

13 – Core Concepts: Antibacterial Drugs I Gram Negative Organisms

Speaker: Pranita Tamma, MD



Core Concepts: Antibacterial Drugs I Gram-Negative Organisms

Pranita D. Tamma, MD, MHS
Johns Hopkins University School of Medicine
Associate Professor, Pediatrics

7/24/2024



• Disclosures of Financial Relationships with Relevant Commercial Interests

- None

Objectives

- Review antibiotic treatment options for infections caused by:
 - Extended-spectrum beta-lactamase producing Enterobacterales (**ESBL-E**)
 - Amp-C producing Enterobacterales (**AmpC-E**)
 - *Pseudomonas aeruginosa* with difficult-to-treat resistance (**DTR P. aeruginosa**)
 - Carbapenem-resistant Enterobacterales (**CRE**)
 - Carbapenem-resistant *Acinetobacter baumannii* (**CRAB**)

ESBL-E Infections

Clinical Case

- 21-year-old female
- Renal transplant secondary to focal segmental glomerulosclerosis
- Dysuria, fevers, rigors, and hypotension
- Urine and blood cultures growing *Escherichia coli*
- ICU to initiate vasopressors

PREVIEW QUESTION

Antibiotic	MIC	Interpretation
Amikacin	>8 µg/mL	S
Aztreonam	16 µg/mL	R
Cefazolin	>16 µg/mL	R
Cefotetan	2 µg/mL	S
Cefepime	4 µg/mL	R
Ceftazidime	>16 µg/mL	R
Ceftriaxone	32 µg/mL	R
Ciprofloxacin	1 µg/mL	R
Ertapenem	0.5 µg/mL	S
Gentamicin	2 µg/mL	R
Meropenem	0.5 µg/mL	S
Piperacillin/tazobactam	8/4 µg/mL	S
Tobramycin	2 µg/mL	S
Trimethoprim/sulfamethoxazole	0.5/4 µg/mL	S

PREVIEW QUESTION

13 – Core Concepts: Antibacterial Drugs I Gram Negative Organisms

Speaker: Pranita Tamma, MD

Antibiotic	MIC	Interpretation
Amikacin	>8 µg/mL	S
Aztreonam	16 µg/mL	R
Cefazolin	>16 µg/mL	R
Cefotetan	2 µg/mL	S
Cefepime	4 µg/mL	R
Ceftazidime	>16 µg/mL	R
Ceftriaxone	32 µg/mL	R
Ciprofloxacin	1 µg/mL	R
Ertapenem	0.5 µg/mL	S
Gentamicin	2 µg/mL	R
Meropenem	0.5 µg/mL	S
Piperacillin/tazobactam	8/4 µg/mL	S
Tobramycin	2 µg/mL	S
Trimethoprim/sulfamethoxazole	0.5/4 µg/mL	S

PREVIEW QUESTION

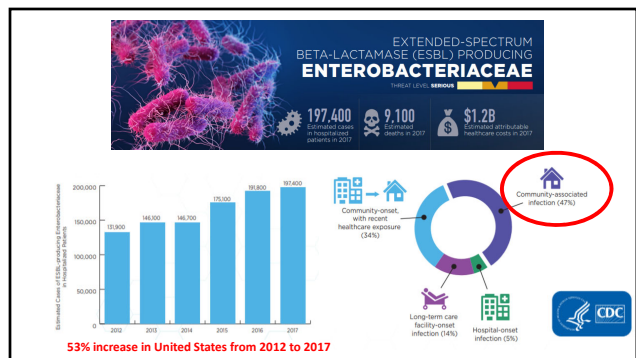
Which one of the following antibiotics represents the most appropriate initial treatment?

- Cefepime
- Trimethoprim-sulfamethoxazole
- Meropenem
- Piperacillin-tazobactam

PREVIEW QUESTION

Which one of the following antibiotics represents the most appropriate initial treatment?

