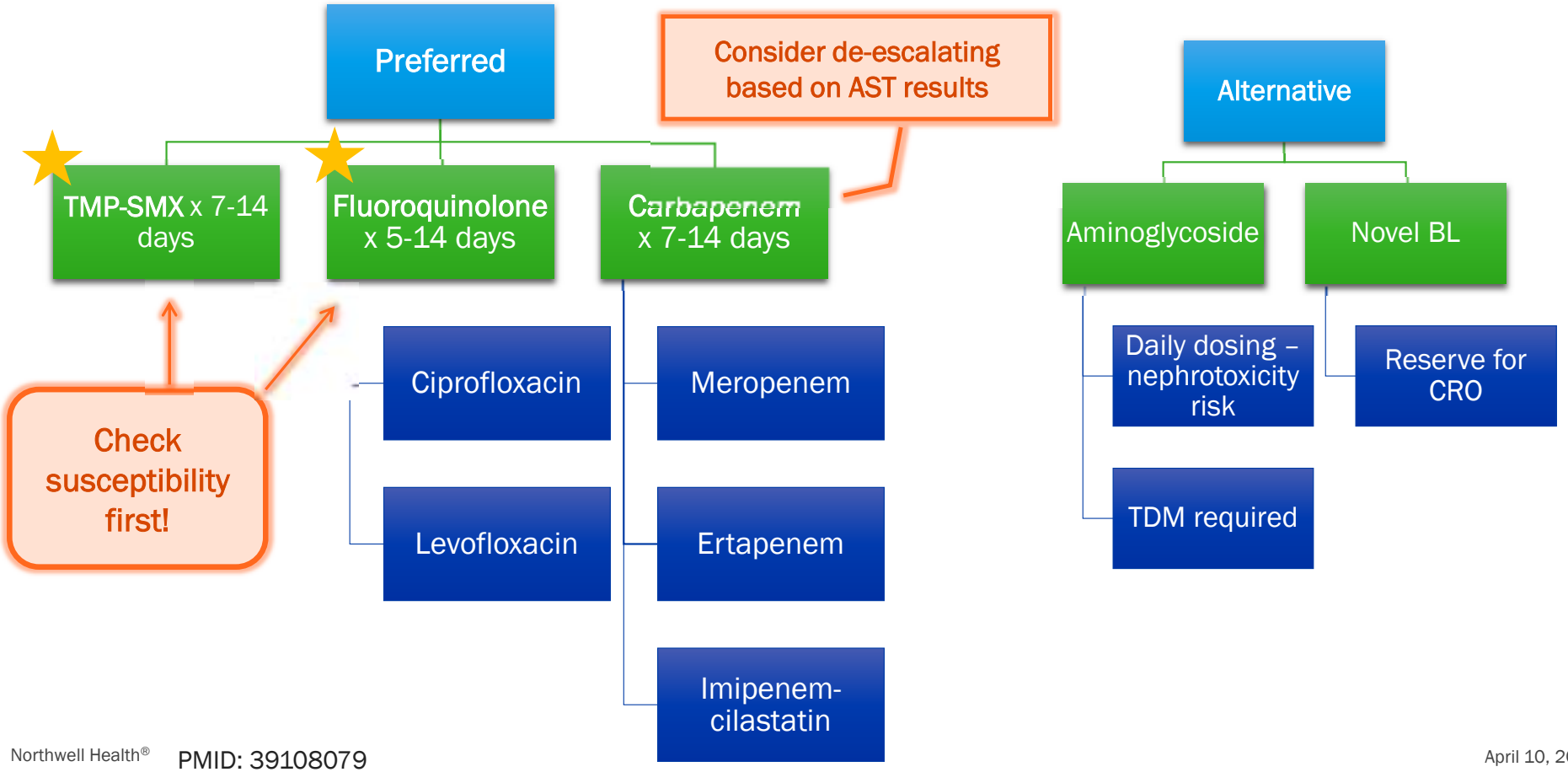
Dosing

- 3g PO x1

Important considerations

- Powder packet must be mixed with 3-4 oz cool water before ingesting
- Only for *E. coli*
- GI upset

ESBL PYELONEPHRITIS/cUTI TREATMENT



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FLUOROQUINOLONES

FQ Targets	
ESBL	
AmpC	
CRE	
DTR-PsAg	
CRAB	
Steno	Levofloxacin only

Fluoroquinolone	Cystitis	Other Infections
Ciprofloxacin	400mg IV q12h 500mg PO q12h	400mg IV q8h 750mg PO q12h
Levofloxacin	750mg IV/PO q24h	750mg IV/PO q24h

Important considerations

- Renal adjustment necessary
- Adverse effects
  - QTc prolongation
  - Glucose dysregulation
  - CNS effects
  - Peripheral neuropathy
  - Tendonitis/tendon rupture
  - Aortic dissection
  - Exacerbation of myasthenia gravis

TRIMETHOPRIM-SULFAMETHOXAZOLE

TMP-SMX Targets	
ESBL	
AmpC	
CRE	
DTR-PsAg	
CRAB	
Steno	

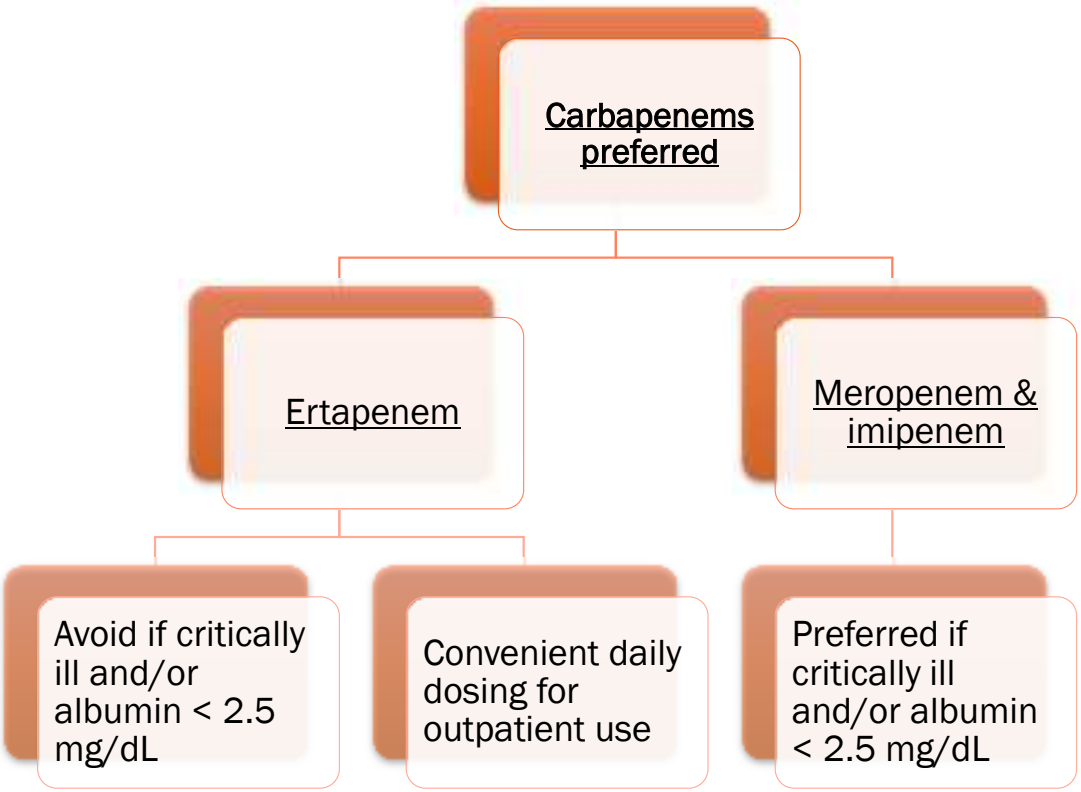
Dosing

- Cystitis: 160mg TMP PO q12h
- Other infections: 10-15 mg/kg/day TMP IV/PO divided q8-12h
- Renal adjustment necessary

Adverse effects

- Hypersensitivity (sulfa)
- Myelosuppression
- Liver injury
- Hyperkalemia
- Hyponatremia
- (Pseudo)nephrotoxicity
- Significant diluent volume (IV formulation)

ESBL INFECTIONS OUTSIDE THE URINARY TRACT



MERINO trial

PMID: 30208454

- Noninferiority RCT of 379 pts with ceftriaxone-R *E. coli* or *K. pneumoniae* BSI
- Randomly assigned 1:1 to pip-tazo 4.5g q6h vs. meropenem 1g q8h
  - Both 30-minute infusions
- 3-fold higher mortality in pip-tazo group (12% vs. 4%) at interim analysis, trial stopped early

CARBAPENEMS

Carbapenem Targets	
ESBL	
AmpC	
CRE	
DTR-PsAg	
CRAB	Used with SUL-DUR, not intrinsically active
Steno	

Carbapenem	Cystitis	Other Infections
Ertapenem*	1g IV q24h over 30 min	1g IV q24h over 30 min
Meropenem	1g IV q8h over 30 min	2g IV q8h over 3 hours
Imipenem	500mg IV q6h over 30 min	500mg IV q6h over 3 hours
Sulopenem**	500mg PO q12h	Not recommended

*Avoid in critically ill patients or hypoalbuminemia

**Sulopenem etzadroxil & probenicid

Important considerations

- Seizure risk (imi > mero > erta)
- Renal adjustment necessary
- Drug interaction with valproic acid

ROLE OF PIPERACILLIN-TAZOBACTAM

Antibiotic	S/R
Amoxicillin	R
Cefazolin	R
Ceftriaxone	R
Cefepime	R
Ciprofloxacin	R
Ertapenem	S
Fosfomycin	S
Gentamicin	S
Levofloxacin	R
Meropenem	S
Nitrofurantoin	S
Piperacillin-tazobactam	S
Trimethoprim-sulfamethoxazole	S

Why is pip-tazo clinically ineffective against ESBL?

- MIC testing may be inaccurate
- High inoculum infections can lead to bacterial regrowth
- Not enough tazobactam to overcome beta-lactamases

Can pip-tazo be used for UTI?

- If pip-tazo is started empirically for cystitis and clinical improvement is demonstrated, no change is necessary
- cUTI may have higher risk of clinical failure, other agents are preferred

PMID: 39108079

NEW ORAL ANTIBIOTICS

Pivmecillinam

- FDA approved 4/2024 for uncomplicated UTI
- Penicillin that preferentially targets PBP-2
- Covers ESBL Enterobacterales
- 185mg PO q8h x 3-7 days

Gepotidacin

- FDA approved 3/2025 for uncomplicated UTI
- First-in-class, targets DNA gyrase and topoisomerase
- Covers ESBL *E. coli*
- 1500mg PO q12h x 5 days

CASE 1



LK is a 31F with no PMH who presents to the hospital with a wound after falling into a pit 5 days ago. Pt hit her LLE on a rock and developed an open wound with deep lacerations. Pt notes worsening pain, erythema, and warmth around the wound over the last 2 days. On day of admission, her temperature at home was 101.7F. Debridement of the wound was performed in the ED and cultures were sent. Patient received ceftriaxone and vancomycin in the ED. 2 hours after debridement she became hypotensive, unresponsive to fluids and requiring pressors, and was escalated to piperacillin-tazobactam. Wound culture resulted today showing many ESBL *Klebsiella pneumoniae* (susceptibilities pending). Which of the following would be the best treatment approach for LK?

