13 – Core Concepts: Antibacterial Drugs I Gram Negative Organisms

Speaker: Pranita Tamma, MD

Core Concepts: Antibacterial Drugs I Gram-Negative Organisms

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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

PREVIEW QUESTION

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

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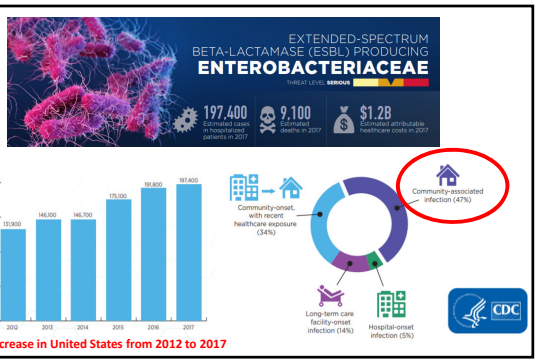
Cefepime	4 µg/mL	R
Ceftazidime	>16 µg/mL	R
Ceftriaxone	32 µg/mL	R
Ciprofloxacin	1 µg/mL	R
Ertapenem	0.5 µg/mL	S
Gentamicin	2 µg/mL	R
Meropenem	0.5 µg/mL	S
Piperacillin/tazobactam	8/4 µg/mL	S
Tobramycin	2 µg/mL	S
Trimethoprim/sulfamethoxazole	0.5/4 µg/mL	S

PREVIEW QUESTION

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

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



53% increase in United States from 2012 to 2017

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

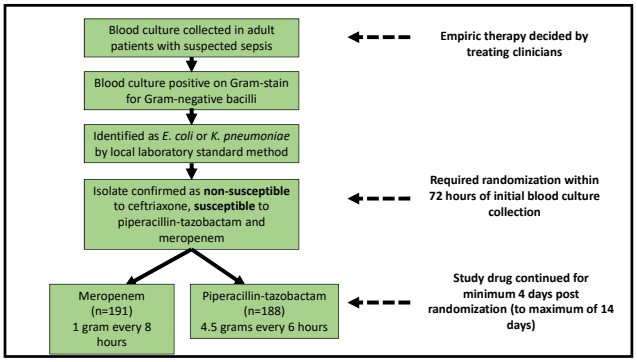
JAMA | Original Investigation

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; Mesut Yilmaz, MD; Thamer H. Alenazi, MD; Yaseen Arabi, MD; Marco Falcone, MD; Matteo Bassetti, MD, PhD; Elda Righi, MD, PhD; Benjamin A. Rogers, MBBS, PhD; Souha Kanj, MD; Hasan Bhally, MBBS; Jon Iredell, MBBS, PhD; Marc Mendelson, MBBS, PhD; Tom H. Boyles, MD; David Looke, MBBS; Spiros Miyakis, MD, PhD; Genevieve Walls, MB, ChB; Mohammed Al Khamis, MD; Ahmed Zikri, PharmD; Amy Crowe, MBBS; Paul Ingram, MBBS; Nick Daneman, MD; Paul Griffin, MBBS; Eugene Athan, MBBS, MPH, PhD; Penelope Lorenc, 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.



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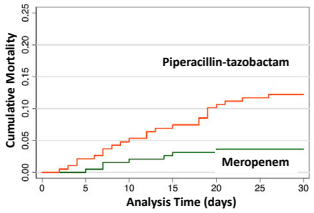
Results

- 30-day mortality
  - Piperacillin-tazobactam 12% vs. meropenem 4% (p<0.05)
- Study terminated early
  - Unlikely to demonstrate non-inferiority



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

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

Clinical Infectious Diseases
IDSA GUIDELINES

Infectious 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:ciad428. 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~~

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Question 1.3: What are preferred antibiotics for the treatment of infections outside of the urinary tract caused by ESBL-E?

Suggested Approach: Meropenem, imipenem-cilastatin, or ertapenem are preferred for the treatment of infections outside of the urinary tract caused by ESBL-E. After appropriate clinical response is achieved, transitioning to oral trimethoprim-sulfamethoxazole, ciprofloxacin, or levofloxacin should be considered, if susceptibility is demonstrated.