- Cefepime
- Trimethoprim-sulfamethoxazole
- Meropenem ***
- Piperacillin-tazobactam



A Primer on ESBL-E

- Hydrolyze penicillins, cephalosporins, and aztreonam
- E. coli*, *Klebsiella pneumoniae*, *Klebsiella oxytoca*, and *Proteus mirabilis*
- CTX-M enzymes are the most common ESBLs
- Ceftriaxone-resistant *E. coli*, *K. pneumoniae*, *K. oxytoca*, or *P. mirabilis* = think ESBL production

JAMA

Research

JAMA | Original Investigation

Effect of Piperacillin-Tazobactam vs Meropenem on 30-Day Mortality for Patients With *E coli* or *Klebsiella pneumoniae* Bloodstream Infection and Ceftriaxone Resistance

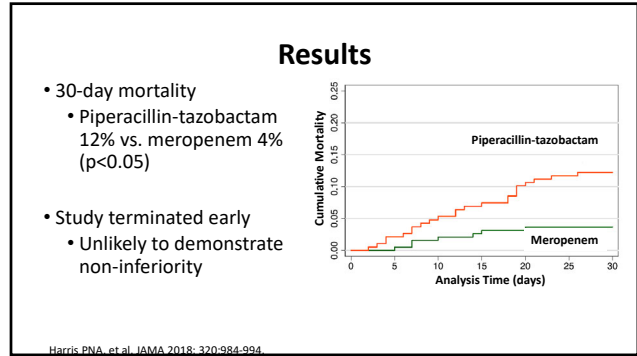
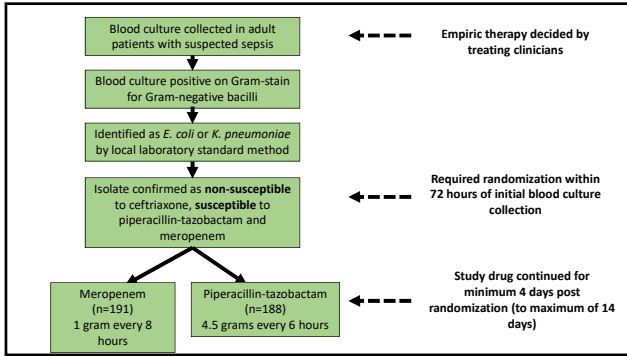
A Randomized Clinical Trial

Patrick N. A. Harris, MBBS, Paul A. Tambyah, MD, David C. Lye, MBBS, Yin Mo, MBBS, Tau H. Lee, MBBS, Meout Yilmaz, MD, Thamer H. Alencat, MD, Yaseen Arabi, MD, Marco Falcone, MD, Matteo Bassetti, MD, PhD, Eisa Rishi, MD, PhD, Benjamin A. Rogers, MBBS, PhD, Souha Karaj, MD, Hasan Bhatti, MBBS, Jon Iredell, MBBS, PhD, Marc Mendelson, MBBS, PhD, Tom H. Boyles, MD, David Louke, MBBS, Spiros Miyakis, MD, PhD, Genevieve Walls, MB, ChB, Mohammed Al Khamis, MD, Ahmed Zeki, PharmD, Amy Crowe, MBBS, Paul Ingram, MBBS, Nick Daneman, MD, Paul Griffin, MBBS, Eugene Athan, MBBS, MPH, PhD, Penelope Lorenz, RN, Peter Baker, PhD, Leah Roberts, BSc, Scott A. Beatson, PhD, Anton Y. Peleg, MBBS, PhD, Tiffany Harris-Brown, RN, MPH, David L. Paterson, MBBS, PhD, for the MERINO Trial Investigators and the Australasian Society for Infectious Disease Clinical Research Network (ASID-CRN)

Harris PNA, et al. JAMA 2018; 320:984-994.

13 – Core Concepts: Antibacterial Drugs I Gram Negative Organisms

Speaker: Pranita Tamma, MD



Which one of the following antibiotics represents the most appropriate initial treatment?

1. Cefepime
2. Trimethoprim-sulfamethoxazole
3. Meropenem
4. ~~Piperacillin-tazobactam~~

Clinical Infectious Diseases
IDSA GUIDELINES

Infected Diseases Society of America 2023 Guidance on the Treatment of Antimicrobial Resistant Gram-Negative Infections

Question 1.5: Is There a Role for Cefepime in the Treatment of Infections Caused by ESBL-E?

Suggested Approach: Cefepime is not suggested for the treatment of infections caused by ESBL-E, even if susceptibility to the agent is demonstrated.

Tamma PD, et al. Clin Infect Dis. 2023 Jul 18;cid428. doi:10.1093/cid/ciad428. Online ahead of print.

