Change in Culture

An Overview of the 2023 IDSA Guidelines on Antimicrobial Resistant Gram-Negative Infections

A presentation for HealthTrust Members
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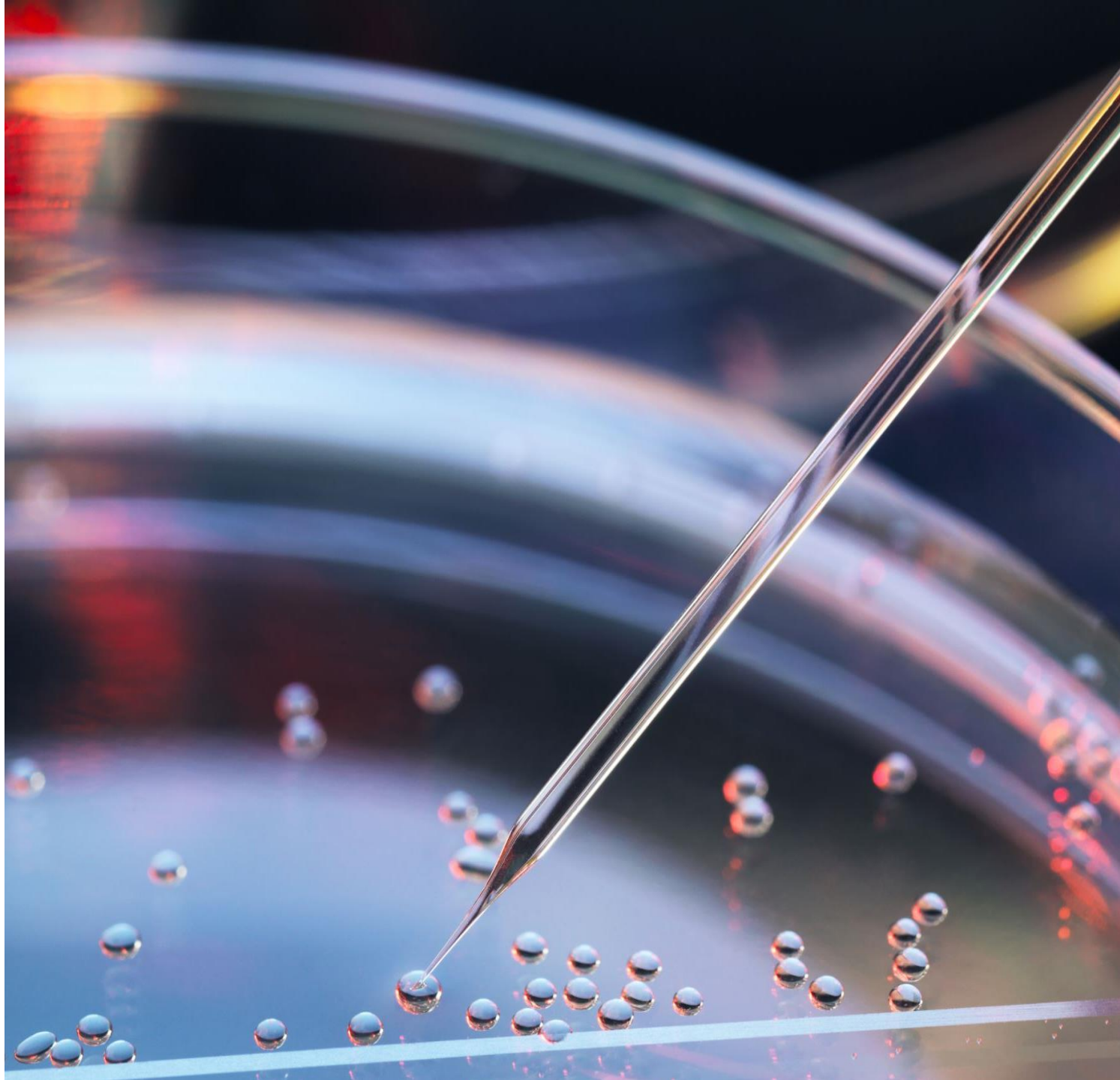

Disclosures

- Drs. Crawford and Gillis have no relevant relationships with ineligible companies to disclose.
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Objectives for Pharmacists & Nurses

1. Recall the importance of antimicrobial resistance among Gram-negative organisms

2. Identify mechanisms of resistance, recommendations for treatment, and their rationale for highly resistant Gram-negative organisms

3. Recognize an appropriate antimicrobial regimen based on resistance patterns of a Gram-negative organism

Abbreviations

- Antimicrobial susceptibility testing (AST)
- Carbapenem resistant Enterobacterales (CRE)
- Carbapenem-resistant *Acinetobacter baumanii (CRAB)*
- Extended spectrum beta-lactamase-producing Enterobacterales (ESBL-E)
- Extended spectrum beta-lactamase (ESBL)
- Multi-drug resistant organism (MDRO)
- *Pseudomonas aeruginosa* with difficult-to-treat resistance (DTR-P)
- Sulfamethoxazole-trimethoprim (SMX/TMP)

Lecture Focus

1. Extended-spectrum beta-lactamase-producing Enterobacterales (ESBL-E)
2. Carbapenem-resistant Enterobacterales (CRE)
3. *Pseudomonas aeruginosa* with difficult-to-treat resistance (DTR-P)
4. Carbapenem-resistant *Acinetobacter baumannii* (CRAB)

Epidemiology of Antimicrobial Resistant Gram-Negative Infections

- Antimicrobial resistance is a global crisis, and it is estimated that 1.3 million deaths were directly attributed to antimicrobial resistant pathogens in 2019
- According to the Centers for Disease Control (CDC), 2.8 million infections were caused by antimicrobial infections, resulting in more than 35,000 deaths between 2012 and 2017 in the United states

Source: Tamma PD et al. IDSA Treatment Guidance: Gram-negative Bacterial Infections. *Infect Dis Soc of Am.* 2023

Empiric Antimicrobial Therapy Considerations

1. Previous organisms identified from the patient and associated AST data in the last 12 months
2. Antibiotic exposure within the past 30 days
3. Local AST patterns for the most likely pathogens
4. Distinction between bacterial colonization and active infection

Source: Tamma PD et al. IDSA Treatment Guidance: Gram-negative Bacterial Infections. *Infect Dis Soc of Am.* 2023

Antimicrobial Classes: β-Lactams

Novel beta-lactams	Traditional Carbapenems	Other Beta-Lactams
Ceftazidime-avibactam	Ertapenem	Ampicillin-sulbactam
Ceftolozane-tazobactam	Imipenem-cilastatin	Piperacillin-tazobactam
Cefiderocol	Meropenem	
Imipenem-cliastatin-relebactam		
Meropenem-vaborbactam		