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

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Trimethoprim-Sulfamethoxazole (TMP-SMX) for ESBL-E Treatment

- TMP-SMX (and fluoroquinolones) not hydrolyzed by ESBL enzymes
- Reasonable treatment option for invasive ESBL-E infections (if susceptible), after clinical improvement observed

ESBL-E: Testable Points

- Hydrolyze traditional β-lactam antibiotics except carbapenems
- *E. coli*, *K. pneumoniae*, *K. oxytoca*, and *P. mirabilis* resistant to ceftriaxone = likely ESBL producer
- Carbapenems are treatment of choice
- TMP-SMX or fluoroquinolones reasonable after clinical improvement is observed

AmpC-E Infections

Clinical Case

- 62-year-old male with colon cancer
- Fevers, abdominal pain, and mental status changes one week after partial colectomy
- Multiple intra-abdominal abscesses
- Blood cultures are growing gram-negative rods

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

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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.

E. coli Isolate	bla_{CMY-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

DTR *P. aeruginosa* Infections

PREVIEW QUESTION

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

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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

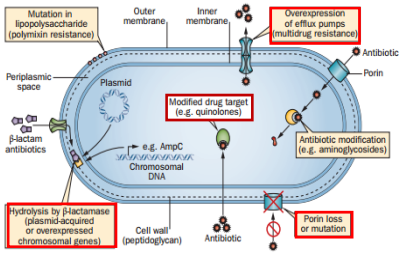
***Pseudomonas aeruginosa* with "difficult-to-treat resistance" = resistance to all traditional beta-lactam and fluoroquinolone agents**

PREVIEW QUESTION

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.

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-*P. aeruginosa*
Ceftolozane-tazobactam (2014)	
Ceftazidime-avibactam (2015)	
Meropenem-vaborbactam (2017)	
Cefiderocol (2019)	
Imipenem-cilastatin-relebactam (2020)	
Sulbactam-durlobactam (2023)	

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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

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

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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 **(IMPs)**
  - Oxacillinases **(OXA-48-like)**

Activity of β-Lactams Against CRE Isolates

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

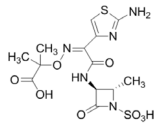
KPC-Producing Enterobacterales

- 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

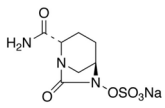
- Class B β-lactamases
- 10% of carbapenemase-producing Enterobacterales in the Untied States
  - Main risk factor: previous medical care in Indian subcontinent
- **Treatment options**
  - Preferred: Cefiderocol or ceftazidime-avibactam PLUS aztreonam

Aztreonam



NDMs

Avibactam



ESBLs, AmpCs, KPCs, OXA-48-like

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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

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://arpsp.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-Mutakabbir JC, 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. Betrosian AP, et al. Scand J Infect Dis. 2007;39:38-43. Assimakopoulos SFet al. Infez Med. 2019;27:11-16. Liu J, et al. J Glob Antimicrob Resist. 2021;24:136-147. Jung SY, et al. Crit Care. 2017;21:319.