Cefepime for ESBL-E Infections

- CTX-M enzymes generally hydrolyze cefepime
- Poorer outcomes with cefepime for the treatment of ESBL-E infections in observational studies

Wang R, Open Forum Infect Dis 2016; 3(3): ofw132. Lee NY, et al. Clin Infect Dis 2013; 56(4): 488-95. Chopra T, et al. Antimicrob Agents Chemother 2012; 56(7): 3936-42. Zanetti G, et al. Antimicrob Agents Chemother 2003; 47(11): 3442-7. Lee NY, et al. Antimicrob Agents Chemother 2015; 59(12): 7558-63.

Which one of the following antibiotics represents the most appropriate initial treatment?

1. ~~Cefepime~~
2. Trimethoprim-sulfamethoxazole
3. Meropenem
4. ~~Piperacillin-tazobactam~~

13 – Core Concepts: Antibacterial Drugs I Gram Negative Organisms

Speaker: Pranita Tamma, MD

Which of the following bacterial species is most likely to produce AmpC β-lactamase enzymes?

1. *Escherichia coli*
2. ***Enterobacter cloacae***
3. *Serratia marcescens*
4. *Proteus mirabilis*

Inducible Chromosomal *ampC* expression

- AmpC enzymes assist with bacterial cell wall recycling.
 - Organisms producing AmpC enzymes even at low levels produce sufficient enzymes to hydrolyze ampicillin, ampicillin-sulbactam, cefazolin, cephamycins
- Inducible AmpC production: Capable of hydrolyzing certain antibiotics even though the bacteria initially seems susceptible to those agents
 - Most notorious = **ceftriaxone** (and other third-generation cephalosporins)
- *Enterobacter cloacae*, *Citrobacter freundii*, *Klebsiella aerogenes* have a reasonable likelihood of excessive AmpC production if exposed to ceftriaxone
 - Emergence of resistance while receiving ceftriaxone **~20%** of the time
- *Serratia marcescens*, *Morganella morganii*, and *Providencia* spp. are significantly less likely to have excessive AmpC production if exposed to ceftriaxone
 - Emergence of resistance while receiving ceftriaxone **<5%** of the time

Clinical Infectious Diseases
IDSA GUIDELINES



Infectious Diseases Society of America 2023 Guidance on the Treatment of Antimicrobial Resistant Gram-Negative Infections

Question 2.3: What is the role of cefepime for the treatment of infections caused by Enterobacterales at moderate risk of clinically significant AmpC production due to an inducible *ampC* gene?

Suggested Approach: Cefepime is suggested for the treatment of infections caused by organisms at moderate risk of significant AmpC production (i.e., *E. cloacae* complex, *K. aerogenes*, and *C. freundii*).

Tamma PD, et al. Clin Infect Dis. 2023 Jul 18;ciad428. doi: 10.1093/cid/ciad428. Online ahead of print.

Cefepime

- Cefepime has the advantage of both being a weak inducer of *ampC* and of withstanding hydrolysis by AmpC β-lactamases
 - It is considered a preferred agent for the treatment of AmpC-E infections

Girlich D, et al. Antimicrob Agents Chemother 2000; 44: 3220-3. Sanders CC, et al. Antimicrob Agents Chemother 1997; 41: 2013-5.

<i>E. coli</i> Isolate	<i>bla</i> _{CMV-2} copy number	Piperacillin-tazobactam (µg/mL)	Aztreonam (µg/mL)	Ceftazidime (µg/mL)	Cefepime (µg/mL)	Imipenem (µg/mL)	Ertapenem (µg/mL)
Parent strain	1	4	2	32	0.12	0.12	0.02
Mutant 1	13	512	64	512	4	0.5	0.38
Mutant 2	3	64	32	128	0.5	0.12	0.12
Mutant 3	7	256	32	256	1	0.25	0.19

Kurpiel KM, et al. J Antimicrob Chemother 2012; 67:339-45.