Antimicrobial Classes: Non-β-Lactams

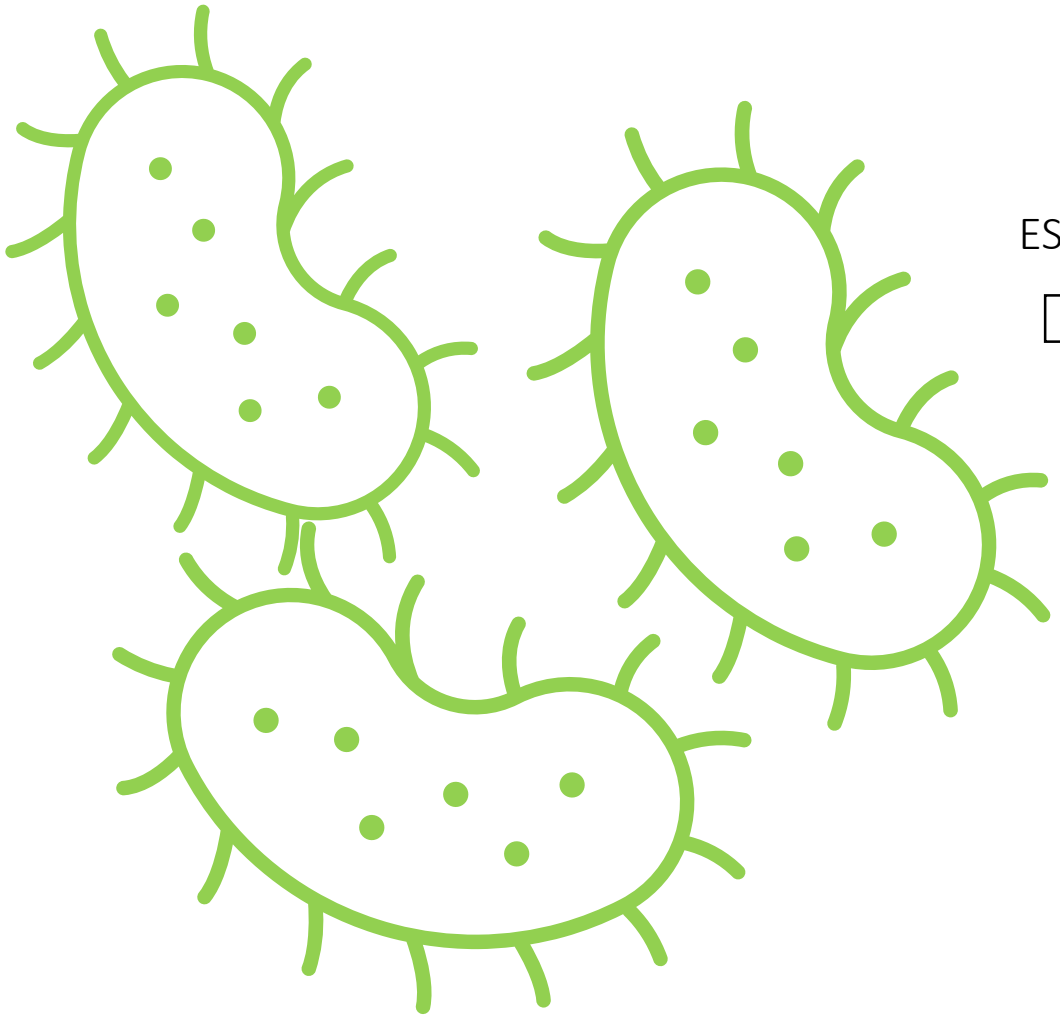
Aminoglycosides	Fluoroquinolones	Sulfonamide	Nitrofuran	Phosphonic
Amikacin	Ciprofloxacin	SMX/TMP	Nitrofurantoin	Fosfomycin
Gentamicin	Levofloxacin			
Tobramycin				
Plazomicin				

Ambler Classification of β-Lactamases

Type	Class	Hydrolysis Activity	Examples	Common Orgamisms
Narrow Spectrum	A	Penicillin	Staphylococcal penicillinase; TEM; SHV-1	*K. pneumoniae*
ESBL	A	Narrow and extended spectrum β-lactams	CTX-M; SHV-2; PER-1, SME-1	*E. coli, K. pneumoniae, Enterobacter spp., Proteus spp., Serratia spp.*
Serine carbapenemases	A	Carbapenems	KPC; IMI; SME-2	*E. cloacae, K. pneumoniae, S. marcescens*
Metallo-beta-lactamases	B	Carbapenems	VIM; IMP; NDM	*E. coli, K. pneumoniae, S. marcescens*
OXA-type enzymes	D	Oxacillin, oxyimino β-lactams, carbapenems	OXA	*E. coli, K. pneumoniae, K. oxytoca, A. baumannii*
Cephalosporinases	C	Cephamycins and oxyimino β-lactams	AmpC; P-99; ACT-1; CMY-2; FOX	*E. cloacae, K. aerogenes, C. freundii, S. marcescens, P. stuarii*

Extended Spectrum β-Lactamase Producing Enterobacterales (ESBL-E)

ESBL Mechanism of Resistance



ESBL production

Beta-lactam antibiotics

Beta-lactam antibiotics

Beta-lactam antibiotics

Beta-lactam antibiotics

Type	Class	Hydrolysis Activity	Examples	Common Organisms
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OXA-type enzymes	D	Oxacillin, oxyimino β-lactams, carbapenems	OXA	*E. coli, K. pneumoniae, K. oxytoca, A. baumannii*

ESBL-E Introduction

Incidence of ESBL-E infections has increased 53% between 2012 and 2017

ESBLs are active against most penicillins, cephalosporins, and aztreonam

NOT active against non-beta-lactam agents like fluroquinolones, SMX/TMP, or aminoglycosides

Source: Tamma PD et al. IDSA Treatment Guidance: Gram-negative Bacterial Infections. *Infect Dis Soc of Am.* 2023

Organisms Associated with ESBL Production

- Any Gram-negative organism has the potential to produce ESBLs
- Most common ESBL producing organisms
  - *E. coli*
  - *K. pneumoniae*
  - *K. oxytoca*
  - *P. mirabilis*

Source: Tamma PD et al. IDSA Treatment Guidance: Gram-negative Bacterial Infections. *Infect Dis Soc of Am.* 2023

Uncomplicated Cystitis Caused by ESBL-E

Uncomplicated ESBL Cystitis Treatment

If an antibiotic not active against the causative organism was administered empirically, but patient has clinical improvement, there is no need to change antibiotic or extend treatment duration

Source: Tamma PD et al. IDSA Treatment Guidance: Gram-negative Bacterial Infections. *Infect Dis Soc of Am.* 2023

Uncomplicated ESBL Cystitis Treatment

Preferred

- Nitrofurantoin
- SMX/TMP

Alternative

- Fluoroquinolone
- Carbapenem
- Single dose aminoglycoside
- Fosfomycin (*E. coli only*)

Source: Tamma PD et al. IDSA Treatment Guidance: Gram-negative Bacterial Infections. *Infect Dis Soc of Am.* 2023

Single Dose Aminoglycoside for UTI

Goodlet et al. (2018)

Meta analysis of 13 trials representing 13,804 patients who received single dose of aminoglycoside for UTI

Bacteria Isolated (n=471)

E. Coli (72%)	Proteus spp. (11%)	Klebsiella spp. (5%)

Aminoglycosides used

Netilmicin (most common), gentamicin, amikacin

Outcomes

Clinical cure: 94.5% ± 4.3%	30-day recurrence rate: 84/443 (19%)	Only 0.5% experienced adverse effects

Source: Goodlet KJ. Single Dose Aminoglycosides for UTI. *Antimicrob Agents Chemother.* 2018

