Fantastic Bugs and How to Treat Them: Gram Negative Resistance

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September 18, 2019

Objectives

- Define Multidrug-, Extensively Drug-, and Pan-Drug Resistant Organisms
- Discuss literature for the management of MDROs
- Select antimicrobial therapy for patients with MDROs

Disclosure

- The presenter does not have (nor does any immediate family member have) a vested interest in or affiliation with any corporate organization offering financial support or grant monies for this continuing education activity, or any affiliation with an organization whose philosophy could potentially bias this presentation

Background

- At least 2 million people are infected with antibiotic-resistant bacteria annually in the United States
  - At least 23,000 people die as a result
- Enterobacteriaceae cause approximately 30% of healthcare-associated infections in the United States
- Carbapenem use has increased with the increasing rate of extended-spectrum β-lactamase (ESBL) producing organisms
  - Resulting in carbapenem resistance among Enterobacteriaceae
- The percentage of carbapenem-resistant *Klebsiella* isolates from US hospitals increased from <1% in 2000, to 8% in 2006–2007, to 12% in 2009–2010

About Antimicrobial Resistance [Internet] Centers for Disease Control and Prevention, National Center for Emerging and Zoonotic Infectious Diseases [updated 10 Sep 2018]
Satlin MJ, et al. Clin Infect Dis. 2014 May;58(9):1274-83.

Definitions

- Multidrug-Resistant Organism (MDRO): non-susceptibility to at least one agent in three or more antimicrobial categories
- Extensively Drug-Resistant Organism (XDRO): non-susceptibility to at least one agent in all but two or fewer antimicrobial categories
  - Bacterial isolates remain susceptible to only one or two categories
- Pan-Drug Resistant Organism (PDRO): non-susceptibility to all agents in all antimicrobial categories

Magiorakos AP, et al. Clin Microbiol Infect. 2012 Mar;18(3):268-81.
[Image] https://weheartit.com/entry/272426040

MDR-*Acinetobacter* spp. or *Pseudomonas aeruginosa* Definition

- Resistant to 3 of 5 antimicrobial agents:
  - Ciprofloxacin
  - Piperacillin-tazobactam OR piperacillin
  - Ceftazidime OR cefepime
  - Imipenem OR meropenem
  - Tobramycin

German GJ, et al. Can Commun Dis Rep. 2016 Apr 7;42(4):96-104. eCollection 2016 Apr 7.

XDR-*Acinetobacter* spp. or *Pseudomonas aeruginosa* Definition

Acinetobacter spp.

- Resistant to 6 of the 8 antimicrobial agents:
  - Gentamicin OR tobramycin
  - Piperacillin-tazobactam
  - Imipenem OR meropenem OR doripenem
  - Cefepime OR ceftazidime
  - Ciprofloxacin
  - Colistin
  - Doxycycline OR minocycline
  - Trimethoprim-sulfamethoxazole

P. aeruginosa

- Resistant to 4 of 6 antimicrobial agents:
  - Tobramycin
  - Piperacillin OR piperacillin-tazobactam
  - Imipenem OR meropenem OR doripenem
  - Cefepime OR ceftazidime
  - Ciprofloxacin
  - Colistin

7 German GJ, et al. Can Commun Dis Rep. 2016 Apr 7;42(4):96-104. eCollection 2016 Apr 7.

How would you classify this isolate?

Pseudomonas aeruginosa		
Amikacin	32	I
Aztreonam	8	S
Cefepime	>16	I
Ceftazidime	16	I
Ciprofloxacin	>2	R
Gentamicin	> 8	R
Imipenem	>4	R
Levofloxacin	>4	R
Meropenem	>8	R
Pip/tazo	>128	R
Tobramycin	>16	R

- Multidrug-Resistant *Pseudomonas aeruginosa*
- Very Drug-Resistant *Pseudomonas aeruginosa*
- Extensively Drug-Resistant *Pseudomonas aeruginosa*
- Pan-Drug Resistant *Pseudomonas aeruginosa*

How would you classify this isolate?