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AmpC-PRODUCING ENTEROBACTERALES

CASE 2

WW is a 50M with PMH of lung cancer, currently undergoing chemotherapy. Pt is not a smoker, works as a high school chemistry teacher. He was admitted to the hospital 5 days ago with pneumonia. Pt was initiated on ceftriaxone 2g q24h with initial improvement, but on day 4 he became febrile to 102.1F and hypoxic to 88% requiring 4L nasal cannula. Sputum culture and susceptibilities are now available, and the team would like to know if WW's antibiotic regimen should be changed. Which of the following would you recommend for WW?

a) Change to cefepime 2g q8h

b) Continue ceftriaxone 2g q24h

c) Change to piperacillin-tazobactam 3.375g q8h

d) Change to levofloxacin 750mg q24h

> 100,000 CFU/mL *Enterobacter cloacae*	
Ampicillin	R
Ampicillin-sulbactam	R
Cefazolin	R
Ceftriaxone	S
Cefepime	S
Ciprofloxacin	R
Ertapenem	S
Gentamicin	S
Imipenem	S
Levofloxacin	S
Meropenem	S
Piperacillin-tazobactam	S

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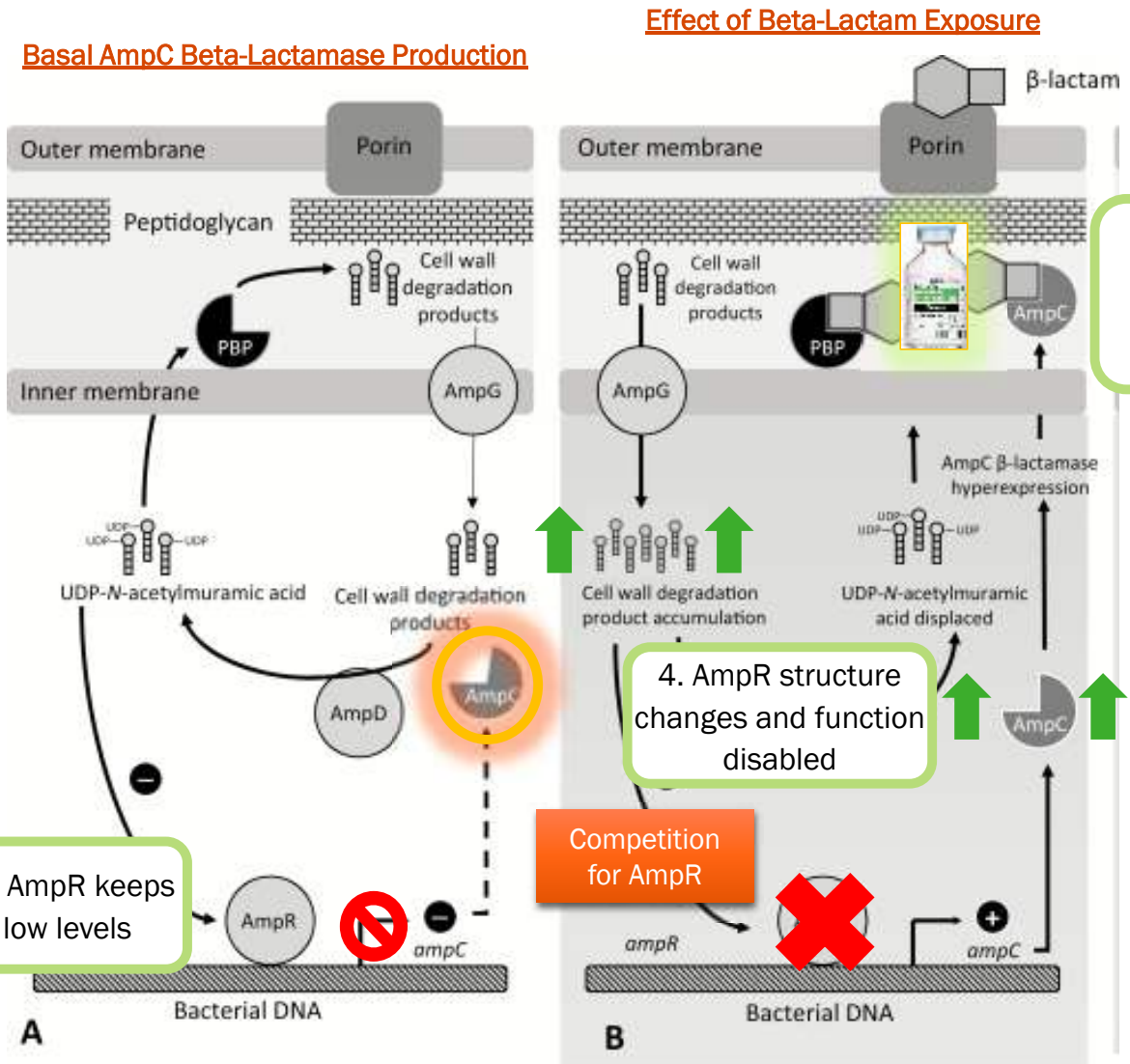
AmpC BETA-LACTAMASE EXPRESSION

1. AmpC is produced at basal levels by many gram-negative organisms

AmpC assists with cell wall recycling



2. Normally, AmpR keeps AmpC at low levels

3. Beta-lactam increases cell wall degradation product accumulation, compete for AmpR

4. AmpR structure changes and function disabled

Competition for AmpR

5. Increases AmpC beta-lactamase production

PMID: 30838380

ORGANISMS AT RISK FOR AmpC PRODUCTION

Hafnia alvei
Enterobacter cloacae
Citrobacter freundii
Klebsiella aerogenes
Yersinia enterocolitica

Moderate Risk (>20%)

- *Enterobacter cloacae,*
- *Klebsiella aerogenes,*
- *Citrobacter freundii*
- Avoid penicillins, 1st - 3rd gen. cephalosporins

Low Risk (< 5%)

- *Serratia marcescens*
- *Morganella morganii*
- *Providencia* sp.
- Can likely use susceptibility results to guide treatment

Less common pathogens

- *Hafnia alvei*
- *Citrobacter youngae*
- *Yersinia enterocolitica*
- Carry AmpC inducible genes, not as well studied

PMID: 39108079

ANTIBIOTIC SELECTION

	Stable vs. AmpC Hydrolysis	Unstable vs. AmpC Hydrolysis
Weak AmpC Inducer	Cefepime	3rd gen. cephalosporins Piperacillin-tazobactam Aztreonam
Strong AmpC inducer	Imipenem	Aminopenicillins 1st-2nd gen. cephalosporins

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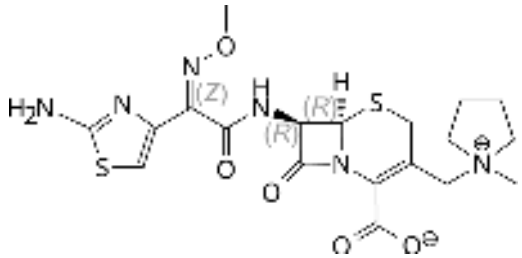
CEFEPIME FOR AmpC BETA-LACTAMASES



Review of evidence

- Meta-analysis included 7 observational studies comparing cefepime to carbapenem
  - No difference in clinical outcomes
  - Several study limitations:
    - Heterogeneity
    - Sicker patients more likely to get carbapenem
    - Risk of AmpC production between species varies
- No clear clinical failure signals demonstrated

PMID: 26542304

Does MIC matter?

- MIC 4-8 mcg/mL is SDD to cefepime
  - SDD: 2g q8h over 3h
- Evaluation of 211 *E. cloacae* isolates from 66 US hospitals
  - 3% carried CTX-M gene
- Evaluation of 77 isolates stratified by MIC showed no correlation between ESBL presence and cefepime MIC

PMID: 26416853

CEFEPIME

Cefepime Targets	
ESBL	
AmpC	
CRE	
DTR-PsAg	
CRAB	
Steno	

Dosing

- Cystitis: 1g IV q8h over 30 min
- Other infections: 2g IV q8h over 3 hours
- Renal adjustment necessary

Adverse effects

- Neurotoxicity
  - Related to GABA antagonism
  - Associated with inappropriate dosing
  - Depressed consciousness, encephalopathy, aphasia, myclonus, seizures

PMID: 34660040

PIPERACILLIN-TAZOBACTAM FOR AmpC BETA-LACTAMASES

Tazobactam

- Less effective than other beta-lactamase inhibitors vs. AmpC

2019 meta-analysis

PMID: 31363762

- 8 observational studies
  - No difference in mortality between pip-tazo and carbapenems
  - Significant heterogeneity, sicker patients more likely to get carbapenem

2021 pilot unblinded clinical trial (MERINO-2)

PMID: 34395716

- 72 patients with infections caused by *E. cloacae, K. aerogenes, C. freundii, M. morganii, Providencia* sp., or *S. marcescens*
- Pip-tazo 4.5g q6h vs. meropenem 1g q8h
- Conflicting findings of components of composite primary outcome
  - Pip-tazo showed lower mortality & microbiological relapse, higher clinical & microbiological failure

OTHER AGENTS FOR AmpC BETA-LACTAMASES

Novel beta-lactams

- Narrower agents preferred
- TOL-TAZ not recommended

Nitrofurantoin

- For uncomplicated cystitis

TMP-SMX

- For cystitis & pyelonephritis/cUTI
- Potential for PO stepdown

Fluoroquinolones

- Alternative for UTI
- Potential for PO stepdown

PMID: 39108079

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Cefepime	S
Ciprofloxacin	R
Ertapenem	S
Gentamicin	S
Imipenem	S
Levofloxacin	S
Meropenem	S
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CARBAPENEM-RESISTANT ENTEROBACTERALES (CRE)

CASE 3

CK is 45M with no PMH admitted to the hospital yesterday with aspiration pneumonia after swimming in the East River. He has received 1 day of meropenem 1g q8h with little improvement in his clinical status. Today, blood culture PCR results identified *Klebsiella pneumoniae*, and KPC gene was detected. Which of the following would be the best treatment approach for CK?

a) Ceftolozane-tazobactam 3g q8h

b) Meropenem-vaborbactam 4g q8h

c) Cefiderocol 2g q8h

d) Eravacycline 1 mg/kg q12h

Respond at pe.app/crab

Poll Everywhere

Which of the following would be the best treatment approach for CK?