Limitations of Single Dose Aminoglycosides in UTI

- Old data → 1978-1991
- Large pediatric population (53%)
- Primary agent used not common in U.S.
- Lack of data in patients with renal impairment
- No report of number of ESBL isolates

Source: Goodlet KJ. Single Dose Aminoglycosides for UTI. *Antimicrob Agents Chemother.* 2018

Pyelonephritis and Complicated UTI (cUTI) Caused by ESBL-E

cUTI Definition Used by IDSA

- Refers to UTIs occurring in association with a structural or functional abnormality of the genitourinary tract
- Any UTI in an adolescent or adult male

Source: Tamma PD et al. IDSA Treatment Guidance: Gram-negative Bacterial Infections. *Infect Dis Soc of Am.* 2023

Pyelonephritis and cUTI Treatment

Preferred	Preferred (critically ill or concern for toxicity with preferred agents)	Alternative
• SMX-TMP • Fluroquinolones	• Meropenem • Imipenem • Ertapenem*	• Aminoglycosides

Source: Tamma PD et al. IDSA Treatment Guidance: Gram-negative Bacterial Infections. *Infect Dis Soc of Am.* 2023

Agents Not Suggested for ESBL Pyelonephritis and cUTI

Not Suggested
• Fosfomycin • Nitrofurantoin • Doxycycline

Source: Tamma PD et al. IDSA Treatment Guidance: Gram-negative Bacterial Infections. *Infect Dis Soc of Am.* 2023

Fosfomycin for Prostatitis caused by ESBL-E

Karaiskos et al. (2019)

Study of 44 males with chronic bacterial prostatitis treated with oral fosfomycin 3g daily for 1 week, then 3g Q48 for 6-12 weeks

Organisms

E. coli (66%), Klebsiella spp. (14%), E. faecalis (14%)	Multi-drug resistant isolates (59%)	ESBL producing isolates (23%)

Outcomes

Clinical cure: 82% at end of treatment	Microbiologic eradication: 86% at end of treatment, 77% at 6 months	Treatment failure in 12 patients

Source: Karaiskos I. Oral fosfomycin for the treatment of chronic bacterial prostatitis. *J Antimicrob Chemother.* 2019

Infections Outside of the Urinary Tract Caused by ESBL-E

Treatment of ESBL Infections Outside of the Urinary Tract

Preferred	Critically ill or hypoalbuminemia
• Meropenem • Ertapenem • Imipenem	• Meropenem • Imipenem

Source: Tamma PD et al. IDSA Treatment Guidance: Gram-negative Bacterial Infections. *Infect Dis Soc of Am.* 2023

New Extended-Spectrum β-Lactam Agents

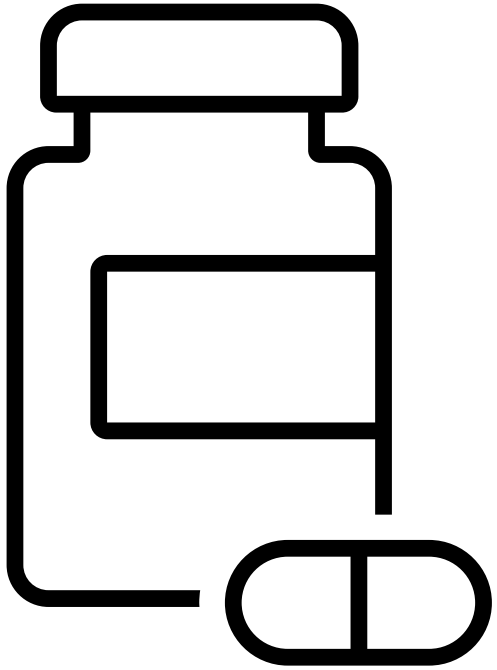
- Newer novel agents like ceftazidime-avibactam, meropenem-vaborbactam, imipenem-relebactam, and cefiderocol should be preferentially **reserved** for treating infections caused by organisms exhibiting carbapenem resistance

- The panel suggests against the use of ceftolozane-tazobactam for the due to the questionable efficacy of tazobactam in ESBL infections

Source: Tamma PD et al. IDSA Treatment Guidance: Gram-negative Bacterial Infections. *Infect Dis Soc of Am.* 2023

Treatment of ESBL Infections Outside of the Urinary Tract: Oral Step-down Therapy

After appropriate clinical response is achieved, transitioning to oral SMX/TMP, ciprofloxacin, or levofloxacin should be considered, if susceptibility is demonstrated



Source: Tamma PD et al. IDSA Treatment Guidance: Gram-negative Bacterial Infections. *Infect Dis Soc of Am.* 2023

Carbapenem Resistant Enterobacterales (CRE)

CRE Background

- Account for over 13,000 infections and 1000 deaths annually in the U.S.
- IDSA CRE definition
  - Isolate displays resistance to meropenem or imipenem*, or isolates that produce carbapenemase enzymes

* *Morganella* spp ., *Proteus* spp., and *Providencia* spp. not generally susceptible to imipenem

Source: Tamma PD et al. IDSA Treatment Guidance: Gram-negative Bacterial Infections. *Infect Dis Soc of Am.* 2023

Common Carbapenemases Produced by CRE

Type	Class	Hydrolysis Activity	Examples	Common Organisms
Narrow Spectrum	A	Penicillin	Staphylococcal penicillinase; TEM; SHV-1	*K. pneumoniae*
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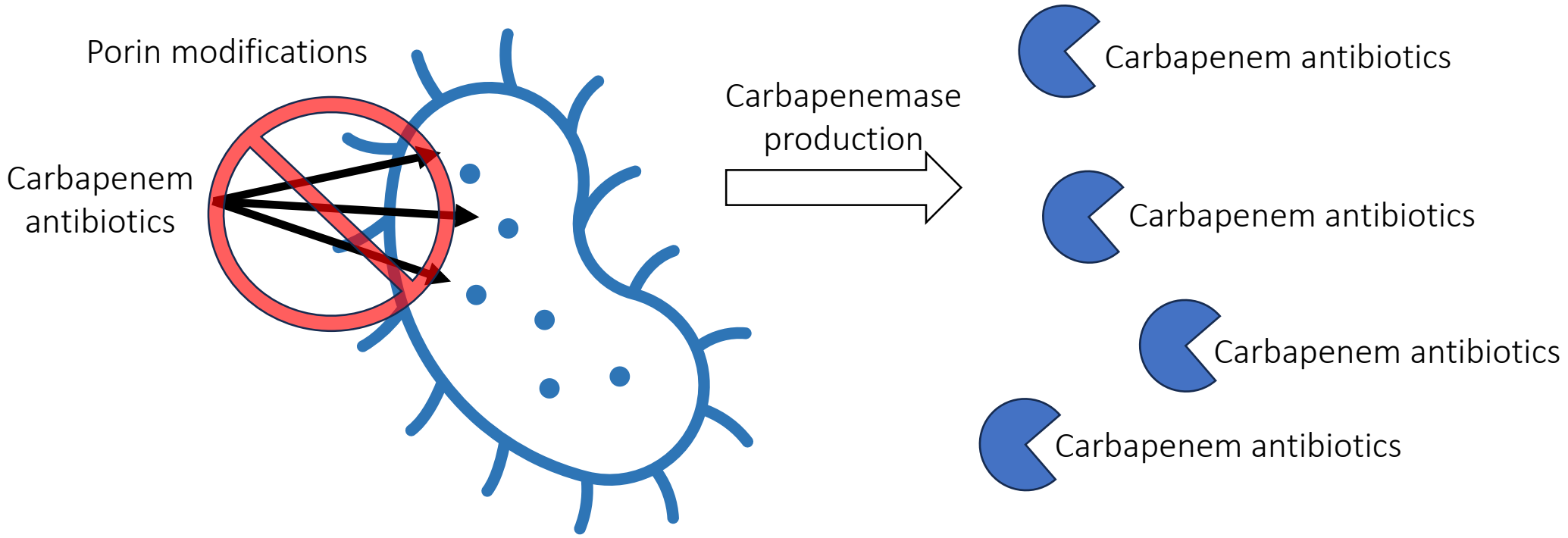
CRE Resistance Mechanisms