AmpC-E: Testable Points

- Inducible AmpC enzymes most problematic for *E. cloacae*, *C. freundii*, & *K. aerogenes*
- Ceftriaxone not suggested for invasive infections caused by these 3 organisms
 - Cefepime generally treatment of choice
- When these 3 organisms are recovered in clinical cultures (outside of an uncomplicated cystitis) cefepime is the preferred treatment
 - Similar to ESBL-E, non-beta-lactam agents are not impacted

13 – Core Concepts: Antibacterial Drugs I Gram Negative Organisms

Speaker: Pranita Tamma, MD

DTR *P. aeruginosa* Infections

Clinical Case

- 24-year-old male with acute myelogenous leukemia
 - Absolute neutrophil count = 0 cells/mL
- Acute onset fevers and respiratory distress
- Multifocal pneumonia
- *P. aeruginosa* recovered from bronchoalveolar lavage fluid

Antibiotic	MIC	Interpretation
Amikacin	> 8 µg/mL	R
Aztreonam	> 16 µg/mL	R
Cefepime	> 16 µg/mL	R
Ceftazidime	> 16 µg/mL	R
Ciprofloxacin	> 2 µg/mL	R
Colistin	2 µg/mL	I
Gentamicin	> 8 µg/mL	R
Meropenem	16 µg/mL	R
Piperacillin/tazobactam	> 64/4 µg/mL	R
Tobramycin	> 8 µg/mL	R

Pseudomonas aeruginosa with "difficult-to-treat resistance" = resistance to all traditional beta-lactam and fluoroquinolone agents

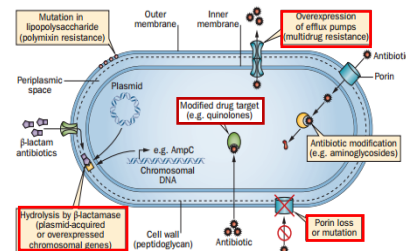
Which one of the following antibiotics is least likely to be effective against DTR-*P. aeruginosa* infections?

1. Ceftolozane-tazobactam
2. Ceftazidime-avibactam
3. Meropenem-vaborbactam
4. Imipenem-cilastatin-relebactam

Which one of the following antibiotics is least likely to be effective against DTR-*P. aeruginosa* infections?

1. Ceftolozane-tazobactam
2. Ceftazidime-avibactam
3. **Meropenem-vaborbactam ***
4. Imipenem-cilastatin-relebactam

Common Mechanisms of Resistance



1. Reduction in outer membrane porins
2. Upregulation of efflux pumps
3. Increased production of Pseudomonal AmpCs
4. Mutations in penicillin binding proteins

Zowawi, et al. Nat Rev Urol 2015;12:570.

13 – Core Concepts: Antibacterial Drugs I Gram Negative Organisms

Speaker: Pranita Tamma, MD

Why Have the Polymyxins Fallen out of Favor?

- Penetration into pulmonary epithelial lining fluid is suboptimal
- Colistin is administered IV as inactive prodrug colistin methanesulfonate; slowly and incompletely converted to colistin
- Difficult to achieve adequate colistin plasma concentrations in patients with normal renal function
- Several reports of clinical failure and resistance emergence during polymyxin monotherapy

Adverse Events Associated with Polymyxins

- **Nephrotoxicity**
 - ~40-60% with colistin
 - ~20-30% with polymyxin B
 - Usually reversible upon drug discontinuation
- **Neurotoxicity**
 - <5% of patients; mostly due to polymyxin B
 - Manifests as paresthesias, seizures, neuromuscular blockade
 - Usually reversible upon drug discontinuation

Activity of β -Lactams Against DTR *P. aeruginosa*

β -Lactam Agents	DTR- <i>P. aeruginosa</i>
Ceftolozane-tazobactam (2014)	Green
Ceftazidime-avibactam (2015)	Green
Meropenem-vaborbactam (2017)	Red
Cefiderocol (2019)	Green
Imipenem-cilastatin-relebactam (2020)	Green
Sulbactam-durlobactam (2023)	Red

Antibiotics Active Against DTR *P. aeruginosa*

- Susceptibility to ceftolozane-tazobactam, ceftazidime-avibactam, and imipenem-cilastatin-relebactam ranges from 50-90%
- Risk of emergence of resistance after a single treatment course is highest for ceftolozane-tazobactam or ceftazidime-avibactam treatment
 - Repeat antibiotic susceptibility testing for future *P. aeruginosa* infections
- Generally avoid imipenem-cilastatin-relebactam if receiving concomitant valproic acid

Rubio AM, et al. Antimicrob Agents Chemother. 2021;65:e00084-21. Tamma PD, et al. Clin Infect Dis. 2022;75:187-212. Tamma PD, et al. Clin Infect Dis 2021;73:e4599-e4606. Canon JP, et al. Journal of Antimicrobial Chemotherapy. 2014;69:2043-2055.