0 0

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Meropenem-vaborbactam 4g q8h

Cefiderocol 2g q8h

Eravacycline 1 mg/kg q12h

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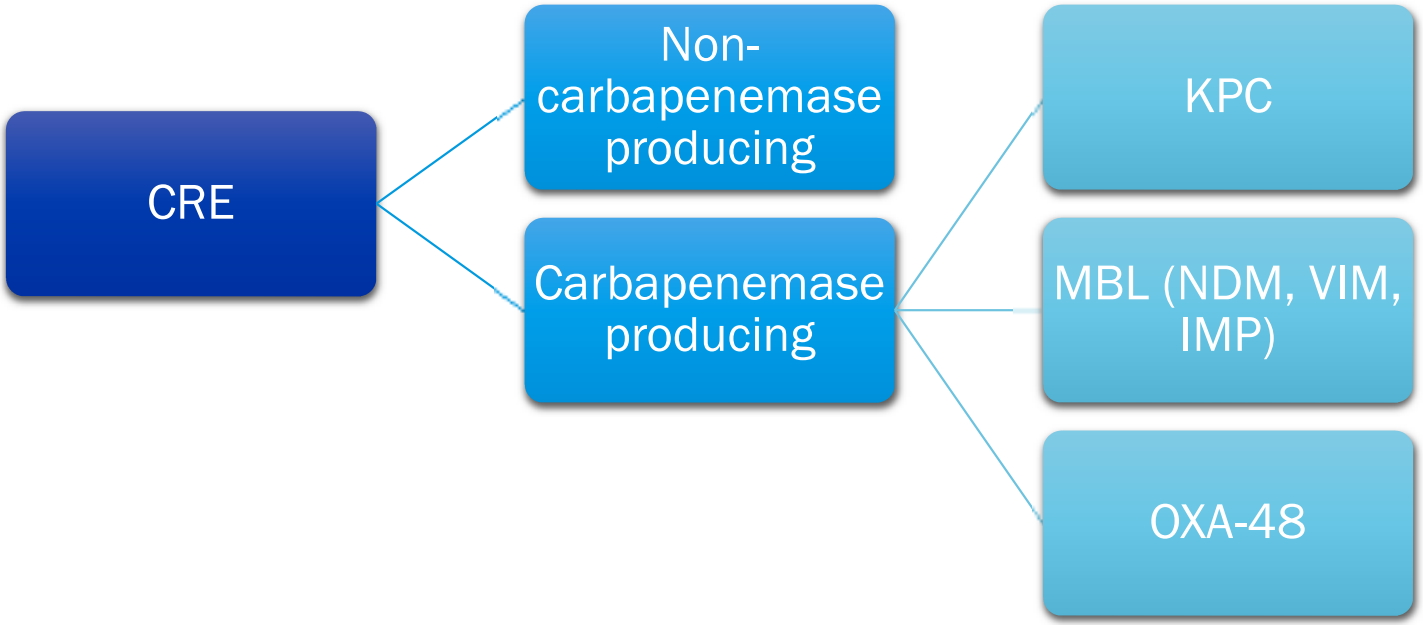
CRE BACKGROUND

CRE are Enterobacterales resistant to at least 1 carbapenem or producing a carbapenemase



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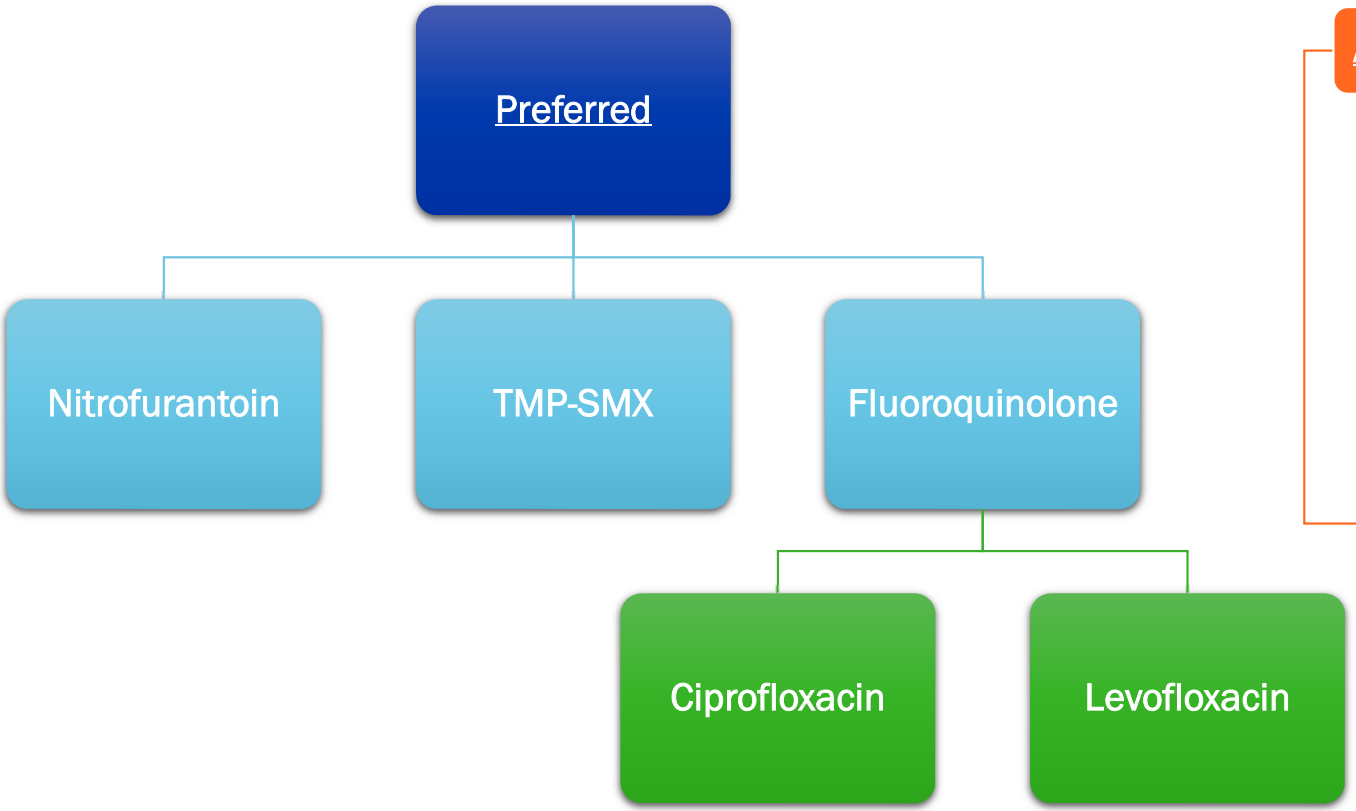
CRE CYSTITIS TREATMENT

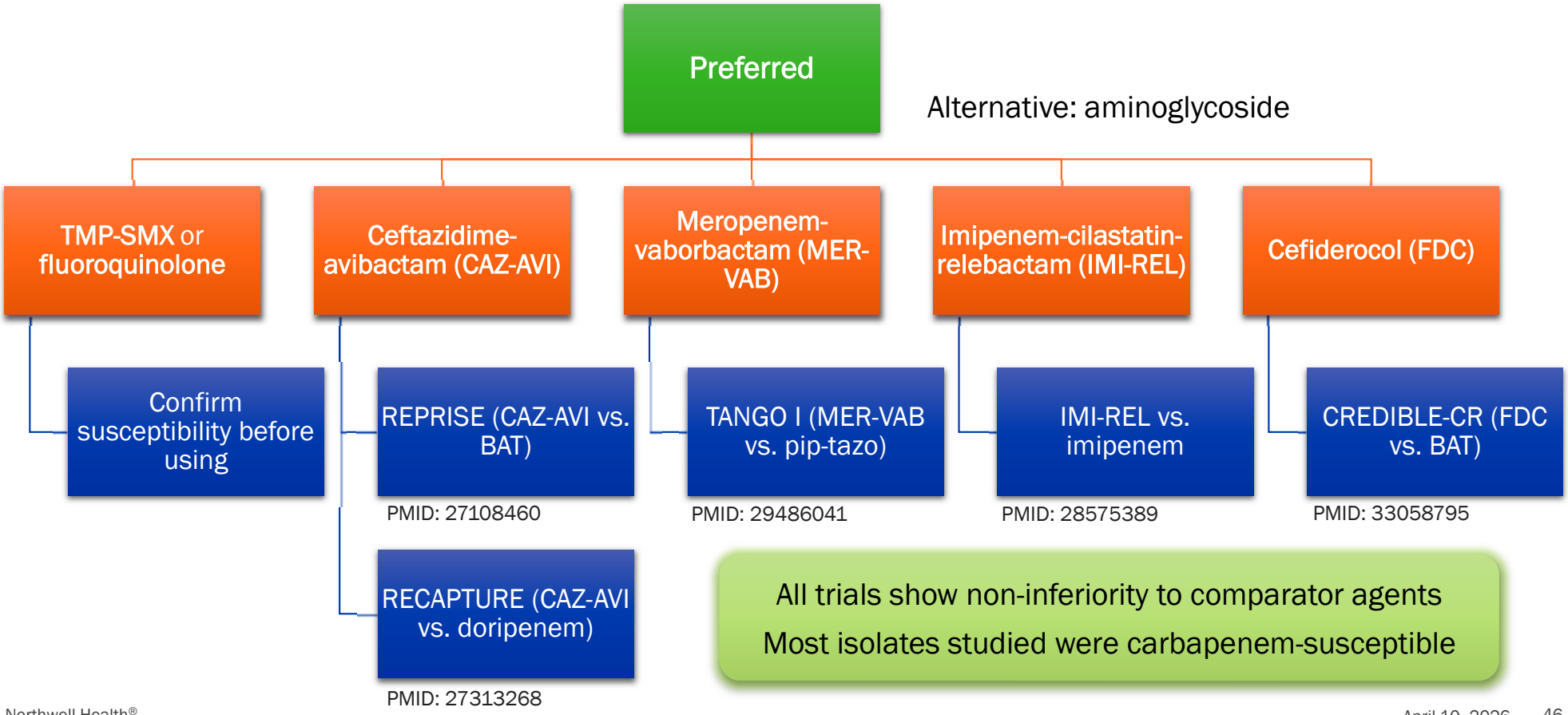


Alternatives

- Single dose IV aminoglycoside
  - Gentamicin
  - Tobramycin
  - Amikacin
- Fosfomycin (*E. coli* only)
- Colistin
- Novel beta-lactams