Treatment of CRE Infections

Treatment of Uncomplicated CRE Cystitis

Preferred

- Nitrofurantoin
- SMX-TMP
- Fluroquinolone

Alternative

- Single dose aminoglycoside
- Oral fosfomycin (*E. coli* only)
- Colistin
- Ceftazidime-avibactam
- Meropenem-vaborbactam
- Imipenem-relebactam
- Cefiderocol

Source: Tamma PD et al. IDSA Treatment Guidance: Gram-negative Bacterial Infections. *Infect Dis Soc of Am.* 2023

Utility of Plazomicin in CRE Infections

Castanheira et al. (2018)

Plazomicin and comparator agents were tested by using the CLSI reference broth microdilution in 4,362 Enterobacterales

Results

Plazomicin inhibited 99.2% of 4,362 Enterobacteriales at MIC ≤4 µg/ml. Amikacin, gentamicin, and tobramycin inhibited 98.9%, 90.3%, and 90.3% of these isolates, respectively

Results in CRE isolates

For 97 CRE isolates, including 87 KPC isolates, plazomicin inhibited 99% of isolates with MIC ≤ 2. Amikacin and gentamicin inhibited 64.9% and 56.7% of the CRE isolates at the respective CLSI breakpoints

Source: Castanheira M. In Vitro Activity of Plazomicin against Gram-Negative and Gram-Positive Isolates .*Antimicrob Agents Chemother* 2018

Treatment of CRE cUTIs and Pyelonephritis

Preferred	Preferred (if susceptible)	Alternative
• Ceftazidime-avibactam • Meropenem-vaborbactam • Imipenem-relebactam • Cefiderocol	• Nitrofurantoin • SMX-TMP • Fluroquinolone	• Aminoglycosides

Source: Tamma PD et al. IDSA Treatment Guidance: Gram-negative Bacterial Infections. *Infect Dis Soc of Am.* 2023

Novel Agents in CRE Cystitis

Insufficient data exists to make favor one novel agent over another

Most organisms isolated in the studies evaluating these newer agents in urinary tract infections were carbapenem susceptible

Source: Tamma PD et al. IDSA Treatment Guidance: Gram-negative Bacterial Infections. *Infect Dis Soc of Am.* 2023

CRE Infections Outside the Urinary Tract with Unknown Carbapenemase Producing Status

Preferred

- Ceftazidime-avibactam
- Meropenem-vaborbactam
- Imipenem-relebactam

CRE isolated within last 12 months

- Ceftazidime-avibactam + aztreonam
- Cefiderocol monotherapy

Source: Tamma PD et al. IDSA Treatment Guidance: Gram-negative Bacterial Infections. *Infect Dis Soc of Am.* 2023

CRE Infections Outside the Urinary Tract with Unknown Carbapenemase Producing Status

Alternative

(Infections not in bloodstream or urinary tract)

- Tigecycline
- Eravacycline

Advised Against

- Extended infusion carbapenem ± a second agent

Source: Tamma PD et al. IDSA Treatment Guidance: Gram-negative Bacterial Infections. *Infect Dis Soc of Am.* 2023

Combination therapy in CRE Infections

Tumbarello et al. (2021)

Observational study compared the clinical outcomes of 165 patients receiving ceftazidime-avibactam and 412 patients receiving ceftazidime-avibactam plus a second agent for the treatment of KPC-producing infections

Results

30-day mortality approximately 25% in both arms

Source: Tumbarello M. Ceftazidime-avibactam use for KPC-Kp infections *Clin Infect Dis.* 2021

Enterobacterales Resistant to Ertapenem

For isolates that exhibit susceptibility to meropenem and imipenem, but are not susceptible to ertapenem and are not carbapenemase producing, the use of extended-infusion meropenem or imipenem is suggested

Source: Tamma PD et al. IDSA Treatment Guidance: Gram-negative Bacterial Infections. *Infect Dis Soc of Am.* 2023