Cefiderocol

- Cephalosporin combined with a siderophore
- Siderophores are iron chelators that enable cefiderocol to bind iron and enter bacteria through iron-transport channels
- Resistance mostly because of mutations in iron transport proteins
- Second-line agent for DTR *P. aeruginosa* infections

O'Donnell JN, et al. Antimicrob Agents Chemother. 2022;66:e0025622.

DTR *P. aeruginosa*: Testable Points

- Polymyxins not suggested for DTR *P. aeruginosa*
 - Exception: colistin for uncomplicated cystitis
- Preferred: ceftolozane-tazobactam, ceftazidime-avibactam, imipenem-cilastatin-relebactam
- Emergence of resistance most concerning for ceftolozane-tazobactam and ceftazidime-avibactam
- Avoid imipenem-cilastatin-relebactam if receiving valproic acid
- Cefiderocol is unique: siderophore enabling entry into bacteria through iron transport channels

13 – Core Concepts: Antibacterial Drugs I Gram Negative Organisms

Speaker: Pranita Tamma, MD

CRE Infections

Clinical Case

- 30-year-old female with a cardiac transplant at age 4 years for a hypoplastic left heart
 - Complicated clinical course requiring multiple, prolonged hospitalizations
- Acute onset fevers, rigors, and hypotension
- *Klebsiella pneumoniae* in blood cultures

Antibiotic	MIC	Interpretation
Amikacin	> 8 µg/mL	R
Aztreonam	> 16 µg/mL	R
Cefepime	> 16 µg/mL	R
Ceftazidime	> 16 µg/mL	R
Ciprofloxacin	> 2 µg/mL	R
Ertapenem	2 µg/mL	R
Gentamicin	> 8 µg/mL	R
Meropenem	8 µg/mL	R
Piperacillin/tazobactam	> 64 µg/mL	R
Tobramycin	> 8 µg/mL	R

*bla*_{KPC} gene present

Which of the following antibiotics is not expected to be effective at treating a KPC-producing infection?

1. Ceftolozane-tazobactam
2. Ceftazidime-avibactam
3. Meropenem-vaborbactam
4. Imipenem-cilastatin-relebactam

Which of the following antibiotics is not expected to be effective at treating a KPC-producing infection?

1. **Ceftolozane-tazobactam ***
2. Ceftazidime-avibactam
3. Meropenem-vaborbactam
4. Imipenem-cilastatin-relebactam

Defining Carbapenem-Resistant Enterobacterales (CRE)

- Resistant to at least one carbapenem
- ~50% of CRE have a carbapenemase gene
- Common carbapenemases:
 - *Klebsiella pneumoniae* carbapenemases (**KPCs**)
 - New Delhi metallo-β-lactamases (**NDMs**)
 - Verona integron-encoded metallo-β-lactamases (**VIMs**)
 - Imipenem-hydrolyzing metallo-β-lactamases (**HIMPs**)
 - Oxacillinases (**OXA-48-like**)

13 – Core Concepts: Antibacterial Drugs I Gram Negative Organisms

Speaker: Pranita Tamma, MD

Activity of β -Lactams Against CRE Isolates

β -Lactam Agents	KPCs	NDMs	OXA-48-like
Ceftazidime-avibactam (2015)	Green	Red	Green
Cefotolozane-tazobactam (2014)	Red	Red	Red
Meropenem-vaborbactam (2017)	Green	Red	Green
Cefiderocol (2019)	Green	Green	Green
Imipenem-cilastatin-relebactam (2020)	Green	Red	Green
Sulbactam-durlobactam (2023)	Red	Red	Red

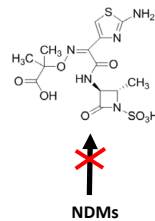
KPC-Producing Enterobacterales

- Class A β -lactamases
- Most common carbapenemases in the United States
- In many Enterobacterales species; not unique to *K. pneumoniae*
- **Treatment options**
 - Preferred: Ceftazidime-avibactam, meropenem-vaborbactam, imipenem-cilastatin-relebactam
 - Alternative: Cefiderocol