Multidrug-Resistant Pseudomonas aeruginosa

Very Drug-Resistant Pseudomonas aeruginosa

Extensively Drug-Resistant Pseudomonas aeruginosa

Pan-Drug Resistant Organism Pseudomonas aeruginosa

How would you classify this isolate?

Pseudomonas aeruginosa		
Amikacin	32	I
Aztreonam	8	S
Cefepime	>16	I
Ceftazidime	16	I
Ciprofloxacin	**>2**	**R**
Gentamicin	> 8	R
Imipenem	**>4**	**R**
Levofloxacin	>4	R
Meropenem	**>8**	**R**
Pip/tazo	**>128**	**R**
Tobramycin	**>16**	**R**

- Extensively Drug-Resistant *Pseudomonas aeruginosa*
- Resistant to 4 of 6 antimicrobial agents:
  - Tobramycin
  - Piperacillin OR piperacillin-tazobactam
  - Imipenem OR meropenem OR doripenem
  - Cefepime OR ceftazidime
  - Ciprofloxacin
  - Colistin

10 German GJ, et al. Can Commun Dis Rep. 2016 Apr 7;42(4):96-104. eCollection 2016 Apr 7.

Extended-Spectrum β-Lactamases (ESBLs)

- Produced by:
  - *Klebsiella pneumoniae, Klebsiella oxytoca, Escherichia coli*, and *Proteus* spp.
- May be plasmid-mediated or chromosomal
- Confer multidrug resistance
  - Temoneira (TEM) or Sulhydryl Variable (SHV) types
- Cefotaximase-Munich (CTX-M) type ESBLs are the most prevalent ESBL types worldwide
- Detected by *in vitro* resistance to ceftazidime and aztreonam
  - Confirmed by the microbiology lab with ESBL test
    - Ceftazidime + Ceftazidime-clavulanate
    - Cefotaxime + Cefotaxime-clavulanate

Spacek, Lisa A. "Klebsiella Species." Johns Hopkins ABX Guide, The Johns Hopkins University, 2016. Johns Hopkins Guide,
CLSI M100-ED29:2019 Performance Standards for Antimicrobial Susceptibility Testing, 29th Edition

CRE (Carbapenem Resistant Enterobacteriaceae)

- 2015 CDC definition: resistant to imipenem, meropenem, doripenem, or ertapenem OR documentation that the isolate possess a carbapenemase (carbapenemase producing (CP-CRE))

- Non-Carbapenemase CRE caused by:
  - ESBL production
  - Overproduction of AmpC enzyme
  - Lose outer membrane porin expression (OMP)

- In the US carbapenem resistance is typically a combination of several mechanisms (ESBL + porin loss)
  - These CRE do not constitute a carbapenemase-producing Enterobacteriaceae (CPE)

Satlin MJ, et al. Clin Infect Dis. 2014 May;58(9):1274-83.
[Image] https://weheartit.com/entry/272426040
FAQs about Choosing and Implementing a CRE Definition [Internet] Centers for Disease Control and Prevention [updated 2 Jun 2015]

Mechanisms of Carbapenem Resistance

Table 1. Prominent Mechanisms of Carbapenem Resistance Among Enterobacteriaceae

Carbapenemases	Ambler Molecular Class	Requirement for Enzymatic Activity	Gene Location	Geographic Distribution[a] [6, 11–14]
KPC	A	Serine	Plasmid	US, Colombia, Brazil, Argentina, Greece, Italy, Malta, Israel, China
NDM	B	Zinc	Plasmid	India, Pakistan, Bangladesh, United Kingdom
VIM	B	Zinc	Plasmid	Greece
IMP	B	Zinc	Plasmid	Japan, Taiwan
OXA-48-types	D	Serine	Plasmid	Turkey, Morocco, Algeria, Tunisia, India
Other mechanisms				
ESBL or AmpC-type β-lactamase + OMP mutation	A/C	Serine	Plasmid or chromosomal	Worldwide[b]

Abbreviations: ESBL, extended-spectrum β-lactamase; IMP, "active on imipenem"; KPC, *Klebsiella pneumoniae* carbapenemase; NDM, New Delhi metallo-β-lactamase; OMP, outer membrane porin; VIM, Verona integron–encoded metallo-β-lactamase.