CRE Infections Outside the Urinary Tract with Confirmed KPC Production

Preferred

- Meropenem-vaborbactam*
- Ceftazidime-avibactam
- Imipenem-relebactam

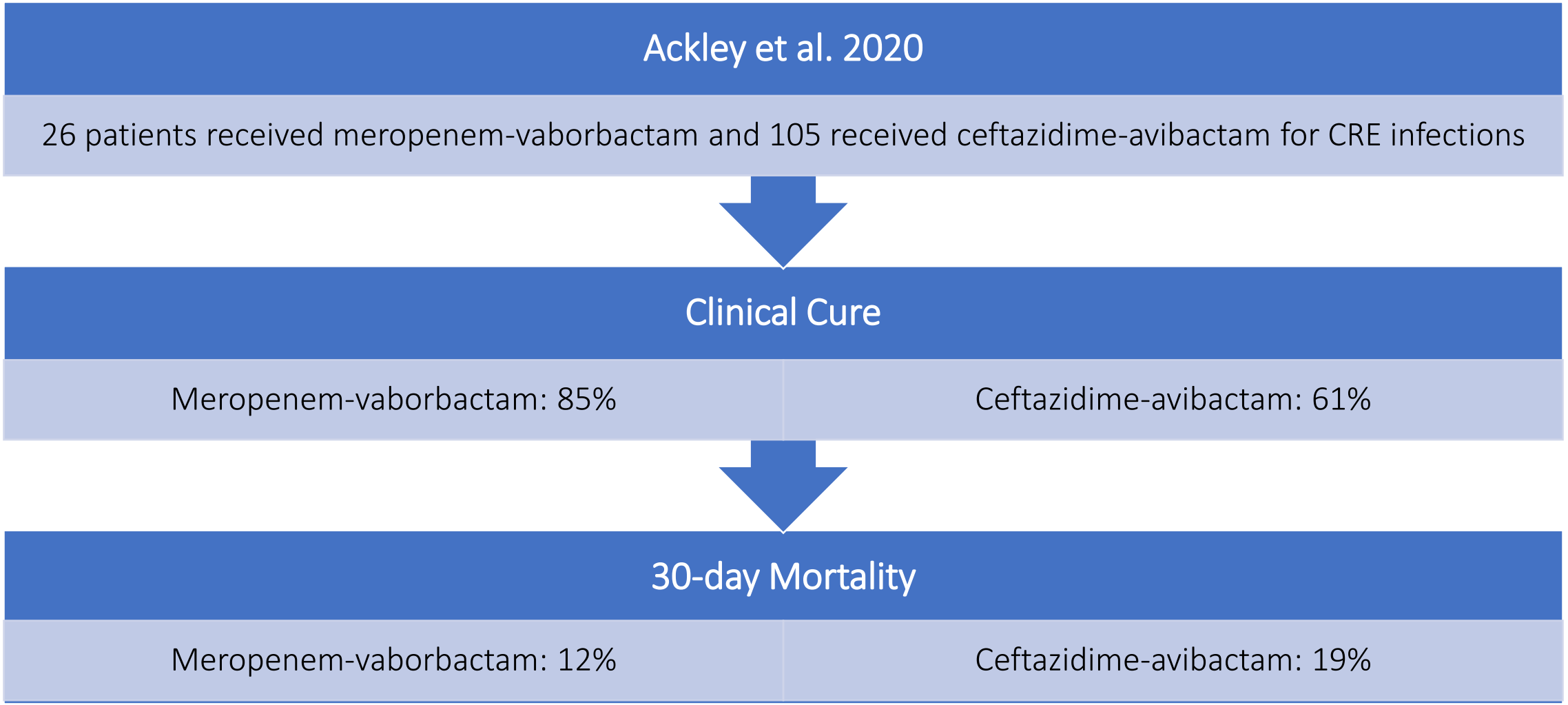
Alternative

- Cefiderocol
- Infection outside of urinary tract and blood stream
  - Tigecycline
  - Eravacycline

*slightly favored based on available data

Source: Tamma PD et al. IDSA Treatment Guidance: Gram-negative Bacterial Infections. *Infect Dis Soc of Am.* 2023

Meropenem-Vaborbactam vs. Ceftazidime-Avibactam for CRE Infections



Source: Ackley et al. Meropenem-Vaborbactam v Ceftazidime-avibactam for Treatment of CRE Infections. *Antimicrob Agents Chemother.* 2020.

CRE Infections Outside the Urinary Tract with Confirmed NDM, IMP, or VIM Production

Preferred

- Ceftazidime-avibactam + aztreonam
- Cefiderocol

Alternative

(Infections not in bloodstream or urinary tract)

- Tigecycline
- Eravacycline

Source: Tamma PD et al. IDSA Treatment Guidance: Gram-negative Bacterial Infections. *Infect Dis Soc of Am.* 2023

CRE Infections Outside the Urinary Tract with Confirmed OXA Production

Preferred

- Ceftazidime-avibactam

Alternative

- Cefiderocol
- Infection outside of urinary tract and blood stream
  - Tigecycline
  - Eravacycline

Source: Tamma PD et al. IDSA Treatment Guidance: Gram-negative Bacterial Infections. *Infect Dis Soc of Am.* 2023

Carbapenemase Treatment Recap

	KPC	NDM/IMP/VIM	OXA
Ceftazidime-avibactam		+ aztreonam	
Imipenem-relebactam			
Meropenem-vaborbactam	Preferred		
Cefiderocol	Alternative		Alternative

Development of Antibiotic Resistance in CRE Infections

Ceftazidime-avibactam

- Resistance in KPC due to amino acid alterations in the carbapenemase enzyme

Meropenem-vaborbactam

- Resistance primarily driven by efflux pump alterations

Cefiderocol

- Mutations in TonB iron transport system
- AmpC amino acid mutations
- PBP3 alterations in NDM producing *E. coli*

Source: Tamma PD et al. IDSA Treatment Guidance: Gram-negative Bacterial Infections. *Infect Dis Soc of Am.* 2023

Development of Antibiotic Resistance in CRE Infections

Resistance After Exposure
Resistance after exposure to ceftazidime-avibactam and meropenem-avibactam estimated to be 10-20% and 3%, respectively

Source: Tamma PD et al. IDSA Treatment Guidance: Gram-negative Bacterial Infections. *Infect Dis Soc of Am.* 2023

Pseudomonas aeruginosa with Difficult-to-Treat Resistance (DTR-P)

Difficult-to-Treat Definition

Non-susceptibility to:

Piperacillin-tazobactam

Ceftazidime

Cefepime

Aztreonam

Meropenem

Imipenem

Ciprofloxacin/ levofloxacin

Source: Tamma PD et al. IDSA Treatment Guidance: Gram-negative Bacterial Infections. *Infect Dis Soc of Am.* 2023

Mechanisms of Resistance in DTR-P

- Decreased expression of outer membrane porins (OprD)
- Upregulation of efflux pumps (MexAB-OprM)
- Mutations in penicillin-binding protein targets
- Increased production of or amino acid substitutions within *Pseudomonas*-derived cephalosporinase (PDC) enzymes
- Presence of expanded-spectrum β-lactamases (OXA-10)

Source: Tamma PD et al. IDSA Treatment Guidance: Gram-negative Bacterial Infections. *Infect Dis Soc of Am.* 2023

Treatment of Uncomplicated DTR-P Cystitis

Preferred	Alternative	Not Recommended
• Ceftazidime-avibactam • Ceftolozane-tazobactam • Imipenem-relebactam • Cefiderocol	• Single dose amikacin or tobramycin • Colistin	• Fosfomycin • Polymyxin B

Source: Tamma PD et al. IDSA Treatment Guidance: Gram-negative Bacterial Infections. *Infect Dis Soc of Am.* 2023

Treatment of DTR-P cUTI and Pyelonephritis

Preferred

- Ceftazidime-avibactam
- Ceftolozane-tazobactam
- Imipenem-relebactam
- Cefiderocol

Source: Tamma PD et al. IDSA Treatment Guidance: Gram-negative Bacterial Infections. *Infect Dis Soc of Am.* 2023

Treatment of DTR-P Infections Outside of the Urinary Tract

Preferred	Alternative
• Ceftazidime-avibactam • Ceftolozane-tazobactam • Imipenem-relebactam	• Cefiderocol

Source: Tamma PD et al. IDSA Treatment Guidance: Gram-negative Bacterial Infections. *Infect Dis Soc of Am.* 2023

Effectiveness of Novel Antimicrobials in Carbapenem-Resistant *P. aeruginosa*

Ceftolozane-tazobactam → 76%

Ceftazidime-avibactam → 74%

Imipenem-relebactam → 69%

Source: Tamma PD et al. IDSA Treatment Guidance: Gram-negative Bacterial Infections. *Infect Dis Soc of Am.* 2023

Comparison of the Novel Antimicrobials in DTR-P

- Ceftolozane is less impacted by PDC hydrolysis and porin loss than ceftazidime and does not rely on an inhibitor to restore susceptibility to an otherwise inactive β-lactam agent
- Avibactam and relebactam expand activity of ceftazidime and imipenem mainly through inhibition of PDC

Source: Tamma PD et al. IDSA Treatment Guidance: Gram-negative Bacterial Infections. *Infect Dis Soc of Am.* 2023

Comparison of the Novel Antimicrobials in DTR-P

- Vaborbactam only marginally expands the activity of meropenem against DTR-*P. aeruginosa*
- Combining data from 1,500 carbapenem non-susceptible *P. aeruginosa* isolates in 8 surveillance studies, over 97% of isolates exhibited susceptibility to cefiderocol