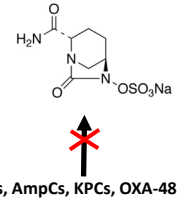
NDM-Producing Enterobacterales

- Class B β -lactamases
- 10% of carbapenemase-producing Enterobacterales in the United States
 - Main risk factor: previous medical care in Indian subcontinent
- **Treatment options**
 - Preferred: Cefiderocol or ceftazidime-avibactam PLUS aztreonam

Aztreonam



Avibactam



OXA-48-like-Producing Enterobacterales

- Class D β -lactamases
- Rare in the United States (<5% of carbapenemase-producing Enterobacterales)
 - Main risk factor: previous medical care in Indian subcontinent, Middle East, or Europe
- **Treatment options**
 - Preferred: Ceftazidime-avibactam or cefiderocol

CRE: Testable Points

- CRE: carbapenemase or non-carbapenemase-producing
- KPC: most common carbapenemase
- NDM: medical care in South Asia
- Unlikely to be tested on VIM, IMP, OXA-48-like carbapenemases
- **Preferred treatment**
 - KPC-producers: ceftazidime-avibactam, meropenem-vaborbactam, imipenem-cilastatin-relebactam
 - NDM-producers: cefiderocol, ceftazidime-avibactam PLUS aztreonam

13 – Core Concepts: Antibacterial Drugs I Gram Negative Organisms

Speaker: Pranita Tamma, MD

CRAB Infections

Clinical Case

- 39-year-old male recovering from a motor vehicle accident in a burn unit
 - Prolonged hospitalization
 - Requiring intubation
- Fevers, increased oxygen support, new pulmonary infiltrates
- *Acinetobacter baumannii* recovered in endotracheal aspirate

General Challenges with CRAB

- Distinguishing colonization from infection can be difficult
 - Commonly recovered from non-sterile sites (e.g., respiratory specimens, wounds)
- Patient population at risk has underlying reasons for poor outcomes (e.g., burn patients, mechanical ventilation, combat wounds)
- Interpretation of comparative effectiveness studies difficult



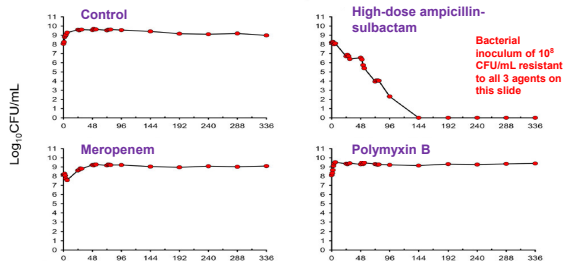
<https://arppsp.cdc.gov/profile/antibiotic-resistance/carbapenem-resistant-acinetobacter>

Benefits of Sulbactam

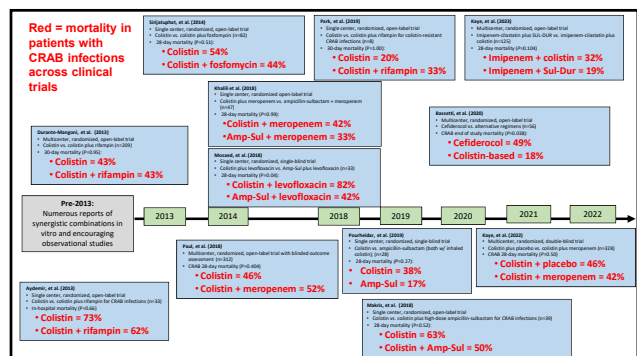
- Ability to function as a β -lactam and can saturate PBP1a/1b and PBP3 of *A. baumannii* isolates
- Unique activity against *A. baumannii* isolates demonstrated through in vitro studies, animal models, and clinical outcomes data

Lenhard JR, et al. Antimicrob Agents Chemother. 2017;61:e01268-01216. Beganovic M, et al. Antimicrob Agents Chemother. 2021;65:e01680-01620. Abdul-Mutalabir C, et al. Antibiotics (Basel). 2021;10. Rodriguez-Hernandez MJ, et al. J Antimicrob Chemother. 2001;47:479-482. Makris D, et al. Indian J Crit Care Med. 2018;22:67-77. Bretrosian AP, et al. Scand J Infect Dis. 2007;39:38-43. Assimakopoulos Sfet al. Infect Med. 2019;27:11-16. Liu J, et al. J Glob Antimicrob Resist. 2021;24:136-147. Jung SV, et al. Crit Care. 2017;21:319.