Satlin MJ, et al. Clin Infect Dis. 2014 May;58(9):1274-83.

Organism Threat Category

Organism/ Resistance	CDC Category (2013)	WHO Category (2017)	Infections/year	Deaths/year
CRE	Urgent	Critical	9,000	600
ESBL	Serious	Critical	26,000	1,700
Acinetobacter baumannii	Serious	Critical	7,300	500
Pseudomonas aeruginosa	Serious	Critical	6,700	440

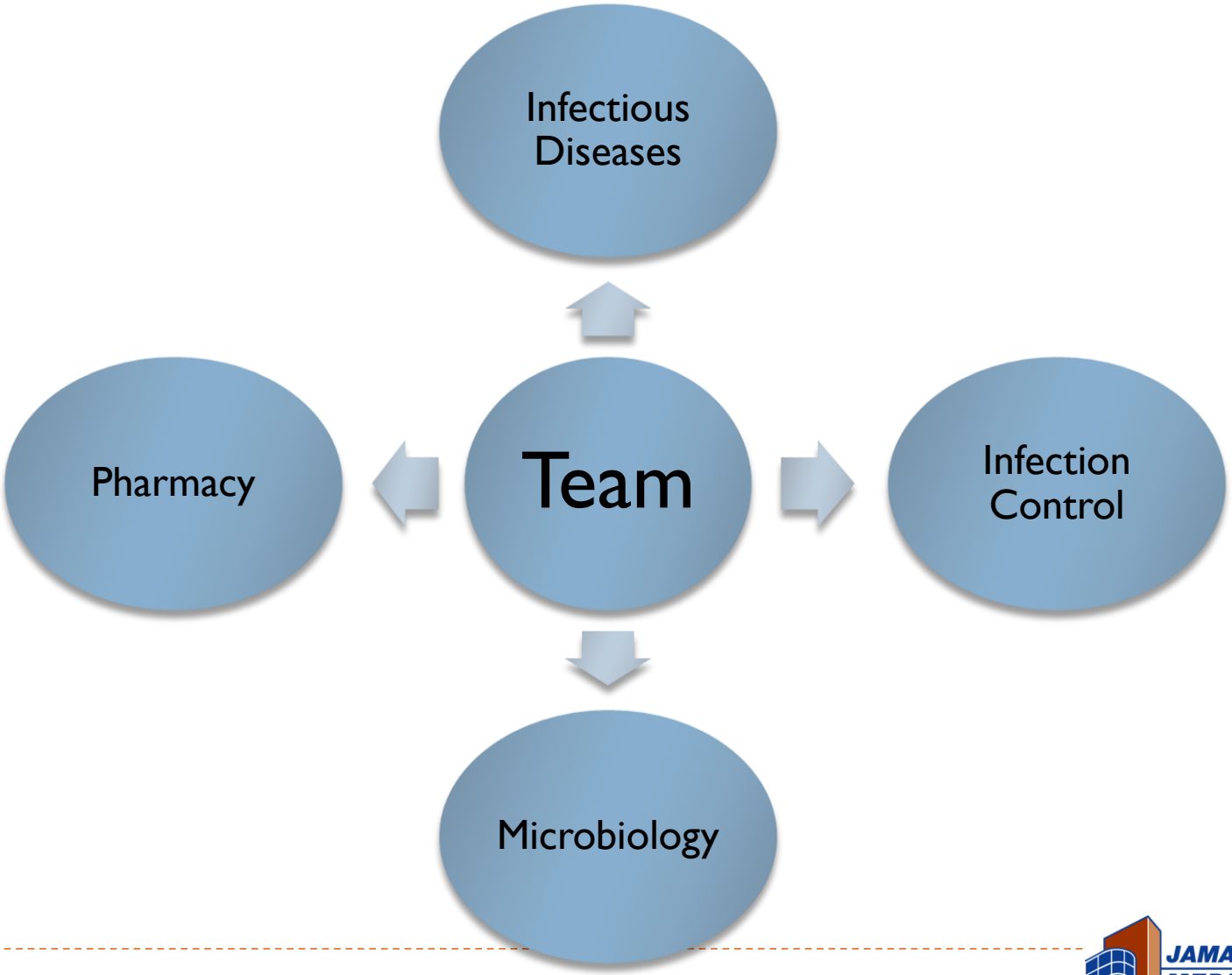
Biggest Threats and Data [Internet]. Centers for Disease Control and Prevention. [Updated 2018 Nov 26]
WHO publishes list of bacteria for which new antibiotics are urgently needed [Internet] World Health Organization [2017 Feb 27]