Source: Tamma PD et al. IDSA Treatment Guidance: Gram-negative Bacterial Infections. *Infect Dis Soc of Am.* 2023

Susceptibility to Traditional Beta-Lactam

- Some DTR-P isolates can demonstrate susceptibility to traditional β-lactams like cefepime and piperacillin/tazobactam, but have resistance to carbapenems
- If repeat AST confirms susceptibility to traditional agents, the panel suggests high dose, extended-infusion of these agents
  - ie. Cefepime 2g every 8 hrs, infused over 3 hours

Source: Tamma PD et al. IDSA Treatment Guidance: Gram-negative Bacterial Infections. *Infect Dis Soc of Am.* 2023

Relebactam Utility in DTR-P

Motsch et al. (2020)

24 patients infected with imipenem non-susceptible *P. aeruginosa* to receive either imipenem-cilastatin-relebactam or imipenem-cilastatin + colistin

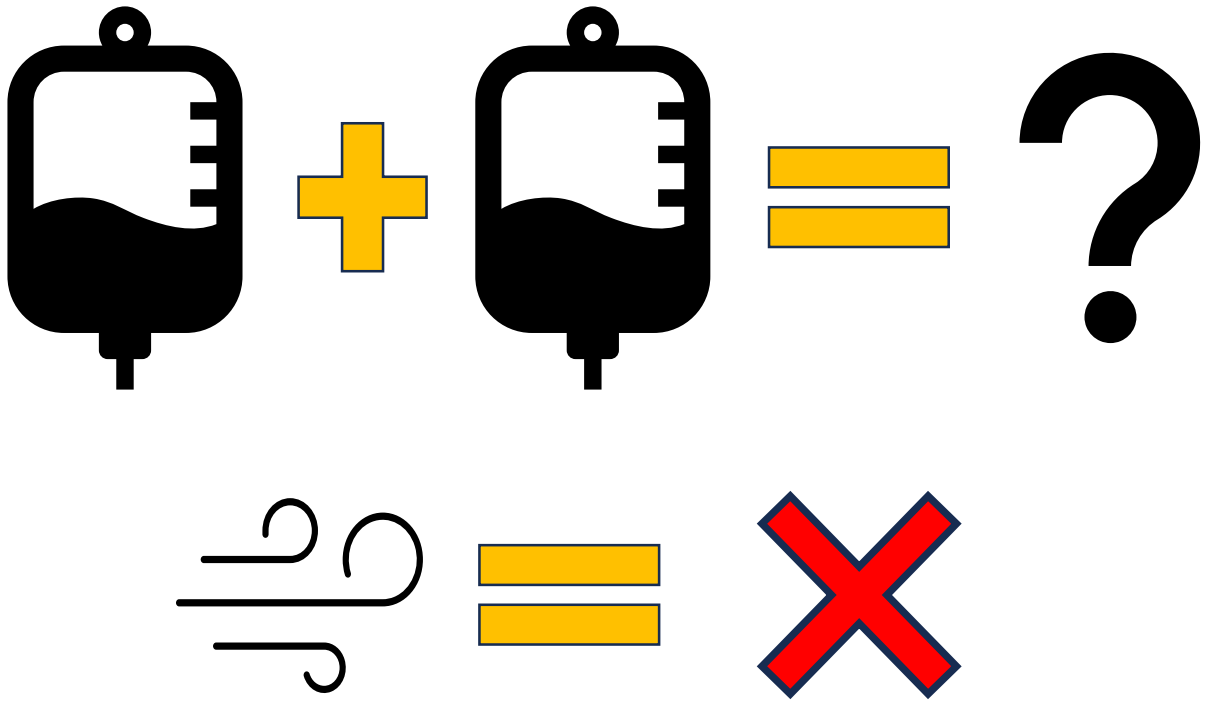
Result

Favorable clinical response in 81% of patients receiving imipenem-cilastatin-relebactam compared to 63% receiving imipenem-cilastatin + colistin

Source: Motsch J el al. Comparing Efficacy and Safety of Imipenem/Relebactam vs Colistin Plus Imipenem in Patients With Imipenem-nonsusceptible Bacterial Infections *Clin Infect Dis.* 2020

Combination Therapy for DTR-Pa

- The panel does not suggest combination therapy in DTR-P
- However, addition of agents such as tobramycin, polymyxin, and colistin to recommended therapies may be reasonable until susceptibilities confirmed
- Nebulized antibiotics not recommended



Source: Tamma PD et al. IDSA Treatment Guidance: Gram-negative Bacterial Infections. *Infect Dis Soc of Am.* 2023

Patients With Previously Treated for DTR-P Infections

For patients recently treated with ceftolozane-tazobactam or ceftazidime-avibactam, the panel suggests:

Imipenem-relebactam

Cefiderocol

Source: Tamma PD et al. IDSA Treatment Guidance: Gram-negative Bacterial Infections. *Infect Dis Soc of Am.* 2023

Carbapenem Resistant *Acinetobacter baumanii* (CRAB)

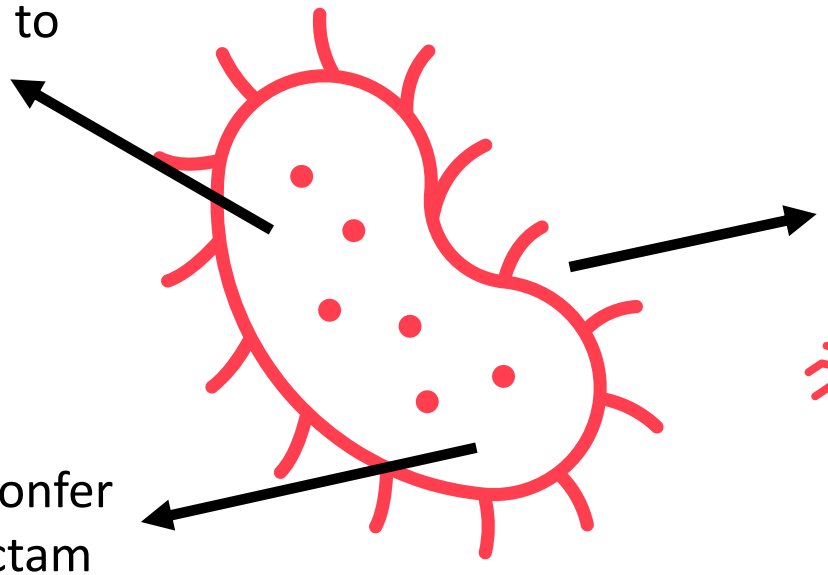
CRAB Background

- Commonly recovered from respiratory specimens or wounds, and often patients can be colonized with *A. baumannii*
- It is not always clear if an isolate is a colonizing organism or if CRAB represents a true pathogen
- High bacterial burdens are expected with CRAB infections due to almost universal delays in initiating effective therapy as common empiric antibiotic regimens are generally not active against CRAB
- Antibiotics that initially appear active against CRAB may rapidly develop resistance

Source: Tamma PD et al. IDSA Treatment Guidance: Gram-negative Bacterial Infections. *Infect Dis Soc of Am.* 2023