PMID: 39108079

CRE PYELONEPHRITIS/cUTI TREATMENT



AMINOGLYCOSIDES

ZEMDRI
(plazomicin) injection

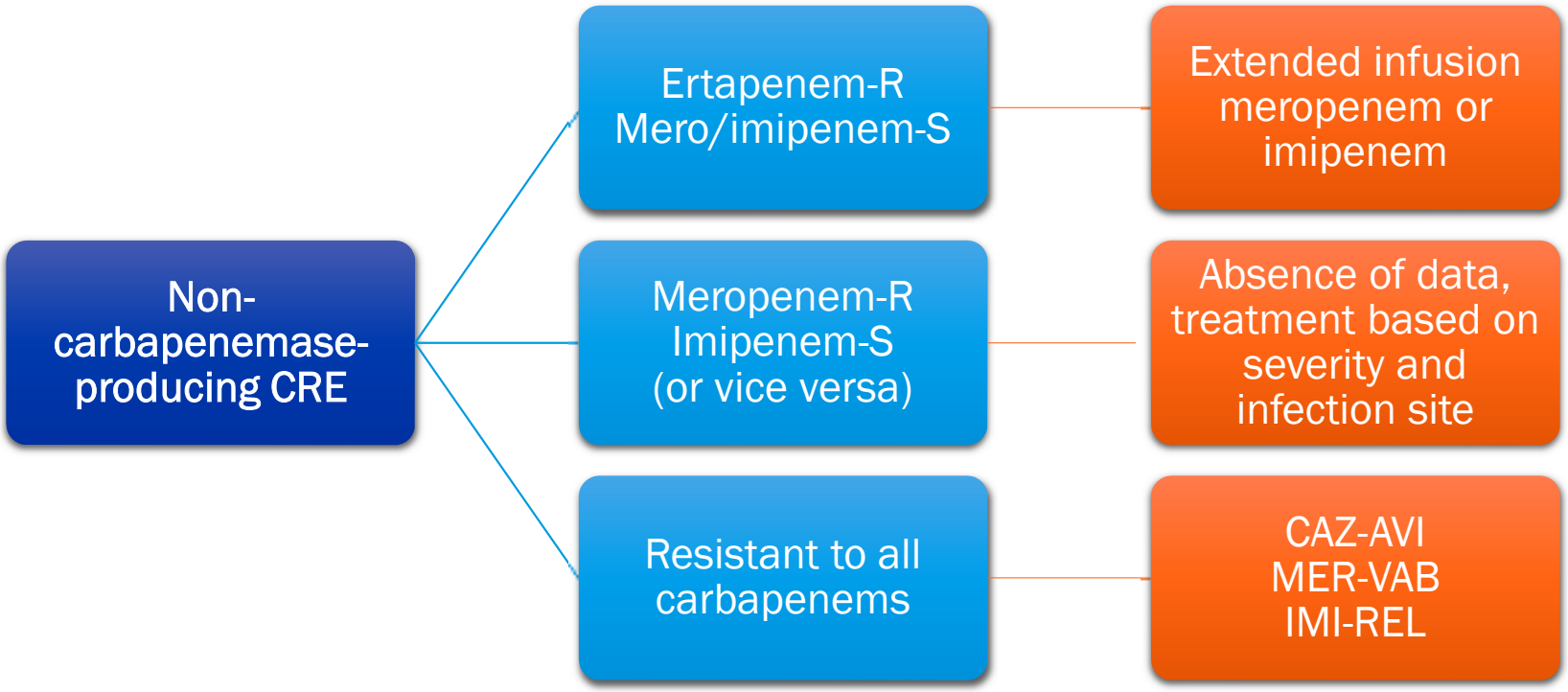
AG Targets	
ESBL	
AmpC	
CRE	
DTR-PsAg	
CRAB	
Steno	

Aminoglycoside	Cystitis	Other Infections
Gentamicin	5 mg/kg IV x1	7 mg/kg IV x1, then use TDM
Tobramycin	5 mg/kg IV x1	7 mg/kg IV x1, then use TDM
Amikacin	15 mg/kg IV x1	15 mg/kg IV x1, then use TDM
Plazomicin	15 mg/kg IV x1	15 mg/kg IV x1, then use TDM

Important considerations

- Not for monotherapy outside of urinary tract
- Duration-dependent nephrotoxicity & ototoxicity
- Requires TDM – extended interval dosing
- *P. aeruginosa*
  - Gentamicin – not recommended
  - Tobramycin – can be used
  - Amikacin – can be used for UTI only

CRE INFECTIONS OUTSIDE THE URINARY TRACT



Can consider tigecycline or eravacycline for non-bloodstream infections

PMID: 39108079

CRE INFECTIONS OUTSIDE THE URINARY TRACT – KPC

- TANGO II – increased clinical cure, decrease mortality, reduced nephrotoxicity compared to BAT

PMID: 30270406

- Superior to aminoglycosides/ polymyxin
- Lower 14-day mortality compared to colistin for CRE bacteremia

PMID: 28559250 34091006

- RESTORE-IMI – favorable overall response and safer than colistin + imipenem

PMID: 39108079

Alternative agents:

Cefiderocol (reserve for MBL)

Tigecycline & eravacyline (non-bloodstream or urinary tract infections)

CEFTAZIDIME-AVIBACTAM

CAZ-AVI Targets		
ESBL		
AmpC		
CRE	KPC OXA-48	MBL
DTR-PsAg		
CRAB		
Steno		

Dosing

- 2.5g IV q8h over 3 hours
- Renal adjustment necessary

Adverse effects

- Seizures
- GI upset
- Hypersensitivity (cross-reacts with aztreonam)

MEROPENEM-VABORBACTAM

MER-VAB Targets		
ESBL		
AmpC		
CRE	KPC	MBL OXA-48
DTR-PsAg		
CRAB		
Steno		

Dosing

- 4g IV q8h over 3 hours
  - 2g meropenem 2g vaborbactam
- Renal adjustment necessary

Adverse effects

- Seizures
- GI upset
- Drug interaction with valproic acid

Other considerations

- Short product stability after reconstitution
  - 4 hours room temperature
  - 22 hours refrigerator

IMIPENEM-CILASTATIN-RELEBACTAM

IMI-REL Targets		
ESBL		
AmpC		
CRE	KPC	MBL OXA-48
DTR-PsAg		
CRAB		
Steno		

Dosing

- 1.25g IV q6h over 3 hours
  - 500mg imipenem, 500mg cilastatin, 250mg relebactam
- Renal adjustment necessary

Adverse effects

- Seizures
- GI upset
- Drug interaction with valproic acid

CRE INFECTIONS OUTSIDE THE URINARY TRACT – MBL

- FDA approved 2/2025
- Replaced CAZ-AVI + AZT combination
- REVISIT – comparable efficacy clinical cure at day-28 compared to meropenem ± colistin
- ASSEMBLE – higher clinical cure compared to BAT in confirmed MBL infections

PMID: 39389071, 40727714

- Novel beta-lactam mechanism utilizing active transport via iron transporters
- Cohort of 200 MBL-producing Enterobacterales – 92% susceptible to cefiderocol PMID: 37390312
- MBL in CREDIBLE-CR + APEKS-NP: higher clinical cure and lower mortality compared to polymyxin-based regimen PMID: 35148378

Alternative: tigecycline or eravacycline for non-bloodstream or urinary tract infections

AZTREONAM-AVIBACTAM

AZT-AVI Targets		
ESBL		
AmpC		
CRE	KPC MBL	OXA-48
DTR-PsAg		
CRAB		
Steno		

Dosing

- 2.67g IV x1, then 2g IV q6h over 3 hours
  - 2g dose = 1.5g aztreonam + 500mg avibactam
- Renal adjustment necessary

Adverse effects

- Increase in AST/ALT
- GI upset
- Hypersensitivity (cross-reacts with ceftazidime)
- Toxic epidermal necrolysis (TEN)
  - Bone marrow transplant patients with risk factors

CEFIDEROCOL

FDC Targets		
ESBL		
AmpC		
CRE	KPC MBL	OXA-48
DTR-PsAg		
CRAB		
Steno		

Dosing

- 2g IV q8h over 3 hours
- Renal adjustment necessary
  - CrCl > 120 mL/min: 2g IV q6h over 3 hours

Adverse effects

- Seizures/CNS effects
- Increase in AST/ALT
- GI upset
- Hypersensitivity (cross-reacts with aztreonam)

GAME-CHANGER TRIAL (10/2025)

- Open label RCT: FDC vs. SOC for patient with nosocomial gram-negative PNA
- FDC non-inferior, not superior to SOC antibiotics
- 14-day all cause mortality 14% FDC vs. 10% SOC

Organisms in index blood culture		
Escherichia coli	90 (36%)	77 (30%)
Klebsiella pneumoniae	73 (29%)	80 (31%)
Enterobacter spp	19 (8%)	21 (8%)
Other Enterobacterales spp‖	26 (10%)	33 (13%)
Pseudomonas spp**	27 (11%)	24 (9%)
Acinetobacter spp††	18 (7%)	25 (10%)
Stenotrophomonas maltophilia	5 (2%)	3 (1%)
Aeromonas spp	7 (3%)	3 (1%)
Miscellaneous non-fermenter	8 (3%)	7 (3%)
Other species	1 (<1%)	2 (1%)

Antimicrobial-resistant organisms		
Third-generation cephalosporin-resistant Enterobacterales spp	66 (26%)	72 (28%)
Carbapenem-resistant Enterobacterales spp	32 (13%)	32 (13%)
Cefiderocol-resistant Enterobacterales spp	12 (5%)	10 (4%)
KPC-producing Enterobacterales spp	1 (<1%)	3 (1%)
OXA-48-like-producing Enterobacterales spp	11 (4%)	15 (6%)
MBL-producing Enterobacterales spp	16 (6%)	11 (4%)
Carbapenem-resistant *Acinetobacter* spp	11 (4%)	14 (6%)
Cefiderocol-resistant *Acinetobacter* spp	2 (1%)	0 (0)
Carbapenem-resistant *Pseudomonas* spp‡‡	8 (3%)	8 (3%)
Cefiderocol-resistant *Pseudomonas* spp	2 (1%)	0 (0)
Carbapenem-resistant Gram-negative bacilli	64 (26%)	63 (25%)

PMID: 41067237

CRE INFECTIONS OUTSIDE THE URINARY TRACT – OXA-48

Preferred: ceftazidime-avibactam

- Retrospective single-center observational study of CAZ-AVI vs. BAT
  - Clinical success more common in CAZ-AVI group PMID: 35939239
- Observational study of 171 patients with OXA-48 treated with CAZ-AVI (no comparator)
  - 30-day mortality in 22% of patients PMID: 36237571

Alternative: cefiderocol

- OXA-48 included in CREDIBLE-CR + APEKS-NP PMID: 36094308
  - All were alive at day 28 and 7 achieved clinical cure
- Fewer supporting data compared to CAZ-AVI

Alternative: tigecycline or eravacycline

- For non-bloodstream or urinary tract infections

ROLE OF NON-BETA-LACTAM ANTIBIOTICS FOR CRE INFECTIONS

Tetracyclines

- Tigecycline & eravacycline
- Achieve rapid tissue distribution after administration
  - Results in limited serum and urinary concentrations
- Consider as alternatives for IAI, SSTI, OM, respiratory infections
- Nausea & emesis in 20-40% of patients

Polymyxins

- Associated with increased mortality and nephrotoxicity
- Concerns about:
  - Clinical efficacy
  - PK/PD data
  - Accuracy of susceptibility testing

Combination therapy

- e.g. beta-lactam + non-beta-lactam agent
- Does not offer additional benefit after susceptibility to a beta-lactam has been demonstrated

PMID: 39108079

CASE 3

CK is 45M with no PMH admitted to the hospital yesterday with aspiration pneumonia after swimming in the East River. He has received 1 day of meropenem 1g q8h with little improvement in his clinical status. Today, blood culture PCR results identified *Klebsiella pneumoniae*, and KPC gene was detected. Which of the following would be the best treatment approach for CK?

a) Ceftolozane-tazobactam 3g q8h

b) Meropenem-vaborbactam 4g q8h

c) Cefiderocol 2g q8h

d) Eravacycline 1 mg/kg q12h

Respond at
pe.app/crab

Poll Everywhere

Which of the following would be the best treatment approach for CK?