Ambler Class

Ambler Class	Beta-lactamase Type	Activity	Enzyme Examples	Common Bacteria
A	Penicillinases	Hydrolizes penicillins and cephalosporins	CTX-M, KPC, SHV, TEM	*E. coli, Klebsiella, Enterobacteriaceae, Pseudomonas*
B	Metallo-beta-lactamases	Uses zinc for hydrolysis of beta-lactam ring	IMP, NDM, VIM	*Pseudomonas, Acinetobacter*
C	Cephalosporinases	Hydrolyzes broad and extended-spectrum cephalosporins	AmpC	*Enterobacter, Citrobacter, Proteus, Serratia, Pseudomonas*
D	Oxacillinases	Beta-lactamase production and reduced permeability or increased efflux	OXA	*Acinetobacter, E. coli, Pseudomonas*

A Comparison of Avycaz, Vabomere, and Zerbaxa [Internet] IDStewardship [updated 24 July 2019] [Image] https://weheartit.com/entry/272426040

Who Should be on the Team?



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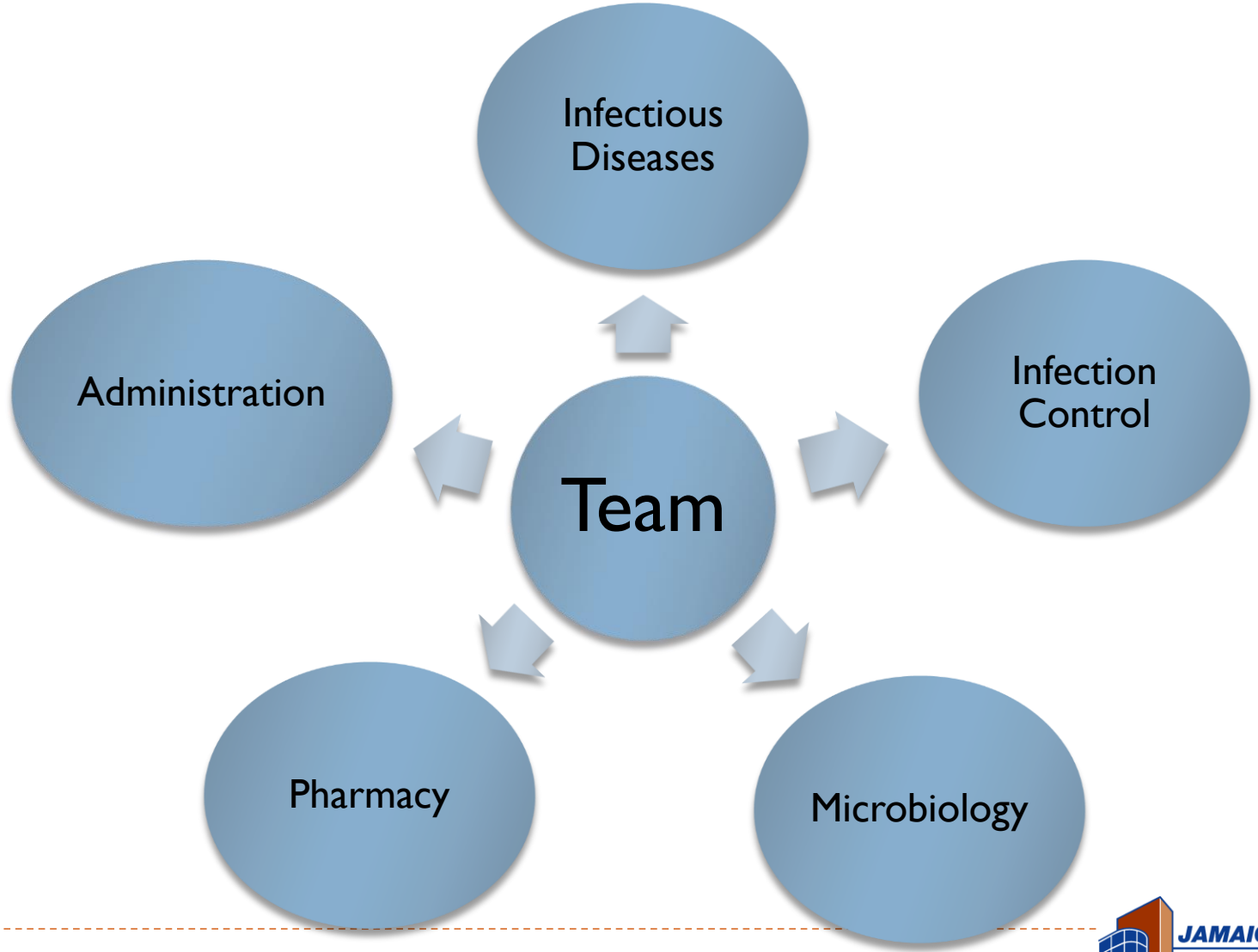
Who Should be on the Team?