CRAB Resistance Mechanisms

Other intrinsic resistance mechanisms cause resistance to aminoglycosides and fluoroquinolones



OXA carbapenemase production

Able to produce other carbapenemases

PBP1a/b and PBP3 confer resistance to sulbactam

Common Carbapenemases Produced by CRAB

Type	Class	Hydrolysis Activity	Examples	Common Organisms
Narrow Spectrum	A	Penicillin	Staphylococcal penicillinase; TEM; SHV-1	K. pneumoniae
ESBL	A	Narrow and extended spectrum β-lactams	CTX-M; SHV-2; PER-1, SME-1	E. coli, K. pneumoniae, Enterobacter spp., Proteus spp., Serratia spp.
Serine carbapenemases	A	Carbapenems	KPC; IMI; SME-2	E. cloacae, K. pneumoniae, S marcescens
Metallo-beta-lactamases	B	Carbapenems	VIM; IMP; NDM	E. coli, K. pneumoniae, S. marcescens
OXA-type enzymes	D	Oxacillin, oxyimino β-lactams, carbapenems	**OXA**	E. coli, K. pneumoniae, K. oxytoca, **A. baumannii**
Cephalosporinases	C	Cephamycins and oxyimino β-lactams	AmpC; P-99; ACT-1; CMY-2; FOX	E. cloacae, K. aerogenes, C. freundii, S. marcescens, P. stuarii

General Treatment of CRAB Infections

The use of high-dose ampicillin-sulbactam (total daily dose of 6-9 grams of the sulbactam component) in combination with at least one other agent is suggested for the treatment of CRAB infections

Source: Tamma PD et al. IDSA Treatment Guidance: Gram-negative Bacterial Infections. *Infect Dis Soc of Am.* 2023

Sulbactam Therapy for CRAB Infections

- A meta-analysis published in 2017 included 23 observational studies or clinical trials and 2,118 patients with CRAB infections
- It identified sulbactam as having the greatest impact on reducing mortality when evaluating sulbactam-based, polymyxin-based, or tetracycline-based regimens

Source: Jung SY et al. Antimicrobials for the treatment of drug-resistant Acinetobacter baumannii pneumonia in critically ill patients. *Crit Care.* 2017

Sulbactam Therapy for CRAB Infections

- Another meta-analysis published in 2021 included 18 studies and 1,835 patients
- Found that ampicillin-sulbactam (total daily dose of at least 6 grams of the sulbactam component) in combination with a second agent was the most effective regimen to reduce mortality in critically ill patients infected with CRAB

Source: Liu J et al. high-dose sulbactam or colistin with additional antibacterial agents for multiple drug-resistant and extensively drug-resistant Acinetobacter baumannii infections. *J Glob Antimicrob Resist.* 2021

Combination Therapy for Treatment of CRAB

Options for combination therapy with high dose ampicillin-sulbactam regimens (sulbactam 6-9g daily)

- Minocycline
- Tigecycline
- Polymyxin B
- Cefiderocol

Source: Tamma PD et al. IDSA Treatment Guidance: Gram-negative Bacterial Infections. *Infect Dis Soc of Am.* 2023

Cefiderocol Therapy for CRAB Infections

- Cefiderocol is the only novel FDA-approved β-lactam agent with in vitro activity against CRAB isolates
- Estimated that 95% of CRAB isolates are susceptible to cefiderocol using the CLSI susceptibility criteria ≤4 µg/mL based on data from surveillance studies

Source: Tamma PD et al. IDSA Treatment Guidance: Gram-negative Bacterial Infections. *Infect Dis Soc of Am.* 2023

Cefiderocol Therapy for CRAB Infections

- A clinical trial including 54 patients with CRAB infections identified mortality in 49% versus 18% in the cefiderocol versus alternative therapy arms
- Poor outcomes with cefiderocol were observed in patients with pneumonia and bloodstream infections

Source: Bassetti M et al. *E*fficacy and safety of cefiderocol or best available therapy for the treatment of serious infections caused by carbapenem- resistant Gram-negative bacteria. *Lancet Infect* Dis. 2021

Cefiderocol Therapy for CRAB Infections

- A second randomized trial specifically evaluating patients with pneumonia randomized to cefiderocol or high-dose extended-infusion meropenem
- Found no difference in clinical outcomes between the two treatment regimens, including among 36 patients with CRAB pneumonia

Source: Wunderink RG et al. Cefiderocol versus high-dose, extended- infusion meropenem for the treatment of Gram-negative nosocomial pneumonia. *Lancet Infect Dis.* 2021

Cefiderocol Resistance

Study of 124 patients with CRAB infections received cefiderocol or colistin-based regimens → 30-day mortality was 34% versus 56% in each arm, respectively

Recurrent CRAB infection was more likely in the cefiderocol arm → 17% versus 7%

Among the 8 patients in the cefiderocol group who experienced a recurrent CRAB infection, 50% had subsequent isolates exhibiting resistance to cefiderocol

Source: Falcone M et al. Cefiderocol v Colistin-Based Regimens for the Treatment of Severe Infections Caused by CRAB. *Antimicrob Agents Chemother.* 2022

Agents Not Suggested for CRAB Infections

- Extended infusion meropenem or imipenem
- Rifamycins
- Nebulized antibiotics

Source: Tamma PD et al. IDSA Treatment Guidance: Gram-negative Bacterial Infections. *Infect Dis Soc of Am.* 2023

New Antimicrobial Agents for CRAB Infections

Sulbactam-durlobactam

177 patients received either sulbactam-durlobactam or colistin for up to 14 days. Both treatment arms also received imipenem-cilastatin as background therapy for potential HAP/VAP

Outcome

All cause mortality within 28 days of treatment → sulbactam-durlobactam 12/63 (19%), compared to 20/62 (32%) who received colistin

Safety Outcomes

19% incidence of liver function test (LFT) abnormalities with sulbactam-durlobactam

Source: Kaye KS et al. **Efficacy and safety of Sulbactam–Durlobactam versus Colistin for the treatment of patients with serious infections caused by Acinetobacter baumannii.** *Lancet Infect Dis.* 2023

Beta-Lactam Utility in MDRO Infections

Antibiotic	ESBL	CRE	DTR-P	CRAB
Ampicillin-sulbactam	×	×	×	✓
Ceftazidime-avibactam	×	✓	✓	×
Ceftolozane-tazobactam	×	×	✓	×
Cefiderocol	×	✓	✓	✓
Imipenem-relebactam	×	✓/×	✓	×
Meropenem-vaborbactam	×	✓/×	×	×
Traditional Carbapenems	✓	×	×	×

Non-Beta-Lactam Utility in MDRO Infections

Antibiotic	ESBL	CRE	DTR-P	CRAB
Fosfomycin	✓*	✓*	×	×
Fluroquinolones	✓	✓	×	×
Nitrofurantoin	✓	✓	×	×
SMX/TMP	✓	✓	×	×

Duration of Therapy

- Duration of therapy should not differ for infections caused by organisms with resistant phenotypes compared to infections caused by more susceptible phenotypes
- If AST results indicate a potentially inactive agent was initiated empirically, a change to an active regimen for a full treatment course dated from the start of active therapy is recommended