0 0

Ceftolozane-tazobactam 3g q8h

Meropenem-vaborbactam 4g q8h

Cefiderocol 2g q8h

Eravacycline 1 mg/kg q12h

Edit

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DIFFICULT-TO-TREAT *Pseudomonas aeruginosa* (DTR-PsAg)

CASE 4

JG is a 65M with PMH of HTN, HLD, and DM2. His A1C is 8.1%. He presented to the ED 4 days ago after falling into the creek at Ramsett Park. Pt had a wound on his R foot for 2 weeks before admission. The wound was stable until his fall 3 days before admission, at which point the wound became more painful and purulent. Now, JG has been receiving vancomycin and cefepime and his wound culture results show difficult-to-treat *P. aeruginosa*. Which of the following antibiotic regimens would be most appropriate for JG?

a) Ceftolozane-tazobactam 3g q8h

b) Imipenem-cilastatin 500mg q6h

c) Meropenem-vaborbactam 4g q8h

d) Tobramycin 7 mg/kg q24h

Respond at
pe.app/crab

Poll Everywhere

Which of the following antibiotic regimens would be most appropriate for JG?

0 0

Ceftolozane-tazobactam 3g q8h

Imipenem-cilastatin 500mg q6h

Meropenem-vaborbactam 4g q8h

Tobramycin 7 mg/kg q24h

Edit

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DTR PsAg BACKGROUND

Difference between MDR and DTR

- MDR: not susceptible to at least one antibiotic in at least 3 antibiotic classes
- DTR: non-susceptibility to all of the following:
  - Piperacillin-tazobactam
  - Ceftazidime
  - Cefepime
  - Aztreonam
  - Meropenem/imipenem
  - Ciprofloxacin/levofloxacin

Multiple resistance mechanisms

- ↓ expression of outer membrane porins (OprD)
- ↑ in *Pseudmonas*-derived cephalosporinases
  - AKA Pseudomonas AmpC enzymes
- ↑ efflux pumps (MexAB-OprM)
- Mutations in PBP targets
- Presence of ESBLs (bla_{OXA-10})
- Carbapenemases uncommon in US, prevalent in Latin America & Asia
  - bla_{KPC} or bla_{VIM}

PMID: 39108079

DIFFERENCES IN NOVEL BETA-LACTAM ACTIVITY FOR PsAg

US Surveillance Data for Carbapenem-R PsAg

*lower percentages seen with cystic fibrosis isolates

What is ceftolozane?

- 5th generation cephalosporin with enhanced activity
- Heavier side chain than ceftazidime, limits hydrolysis by beta-lactamase

Role of MER-VAB

- Vaborbactam does not restore activity of meropenem
- No established breakpoints
- Avoid use for DTR PsAg

PMID: 26728849, 25182652

DTR PsAg CYSTITIS TREATMENT

Preferred

- Ceftolozane-tazobactam
- Ceftazidime-avibactam
- Imipenem-relebactam
- Cefiderocol
- All non-inferior to comparator, insufficient data to favor single agent

Alternative

- Single-dose tobramycin or amikacin

PMID: 39108079

Table 1. Status of Breakpoint Revisions for Aminoglycosides in CLSI M100-Ed33

Aminoglycoside	Organism/Organism Group	
	Enterobacterales	*P. aeruginosa*
Gentamicin	Lowered	Deleted
Tobramycin	Lowered	Lowered
Amikacin	Lowered	Changed to urine only
Plazomicin	Added	-

https://clsi.org/about/press-releases/ast-news-update-june-2023-new-clsi-m100-ed33-updated-aminoglycoside-breakpoints-for-enterobacterales-and-pseudomonas-aeruginosa/

DTR PsAg PYELONEPHRITIS/cUTI

Preferred

- Ceftolozane-tazobactam
  - ASPECT-cUTI – non-inferior to levofloxacin (25931244)
- Ceftazidime-avibactam
  - REPRISE – effective against BAT (27107460)
- Imipenem-relebactam
  - Noninferior to imipenem (28575389)
- Cefiderocol
  - Non-inferior to imipenem (30509675)

Alternative

- Once-daily tobramycin or amikacin
  - Duration-dependent risk of nephrotoxicity
  - Useful for completing treatment course

PMID: 39108079

DTR PsAg INFECTIONS OUTSIDE THE URINARY TRACT

Ceftolozane-tazobactam

Ceftazidime-avibactam

Imipenem-relebactam

- Majority of studied patients were not infected with DTR PsAg
  - Focus on MDR PsAg, not DTR PsAg
  - Compare novel beta-lactams with older agents (e.g. polymyxin)
- Antibiotics selected based on *in vitro* activity, observational studies, and clinical trial data

PMID: 39108079

Alternative: Cefiderocol

- Use when preferred agents are inactive, not tolerated, or unavailable
- CREDIBLE-CR – non-inferior to polymyxin, but does not improve outcomes
  (PMID: 33058795)

CEFTOLOZANE-TAZOBACTAM

TOL-TAZ Targets	
ESBL	
AmpC	
CRE	
DTR-PsAg	
CRAB	
Steno	

Dosing

- Cystitis: 1.5g IV q8h over 1 hour
- Other infections: 3g IV q8h over 3 hours
- Renal adjustment necessary

Adverse effects

- GI (nausea, diarrhea)
- Hypersensitivity

OTHER TREATMENT APPROACHES FOR DTR PsAg

Combination therapy

- Empiric combination therapy to broaden likelihood of active agent is reasonable
  - e.g. add tobramycin
- Continued combination therapy after susceptibility available offers no benefit

Nebulized antibiotics

- Conflicting findings in observational trials
- 3 clinical trials compared to placebo showed no survival benefit or improved outcomes
- Meta-analysis showed associated with partial symptom resolution PMID: 33772055
  - Significant heterogeneity

CASE 4

JG is a 65M with PMH of HTN, HLD, and DM2. His A1C is 8.1%. He presented to the ED 4 days ago after falling into the creek at Ramsett Park. Pt had a wound on his R foot for 2 weeks before admission. The wound was stable until his fall 3 days before admission, at which point the wound became more painful and purulent. Now, JG has been receiving vancomycin and cefepime and his wound culture results show difficult-to-treat *P. aeruginosa*. Which of the following antibiotic regimens would be most appropriate for JG?

a) Ceftolozane-tazobactam 3g q8h

b) Imipenem-cilastatin 500mg q6h

c) Meropenem-vaborbactam 4g q8h

d) Tobramycin 7 mg/kg q24h

Respond at
pe.app/crab

Poll Everywhere

Which of the following antibiotic regimens would be most appropriate for JG?

0 0

Ceftolozane-tazobactam 3g q8h

Imipenem-cilastatin 500mg q6h

Meropenem-vaborbactam 4g q8h

Tobramycin 7 mg/kg q24h

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CARBAPENEM-RESISTANT *Acinetobacter baumannii* (CRAB)

CASE 5

TS is a 52M with PMH depression on fluoxetine who is admitted to the hospital for a gunshot to the abdomen by his uncle. TS has been intubated in the ICU for 1 week. 2 days ago, pt was febrile to 101.9F, tachycardic to 133bpm, and requiring pressors. He was started on meropenem 2g q8h + amikacin 15 mg/kg q24h. A sample was taken from his ET tube and sent for culture. Results are now available, showing carbapenem-resistant *A. baumannii*. Which of the following would be the optimal regimen for TS based on his culture results?

a) Ampicillin-sulbactam 9g q8h + polymyxin B

b) Sulbactam-durlobactam 2g q6h (with imipenem) + minocycline 200mg q12h

c) Meropenem 2g q8h + minocycline 200mg q12h

d) Cefiderocol 2g q8h + minocycline 200mg q12h

Respond at pe.app/crab

Poll Everywhere

Which of the following would be the optimal regimen for TS based on his culture results?

0 0

Ampicillin-sulbactam 9g q8h + polymyxin B

Sulbactam-durlobactam 2g q6h + minocycline 200mg q12h

Meropenem 2g q8h + minocycline 200mg q12h

Cefiderocol 2g q8h + minocycline 200mg q12h

Edit

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CRAB BACKGROUND

Colonization vs. infection

- Commonly in respiratory and wound cultures
- Underlying host factors complicate infection diagnosis