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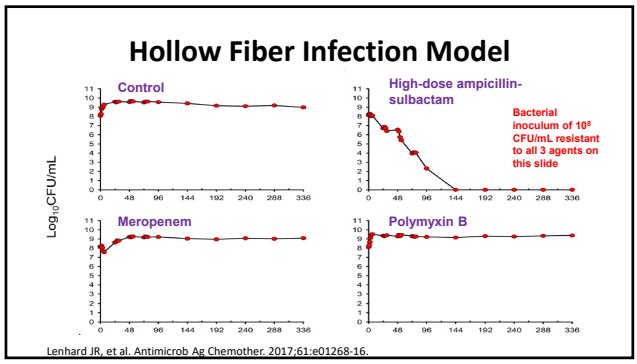
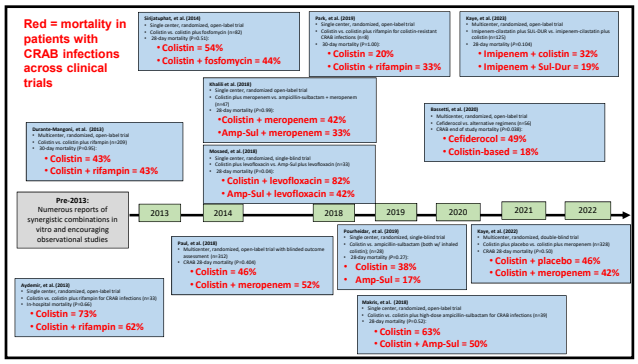
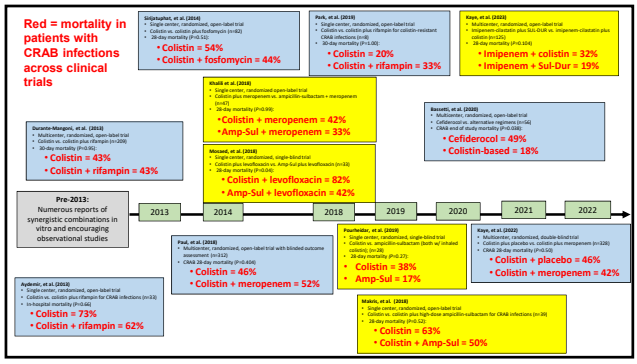
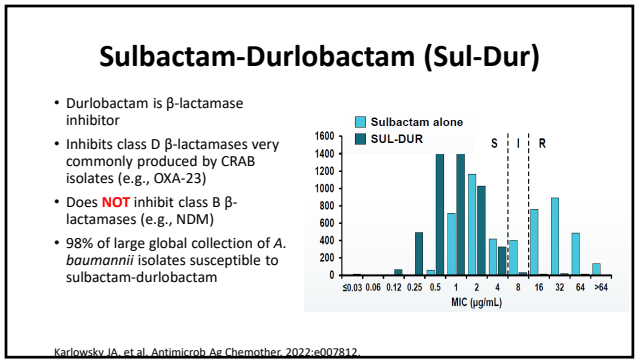


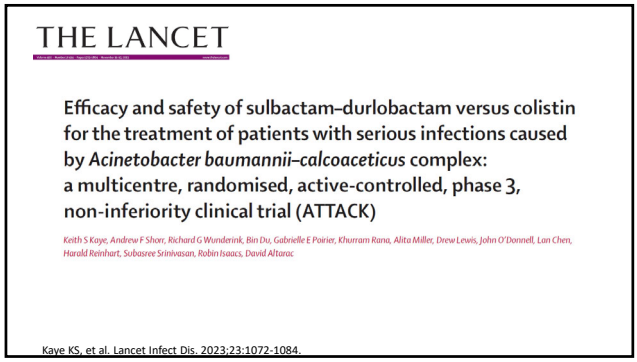
Lenhard JR, et al. Antimicrob Ag Chemother. 2017;61:e01268-16.



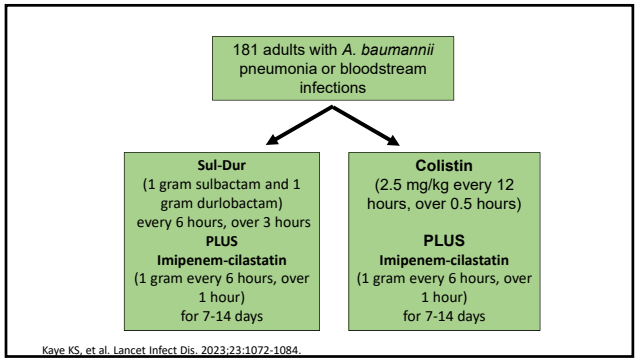




Karlowsky JA, et al. Antimicrob Ag Chemother. 2022:e007812.



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



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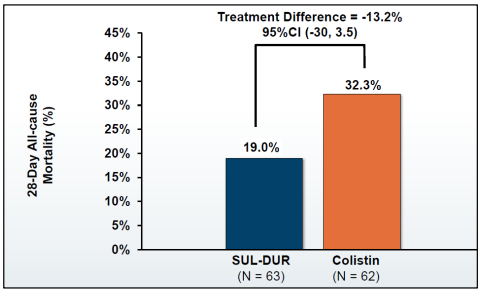

Kaye KS, et al. Lancet Infect Dis. 2023;23:1072-1084.

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**