Source: Tamma PD et al. IDSA Treatment Guidance: Gram-negative Bacterial Infections. *Infect Dis Soc of Am.* 2023

Duration of Therapy in cUTI

In cUTI where the source has been controlled (e.g. removal of a Foley catheter), it is reasonable to treat for durations used for uncomplicated cystitis

Source: Tamma PD et al. IDSA Treatment Guidance: Gram-negative Bacterial Infections. *Infect Dis Soc of Am.* 2023

Transitioning to Oral Therapy

Transitioning to oral therapy should be considering when the following criteria are met:

1. Susceptibility to an appropriate oral agent is demonstrated
2. The patient is hemodynamically stable
3. Reasonable source control measures have occurred
4. Concerns about insufficient intestinal absorption are not present

Source: Tamma PD et al. IDSA Treatment Guidance: Gram-negative Bacterial Infections. *Infect Dis Soc of Am.* 2023

Assessment #1

Antimicrobial resistance can have the following impact in treating Gram-negative infections

a. Delay in starting appropriate antimicrobial therapy
b. Worse clinical outcomes
c. Increased resistance in subsequent infections
d. All the above

Assessment #1

Antimicrobial resistance can have the following impact in treating Gram-negative infections

a. Delay in starting appropriate antimicrobial therapy
b. Worse clinical outcomes
c. Increased resistance in subsequent infections
d. **All the above**

Assessment #2

Which of the following is the preferred antimicrobial agent for treatment of uncomplicated cystitis caused by ESBL-E (assuming no contraindications to any of the medications)?

a. SMX-TMP
b. Ciprofloxacin
c. Levofloxacin
d. Meropenem

Assessment #2: Correct Response

Which of the following is the preferred antimicrobial agent for treatment of uncomplicated cystitis caused by ESBL-E (assuming no contraindications to any of the medications)?

a. SMX-TMP
b. Ciprofloxacin
c. Levofloxacin
d. Meropenem

Self-Assessment #3

What is the most common carbapenemase produced by CRAB?

a. CTX-M
b. OXA
c. VIM
d. NDM

Self-Assessment #3: Correct Response

What is the most common carbapenemase produced by CRAB?

a. CTX-M
b. OXA
c. VIM
d. NDM

Self-Assessment #4

Which of these agents is the treatment of choice for treatment of CRE that produces KPC?

a. Cediferocol
b. Meropenem-vaborbactam
c. Tigecycline
d. Imipenem-cilastatin-relebactam

Self-Assessment #4: Correct Response

Which of these agents is the treatment of choice for treatment of CRE that produces KPC?

a. Cediferocol
b. Meropenem-vaborbactam
c. Tigecycline
d. Imipenem-cilastatin-relebactam

References

1. Tamma PD, Aitken SL, Bonomo RA, Mathers AJ, van Duin D, Clancy CJ. Infectious diseases society of america 2023 guidance on the treatment of antimicrobial resistant gram-negative infections. *Clinical Infectious Diseases*. Published online July 18, 2023. doi:10.1093/cid/ciad428

2. Goodlet KJ, Benhalima FZ, Nailor MD. A systematic review of single-dose aminoglycoside therapy for urinary tract infection: Is it time to resurrect an old strategy? *Antimicrobial Agents and Chemotherapy*. 2019;63(1). doi:10.1128/aac.02165-18

3. Karaiskos I, Galani L, Sakka V, et al. Oral fosfomycin for the treatment of chronic bacterial prostatitis. *Journal of Antimicrobial Chemotherapy*. 2019;74(5):1430-1437. doi:10.1093/jac/dkz015

4. Castanheira M, Davis AP, Mendes RE, Serio AW, Krause KM, Flamm RK. *in vitro* activity of plazomicin against gram-negative and gram-positive isolates collected from U.S. hospitals and comparative activities of aminoglycosides against carbapenem-resistant Enterobacteriaceae and isolates carrying carbapenemase genes. *Antimicrobial Agents and Chemotherapy*. 2018;62(8). doi:10.1128/aac.00313-18

5. Iannaccone M, Boattini M, Bianco G, Corcione S, Cavallo R, Costa C. Ceftazidime-avibactam susceptible to resistant KPC-producing *enterobacterales* bloodstream infections: An observational study. *Journal of Chemotherapy*. 2019;32(3):160-162. doi:10.1080/1120009x.2019.1709363

6. Ackley R, Roshdy D, Meredith J, et al. Meropenem-Vaborbactam versus ceftazidime-avibactam for treatment of carbapenem-resistant *enterobacteriaceae* infections. *Antimicrobial Agents and Chemotherapy*. 2020;64(5). doi:10.1128/aac.02313-19

7. Motsch J, Murta de Oliveira C, Stus V, et al. Restore-IMI 1: A multicenter, randomized, double-blind trial comparing efficacy and safety of imipenem/relebactam vs Colistin plus imipenem in patients with imipenem-nonsusceptible bacterial infections. *Clinical Infectious Diseases*. 2019;70(9):1799-1808. doi:10.1093/cid/ciz530

8. Jung SY, Lee SH, Lee SY, et al. Antimicrobials for the treatment of drug-resistant Acinetobacter baumannii pneumonia in critically ill patients: A systemic review and bayesian network meta-analysis. *Critical Care*. 2017;21(1). doi:10.1186/s13054-017-1916-6

9. Liu J, Shu Y, Zhu F, et al. Comparative efficacy and safety of combination therapy with high-dose sulbactam or colistin with additional antibacterial agents for multiple drug-resistant and extensively drug-resistant Acinetobacter baumannii infections: A systematic review and network meta-analysis. *Journal of Global Antimicrobial Resistance*. 2021;24:136-147. doi:10.1016/j.jgar.2020.08.021

10. Bassetti M, Echols R, Matsunaga Y, et al. 1271. efficacy and safety of CEFIDEROCOL and best available therapy in patients with serious infections caused by carbapenem-resistant gram-negative infections: Results of the pathogen-focused phase 3 credible-CR study. *Open Forum Infectious Diseases*. 2020;7(Supplement_1). doi:10.1093/ofid/ofaa439.1455

11. Wunderink RG, Matsunaga Y, Ariyasu M, et al. Cefiderocol versus high-dose, extended-infusion meropenem for the treatment of gram-negative nosocomial pneumonia (APEKS-NP): A randomised, double-blind, phase 3, non-inferiority trial. *The Lancet Infectious Diseases*. 2021;21(2):213-225. doi:10.1016/s1473-3099(20)30731-3

12. Falcone M, Tiseo G, Leonildi A, et al. Cefiderocol- compared to Colistin-based regimens for the treatment of severe infections caused by carbapenem-resistant Acinetobacter baumannii. *Antimicrobial Agents and Chemotherapy*. 2022;66(5). doi:10.1128/aac.02142-21

13. Kaye KS, Shorr AF, Wunderink RG, et al. Efficacy and safety of Sulbactam–Durlobactam versus Colistin for the treatment of patients with serious infections caused by Acinetobacter baumannii–calcoaceticus complex: A multicentre, randomised, active-controlled, phase 3, non-inferiority clinical trial (attack). *The Lancet Infectious Diseases*. 2023;23(9):1072-1084. doi:10.1016/s1473-3099(23)00184-6

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Thank you!

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