Resistance develops quickly

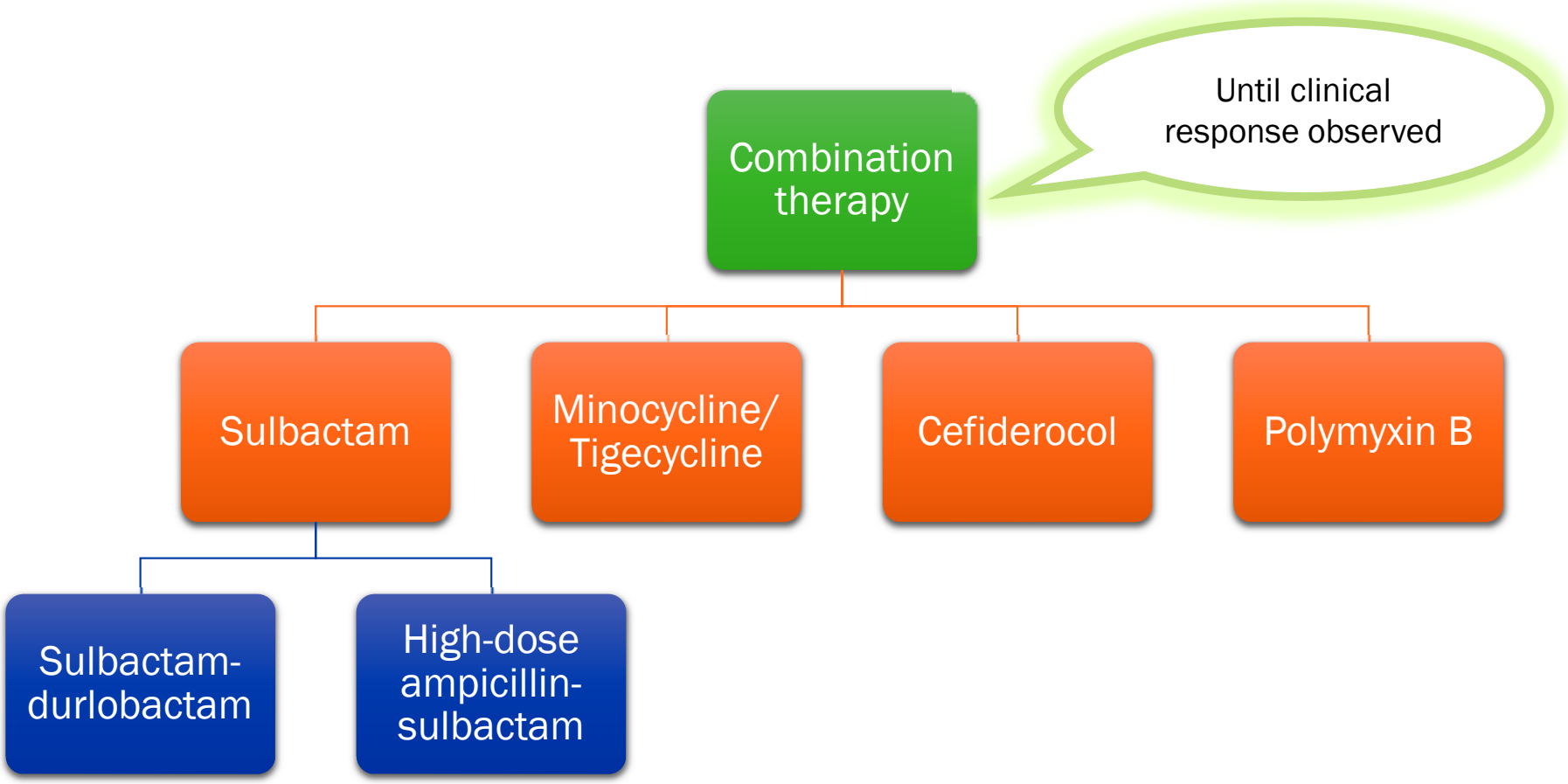
- Production of OXA carbapenemases
- PBP mutations
- Chromosomal mutations

No standard-of-care antibiotics

- Robust comparative studies limited
- Data prioritizing agents or showing benefit of combination therapy not available

PMID: 39108079

GENERAL APPROACH TO TREATMENT OF CRAB



PMID: 39108079

STUDIES EVALUATING COMBINATION THERAPY FOR CRAB

Study	Patients (n)	Infection	Intervention	Outcome	Results
E. Durante-Mangoni et al. 23616495	210 (ICU)	Invasive CRAB	Colistin + rifampin vs. colistin	30-day mortality	No difference
H. Aydemir et al. 22954403	43	CRAB pneumonia	Colistin + rifampin vs. colistin	Clinical response	73% C vs. 62% C+R No significant difference
H.J. Park et al. 30476654	9	Colistin-R A. baumannii	Colistin + rifampin vs. colistin	30-day mortality	No difference
R, Sirijatuphat et al. 24982065	92	Range of CRAB infections	Colistin + fosfomycin vs. colistin	28-day mortality	57% C vs. 47% C+R
M. Paul et al. 29456043	312	CRAB BSI, UTI, pneumonia	Colistin + meropenem vs. colistin	28-day mortality	46% C vs. 52% C+M
K.S. Kaye et al. 37538951	329	CRAB BSI, pneumonia	Colistin + meropenem vs. colistin	28-day mortality	No difference
D. Makris et al. 29531445	39	CRAB pneumonia	Colistin + AMP-SUL vs. colistin	Clinical improvement by day 5	16% C vs. 70% C + AS

ROLE OF SULBACTAM-DURLOBACTAM FOR CRAB

Durlobactam

- Potent inhibition of beta-lactamases:
  - Class A (TEM-1)
  - Class C (ADC)
  - Class D (OXA)
- Reduces likelihood of sulbactam hydrolysis, able to reach PBP target

Formulation

- 1g sulbactam & 1g durlobactam (500mg vial x2) = 2g q6h over 3h
- Achieves PK/PD target attainment for > 90% of isolates
  - MIC ≤ 4/4 mcg/mL (FDA & CLSI breakpoint)

PMID: 39108079

ATTACK trial

- Randomized 125 patients with CRAB PNA or BSI to SUL-DUR vs. colistin, both with imipenem
- 30-day mortality 19% vs. 32%, respectively
  - Non-inferior

PMID: 37182534

Role of imipenem

- Meropenem also can be used
- May lower SUL-DUR MIC 1-2 fold
- Protected by durlobactam
- Not studied without imipenem
- If prolonged duration, reasonable to dc imipenem after clinical improvement

SULBACTAM-DURLOBACTAM

XACDURO (sulbactam for injection; durlobactam for injection), co-packaged for intravenous use

SUL-DUR Targets	
ESBL	
AmpC	
CRE	
DTR-PsAg	
CRAB	
Steno	

Dosing

- 2g IV q6h over 3 hours
  - 1g sulbactam + 1g durlobactam
- Renal adjustment necessary
  - CrCl > 130 mL/min: 2g IV q4h over 3 hours

Adverse effects

- Increase in AST/ALT
- GI upset

Preparation

- 1g sulbactam vial x1 + 500mg durlobactam vial x2
- Reconstitute with NS and store in refrigerator, use within 24 hours

ROLE OF AMPICILLIN-SULBACTAM FOR CRAB

Utilize when SUL-DUR is unavailable

High-dose

- 9g/day sulbactam = 27g/day AMP-SUL

< 50% CRAB isolates test susceptible

- Role of high vs. standard dose unclear

2021 meta-analysis

PMID: 32889142

> 5 clinical trials showed mortality benefit in sulbactam arm

PMID: 39108079

AMPCILLIN-SULBACTAM

AMP-SUL Targets	
ESBL	
AmpC	
CRE	
DTR-PsAg	
CRAB	
Steno	

Dosing

- Total daily sulbactam dose = 9g
  - 9g AMP-SUL IV q8h over 4 hours
  - 27g AMP-SUL IV continuous infusion over 24 hours
- Renal adjustment necessary

Adverse effects

- GI upset
- Hypersensitivity

ROLE OF TETRACYCLINES FOR CRAB

Nausea in 20-50% of patients

Minocycline, tetracycline, and eravacycline have activity

Limited serum and urine concentrations

Minocycline

- Available IV & PO
- High-dose 200mg q12h
  - Caution when MIC 2-4 mcg/mL
- Case series
  - Small sample size
  - Colonization vs. infection
  - Heterogenous sites of infection

Tigecycline

- No breakpoints available
  - Cannot use minocycline breakpoints as surrogate
- High-dose 200mg x1 then 100mg q12h
  - Reduces mortality risk

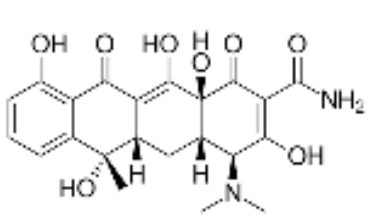
Eravacycline

- MICs 2-8 fold lower than mino/tigecycline
  - Clinical relevance unclear
- No breakpoints
- Observational study – longer duration of mechanical ventilation & higher 30-day mortality PMID: 35511209
- Limit use to when other agents cannot be given

PMID: 39108079

TETRACYCLINES

Tetracycline Targets	
ESBL	
AmpC	
CRE	
DTR-PsAg	
CRAB	
Steno	Minocycline only



Tetracycline	Dose
Tigecycline	200mg IV x1, then 100mg IV q12h
Minocycline	200mg IV/PO q12h
Eravacycline	1 mg/kg/dose IV q12h

Important considerations

- Not for UTI/BSI
- 20-40% nausea incidence
- Tissue hyperpigmentation & tooth discoloration if < 8 y/o
- Avoid in pregnancy
- Minocycline – phototoxicity, esophagitis (PO)

ROLE OF POLYMYXINS FOR CRAB

Have reliable *in vitro* activity

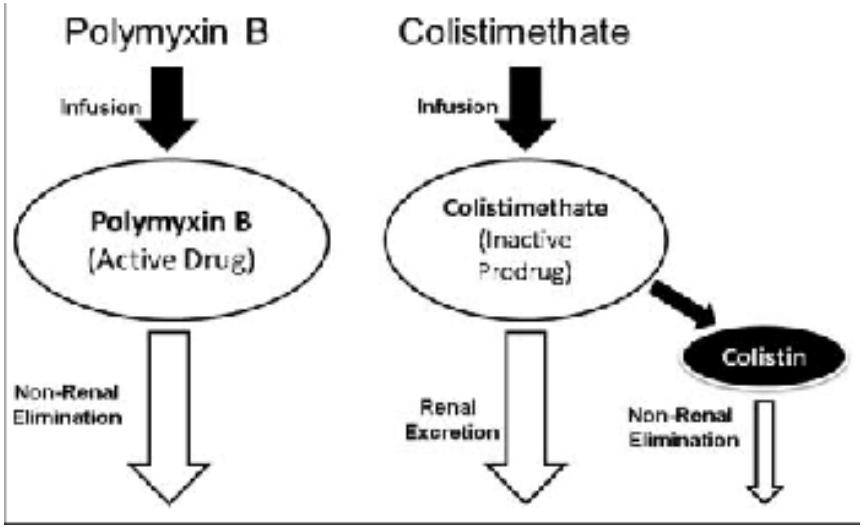
- Most literature with colistin

Polymyxin B favored over colistin

- UTI – colistin preferred

CLSI has no "susceptible" breakpoints

Not used as monotherapy



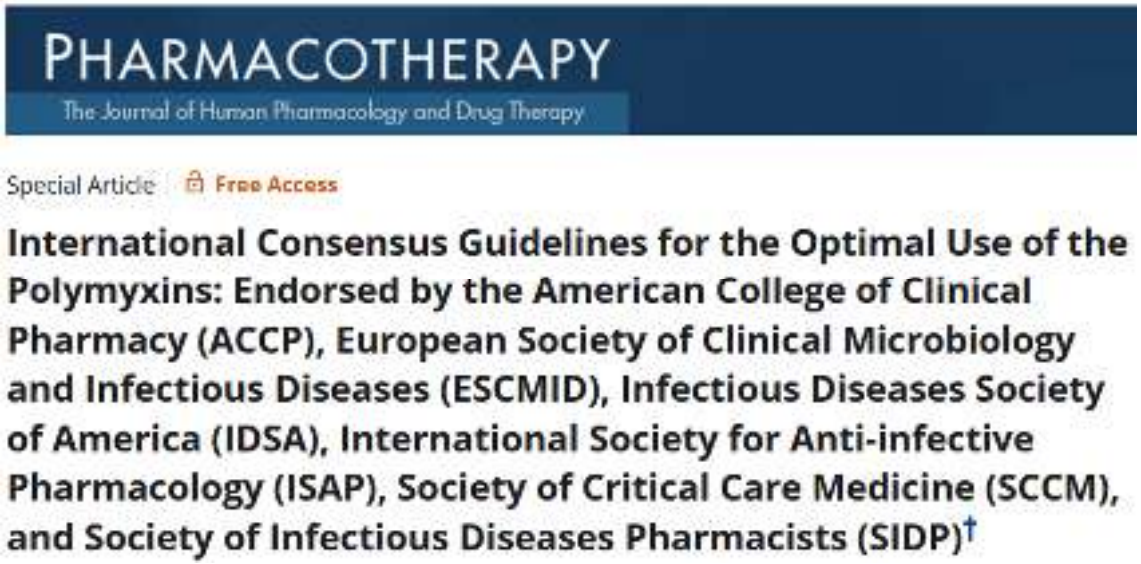
PMID: 27589330

- Serum concentrations highly variable
- Therapeutic dosages approach threshold for nephrotoxicity
- Largest trials of colistin monotherapy show 46% mortality