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CLSI – Zone Diameter and MIC Breakpoints for *Enterobacteriaceae*

Test/Report Group	Antimicrobial Agent	Disk Content	Interpretive Categories and Zone Diameter Breakpoints, nearest whole mm				Interpretive Categories and MIC Breakpoints, µg/mL				Comments
			S	SDD	I	R	S	SDD	I	R	
B	Doripenem	10 µg	≥ 23	-	20-22	≤ 19	≤ 1	-	2	≥ 4	**(32)** Breakpoints are based on a dosage regimen of 500 mg **administered** every 8 h.
B	Ertapenem	10 µg	≥ 22	-	19-21	≤ 18	≤ 0.5	-	1	≥ 2	**(33)** Breakpoints are based on a dosage regimen of 1 g **administered** every 24 h.
B	Imipenem	10 µg	≥ 23	-	20-22	≤ 19	≤ 1	-	2	≥ 4	**(34)** Breakpoints are based on a dosage regimen of 500 mg **administered** every 6 h or 1 g every 8 h.
B	Meropenem	10 µg	≥ 23	-	20-22	≤ 19	≤ 1	-	2	≥ 4	**(35)** Breakpoints are based on a dosage regimen of 1 g **administered** every 8 h.

Culture & Susceptibility vs. Molecular Testing

Antibiotic	Organism
	Enterobacter cloacae - cre
AMIKACIN	<=8 S
AMPICILLIN	>16 R
AMPICILLIN + SULBACTAM	>16/8 R
AZTREONAM	>16 R
CEFAZOLIN	>16 R
CEFEPIME	>16 R
CEFOTAXIME	>32 R
CEFTAZIDIME	>16 R
CEFUROXIME	>16 R
CIPROFLOXACIN	>2 R
ERTAPENEM	>1 R
GENTAMICIN	>8 R
IMIPENEM	>8 R
LEVOFLOXACIN	>4 R
MEROPENEM	>8 R
PIPERACILLIN + TAZOBACTAM	>64 R
POLYMYXIN B	0.38
TIGECYCLINE	<=2 S
TRIMETH/SULFA	>2/38 R

NEW**	MALDI-TOF Mass Spectrometry	Enterobacter cloacae
NEW**		Enterobacter cloacae complex