Hollow Fiber Infection Model

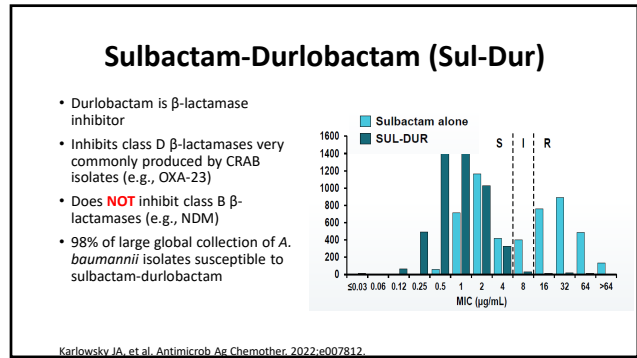
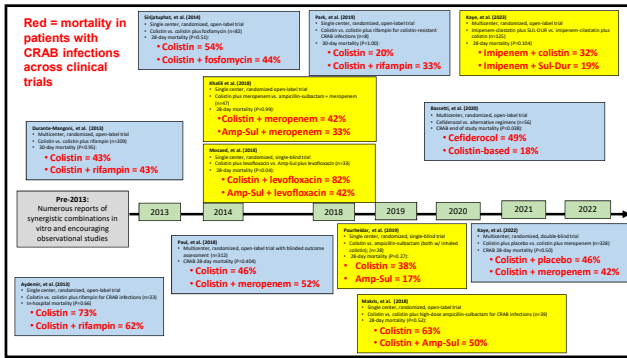


Lenhard JR, et al. Antimicrob Agents Chemother. 2017;61:e01268-16.



13 – Core Concepts: Antibacterial Drugs I Gram Negative Organisms

Speaker: Pranita Tamma, MD

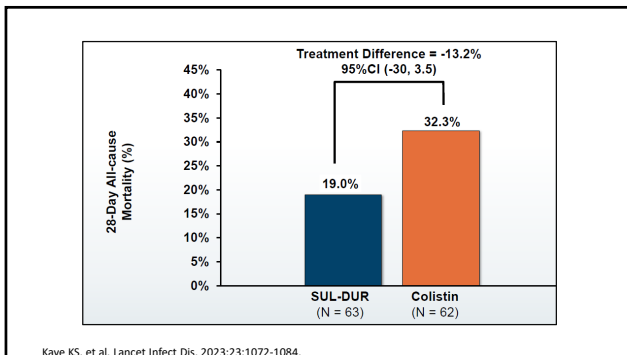
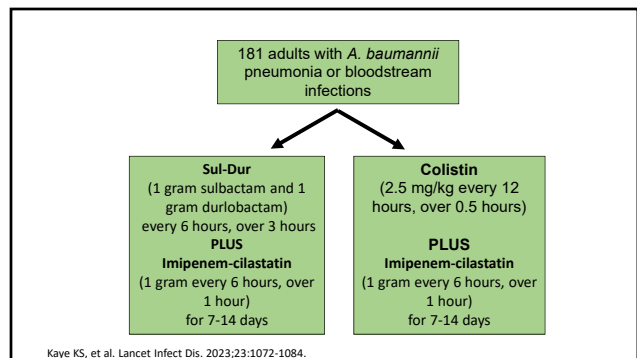


THE LANCET

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)

Keith S Kaye, Andrew F Shore, Richard G Wunderink, Bin Du, Gabrielle E Poiret, Khuram Rana, Alita Miller, Drew Lewis, John O'Donnell, Lam Chen, Harald Reinhart, Sobasree Srinivasan, Robyn Isaac, David Altarac

Kaye KS, et al. Lancet Infect Dis. 2023;23:1072-1084.



- ### CRE: Testable Points
- Identification of CRAB in a clinical specimen does not always mean antibiotic therapy is indicated
 - Sulbactam-based regimens remain the cornerstone of treatment
 - First choice: **Sulbactam-Durlobactam** (with imipenem or meropenem)
 - Second choice: **High-dose Ampicillin-Sulbactam** (with an additional agent)
 - Potential “additional agents” include **polymyxin B** or **minocycline** or **cefiderocol**