PMID: 39108079

POLYMYXINS

Polymyxin Targets	
ESBL	
AmpC	
CRE	
DTR-PsAg	
CRAB	
Steno	


PHARMACOTHERAPY
The Journal of Human Pharmacology and Drug Therapy

Special Article Free Access

International Consensus Guidelines for the Optimal Use of the Polymyxins: Endorsed by the American College of Clinical Pharmacy (ACCP), European Society of Clinical Microbiology and Infectious Diseases (ESCMID), Infectious Diseases Society of America (IDSA), International Society for Anti-infective Pharmacology (ISAP), Society of Critical Care Medicine (SCCM), and Society of Infectious Diseases Pharmacists (SIDP)†

Important considerations

- Narrow therapeutic window
- Nephrotoxicity & neurotoxicity
- Colistin favored for UTI
- Polymyxin B favored for non-urinary infections

ROLE OF CEFIDEROCOL FOR CRAB

CRAB susceptibility

- Surveillance studies show 95% susceptible using breakpoint ≤ 4 mcg/mL
- Determine CRAB susceptibility is difficult
  - Variable iron concentrations in media
  - MICs not always reproducible
- Preclinical data – higher PK/PD targets are needed compared to other GNR

Clinical data

PMID: 33058795
33058798
35311522

- CREDIBLE-CR: 54 patients with CRAB infections showed mortality 49% FDC vs. 18% BAT
  - Poor outcomes in BSI and PNA
- APEKS-NP: 47 patients with CRAB PNA showed 14-day mortality 22% FDC vs. 17% meropenem
  - Similar outcomes to inactive agent
- Observational study: 124 patients with CRAB infections showed 30-day mortality 34% FDC vs. 56% colistin-based treatment
  - Recurrent CRAB more likely with FDC, subsequent isolate more likely to be FDC-R

Use with caution and as a component of combination therapy

CASE 5

TS is a 52M with PMH depression on fluoxetine who is admitted to the hospital for a gunshot to the abdomen by his uncle. TS has been intubated in the ICU for 1 week. 2 days ago, pt was febrile to 101.9F, tachycardic to 133bpm, and requiring pressors. He was started on meropenem 2g q8h + amikacin 15 mg/kg q24h. A sample was taken from his ET tube and sent for culture. Results are now available, showing carbapenem-resistant *A. baumannii*. Which of the following would be the optimal regimen for TS based on his culture results?

a) Ampicillin-sulbactam 9g q8h + polymyxin B

b) Sulbactam-durlobactam 2g q6h (with imipenem) + minocycline 200mg q12h

c) Meropenem 2g q8h + minocycline 200mg q12h

d) Cefiderocol 2g q8h + minocycline 200mg q12h

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Stenotrophomonas maltophilia (STENO)

CASE 6

BB is a 30M who was admitted to the hospital after he fell in the ocean and a seal bit off his hand. On admission he had an open wound with a superficial infection, and was started on vancomycin and piperacillin-tazobactam. A wound culture was obtained. 3 days later the culture results show *Stenotrophomonas maltophilia* (susceptibilities pending). His wound has not improved; it is now more purulent and pt is febrile to 100.9F. Which of the following would be the best treatment regimen for BB?

a) TMP-SMX 15 mg/kg/day + levofloxacin 750mg q24h

b) Cefiderocol 2g q8h

c) Aztreonam-avibactam 2g q6h

d) Cefiderocol 2g q8h + eravacycline 1 mg/kg q12h

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STENO BACKGROUND

Pathogenicity

- Less pathogenic than other nosocomial organisms
- Produces biofilm and virulence factors – causes infection in vulnerable hosts

Resistance

- MBL – hydrolyzes penicillins, cephalosporins, carbapenems
- Serine BL – hydrolyzes cephalosporins and aztreonam
- Intrinsically resistant to aminoglycosides
- Efflux pumps reduce activity of TMP-SMX, tetracyclines, FQ

Colonization vs. infection

- Commonly in respiratory and wound cultures
- Underlying host factors complicate infection diagnosis
- Can cause hemorrhagic pneumonia

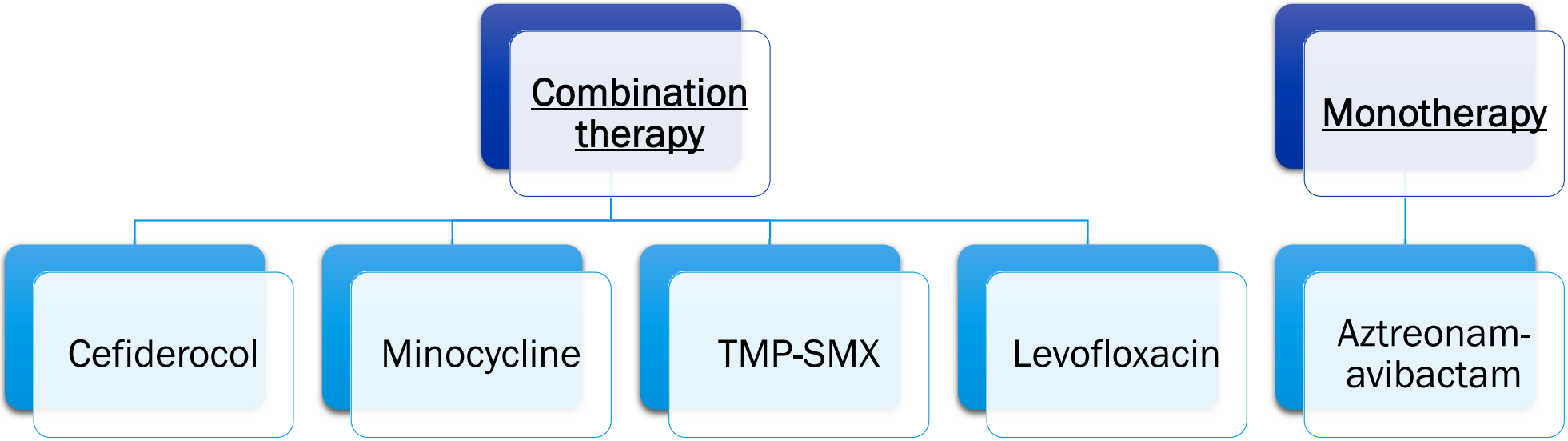
No standard-of-care antibiotics

- Robust comparative studies limited
- Data prioritizing agents or showing benefit of combination therapy not available

Susceptibility testing

- 4 antibiotics with CLSI breakpoints:
  - Cefiderocol
  - Levofloxacin
  - Minocycline
  - TMP-SMX
- Concerns about MIC reproducibility, limited PK/PD data

GENERAL APPROACH TO TREATMENT OF STENO



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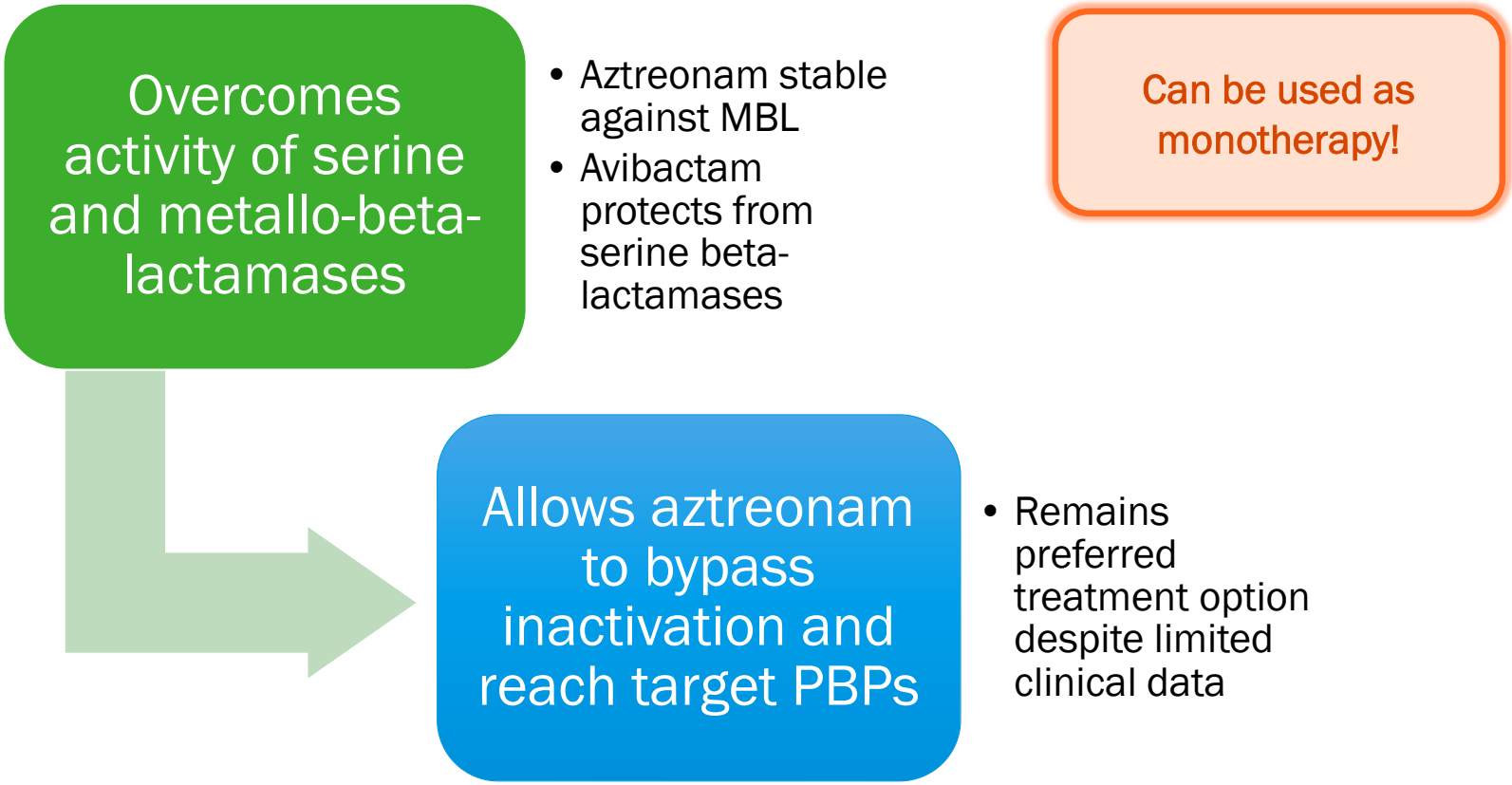
ROLE OF AZTREONAM-AVIBACTAM FOR STENO