Disk Diffusion AST

	Antibiotic Name	Interpretation
NEW**	Aztreonam	Susceptible
NEW**	Ceftriaxone	Resistant
NEW**	Cefepime	Resistant
NEW**	Ceftazidime	Resistant
NEW**	Doripenem	Resistant
NEW**	Ertapenem	Resistant
NEW**	Imipenem	Resistant
NEW**	Meropenem	Resistant
NEW*	Modified Carbapenem Inactivation Method	Carbapenemase detected

Rationale for the development of Aztreonam/avibactam

	Test Name	Result
	PCR Xpert Carba-I	
NEW**	blaIMP	Not Detected
NEW**	blaKPC	Not Detected
NEW**	blaNDM	Detected
NEW**	blaOXA-48-like	Not Detected
NEW**	blaVIM	Not Detected

Culture & Susceptibility vs. Molecular Testing

Culture & Susceptibility

Antibiotic	Organism
	Enterobacter cloacae - cre
AMIKACIN	<=8 S
AMPICILLIN	>16 R
AMPICILLIN + SULBACTAM	>16/8 R
AZTREONAM	<=4 S
CEFAZOLIN	>16 R
CEFEPIME	>16 R
CEFOTAXIME	>32 R
CEFTAZIDIME	>16 R
CEFUROXIME	>16 R
CIPROFLOXACIN	>2 R
ERTAPENEM	>1 R
GENTAMICIN	<=4 S
IMIPENEM	>8 R
MEROPENEM	>8 R
PIPERACILLIN + TAZOBACTAM	>64 R
TIGECYCLINE	<=2 S
TRIMETH/SULFA	>2/38 R

MALDI-TOF Mass Spectrometry Enterobacter cloacae complex

Disk Diffusion AST

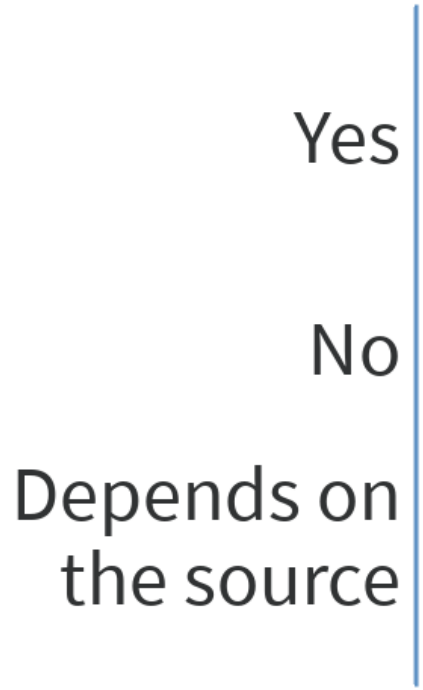
Antibiotic Name	Zone Diameter (mm)	Interpretation
Aztreonam	6	Resistant
Cefepime	26	Susceptible
Ceftazidime	6	Resistant
[illegible]	6	Resistant
Doripenem	24	Susceptible
Ertapenem	19	Intermediate
Imipenem	23	Susceptible
Meropenem	23	Susceptible

Modified Carbapenem Inactivation Method Negative — Carbapenemase not detected

CR Xpert Carba-R

blaIMP	Not Detected
blaKPC	Not Detected
blaNDM	Not Detected
blaOXA-48-like	Not Detected
blaVIM	Not Detected

If you had an ESBL-*E. coli* isolate reported as sensitive to piperacillin/tazobactam, would you recommend it?



MERINO Trial

MERINO Trial

Objective

- To determine whether definitive therapy with piperacillin-tazobactam is noninferior to meropenem in patients with bloodstream infection caused by ceftriaxone-nonsusceptible *E. coli* or *K. pneumoniae*
  - AKA ESBLs

Design

- International
  - 26 sites in 9 countries
- Multicenter
- Open-label
- Parallel group
- Randomized clinical trial

Inclusion Criteria

- Adult patients
  - Aged ≥18 years or ≥21 years in Singapore
- ≥1 positive blood culture with *E. coli* or *Klebsiella* spp testing nonsusceptible to ceftriaxone

Exclusion Criteria

- Allergy to trial drug/ antibiotic class
- No expectation of survival >96 hours
- Treatment without curative intent
- Polymicrobial bacteremia
  - Likely skin contaminants excepted
- Previous enrollment in the trial
- Pregnancy or breastfeeding
- Requirement for concomitant antibiotics with activity against gram-negative bacilli

 Harris PNA, et al. JAMA. 2018 Sep 11;320(10):984-994.