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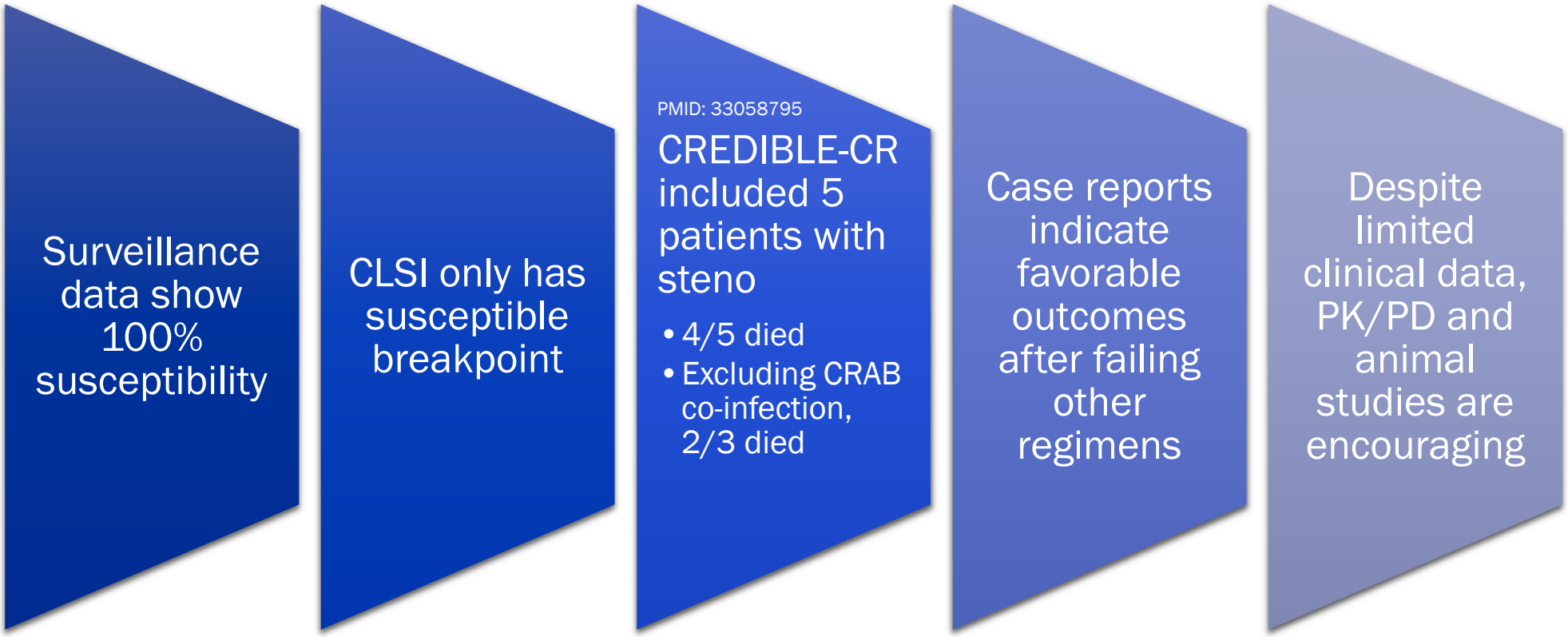
ROLE OF CEFIDEROCOL FOR STENO

Use in combination



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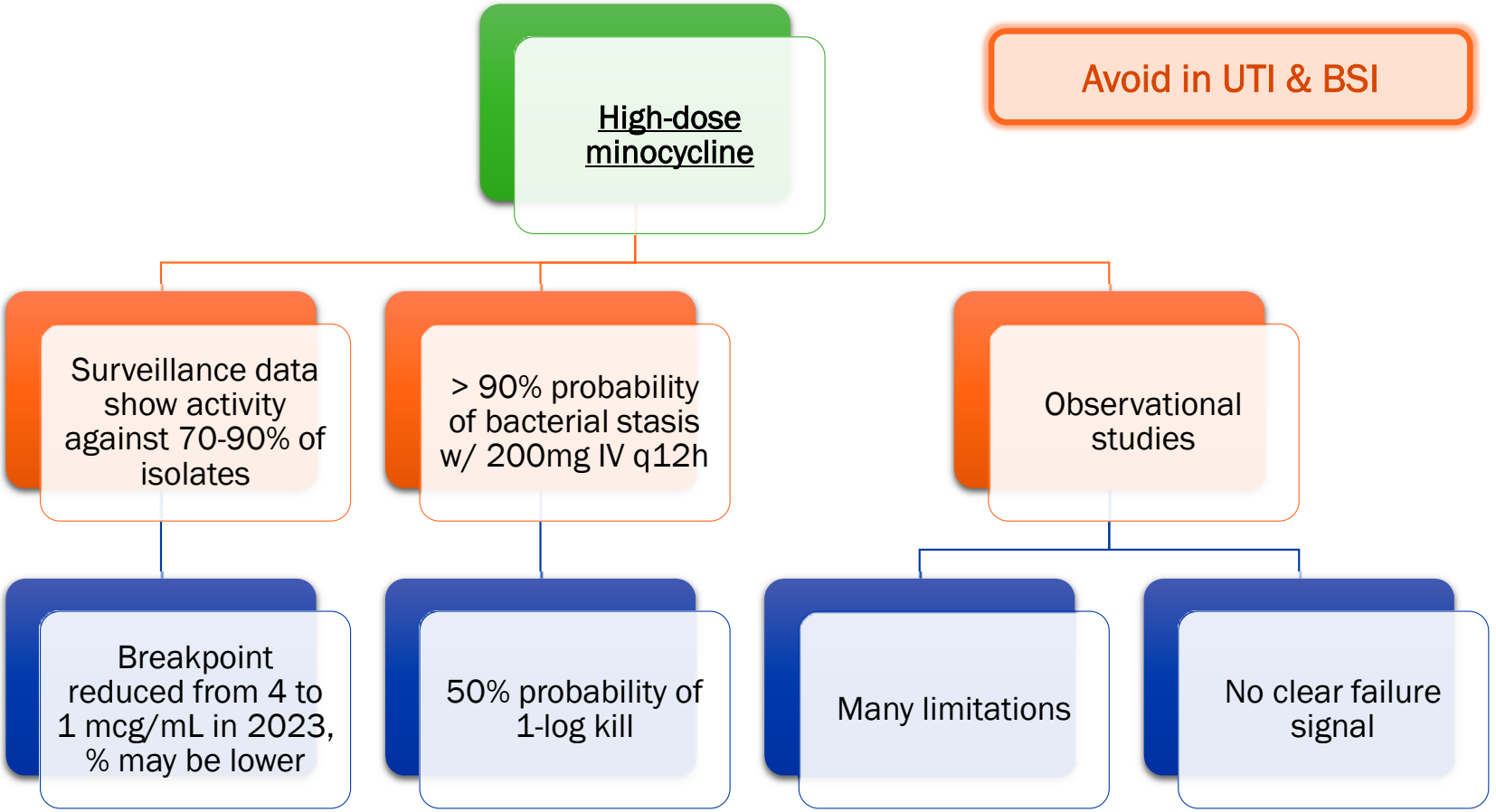
ROLE OF TETRACYCLINES FOR STENO

Use in combination

Avoid in UTI & BSI



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ROLE OF TMP-SMX FOR STENO

Use in combination

Surveillance data show > 90% *in vitro* activity

- Resistance is rising

Longstanding experience, but PK/PD data show only bacteriostatic

- Even with high doses and low MIC

Observational study of 1581 patients

- May be associated with increased mortality compared to levofloxacin
- Many limitations

PMID: 35097154

10-15 mg/kg/day TMP suggested

- Higher doses associated with toxicity
- No dose-response relationship established

PMID: 39108079

ROLE OF LEVOFLOXACIN FOR STENO

Use in combination

Susceptibility varies from 30-80%

Can develop elevated MIC during treatment

Monotherapy inadequate for inhibiting growth

- May have sufficient activity in combination

Meta-analysis of 663 patients from 14 observational studies

- Marginally significant in protecting against mortality compared to TMP-SMX
- Patients with BSI (true infection) – benefit not seen

PMID: 39108079

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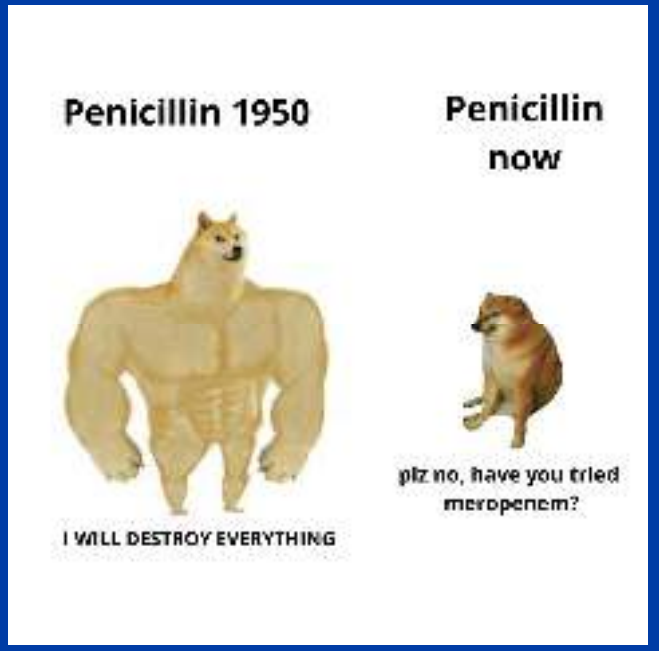
THANK YOU!

QUESTIONS?



A PAIN IN THE ACINETOBACTER: MANAGING INFECTIONS CAUSED BY MULTIDRUG RESISTANT GRAM-NEGATIVE PATHOGENS

Bessma Hassani, PharmD, BCPS, BCIDP
Clinical Pharmacy Specialist – Infectious Diseases & Antimicrobial Stewardship
Long Island Jewish Valley Stream
bhassani@northwell.edu

NYSCHP Annual Assembly – Saratoga Springs, NY

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