MERINO Trial

Intervention

- Meropenem 1 g IV q8hr, infused over 30 minutes
- Piperacillin-tazobactam 4.5 g IV q6h, infused over 30 minutes

Outcomes

- Primary: all-cause mortality at 30 days after randomization
- Secondary:
  - Time to clinical and microbiologic resolution of infection (days)
  - Clinical and microbiologic success at day 4 after randomization
  - Microbiologic resolution of infection (sterility of blood cultures) on or before day 4 after randomization
  - Relapsed bloodstream infection
  - Secondary infection with meropenem- or pip/tazo-resistant organism or *Clostridium difficile* infection
- Noninferiority margin of 5%

Harris PNA, et al. JAMA. 2018 Sep 11;320(10):984-994.

MERINO Trial – Demographics

Characteristic	Pip/Tazo (n = 188)	Meropenem (n = 191)
E. coli	162 (86.2%)	166 (86.9%)
Less severe infection	159 (84.6%)	162 (84.8%)
More severe infection	3 (1.6%)	3 (1.6%)
K. pneumoniae	26 (13.8%)	25 (13.1%)
Less severe infection	23 (12.2%)	25 (13.1%)
More severe infection	3 (1.6%)	1 (0.5%)
Age, median (IQE), y	70 (55-78)	68 (59-78)
APACHE II Score, mean (SD)	17.9 (6.1)	21.0 (6.9)
Central venous catheter	35 (18.6)	20 (10.5)
Appropriate empirical antibiotic	126 (67%)	127 (66.5%)
Time to randomization median (IQR), h	53.6 (44.9-65.6)	52.5 (46.0-63.7)
Time to appropriate antibiotics (IQR), h	5.5 (0.4-31.5)	9.6 (0.5-32.1)

MERINO Trial – Demographics

Source	Pip/Tazo (n = 188)	Meropenem (n = 191)
Urinary Tract	103 (54.8%)	128 (67%)
Intra-abdominal tract	34 (18.1%)	28 (14.7%)
Vascular catheter-related	3 (1.6%)	3 (1.6%)
Surgical site infection	8 (4.3%)	4 (2.1%)
Pneumonia	9 (4.8%)	3 (1.6%)
Mucositis/neutropenia	12 (6.4%)	7 (3.7%)
SSTI	4 (2.1%)	1 (0.5%)
Other	2 (1.1%)	1 (0.5%)
Unknown	12 (6.4%)	16 (8.4%)

Harris PNA, et al. JAMA. 2018 Sep 11;320(10):984-994.

Primary Outcome

12.3% of all-cause mortality at 30 days

Piperacillin-tazobactam	Meropenem
• 23 of 187 patients	• 7 of 191 patients

3.7% of all-cause mortality at 30 days

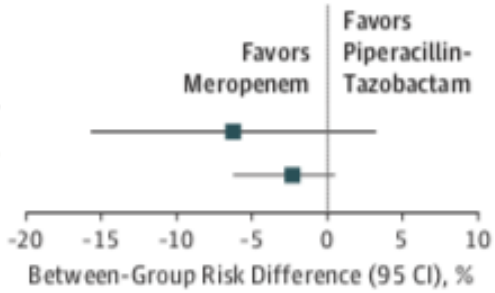
Risk difference, 8.6% [1-sided 97.5% CI, −∞ to 14.5%]
P = .90 for noninferiority
Data and safety monitoring board (DSMB) terminated study

Harris PNA, et al. JAMA. 2018 Sep 11;320(10):984-994.
[Image] https://weheartit.com/entry/272426040

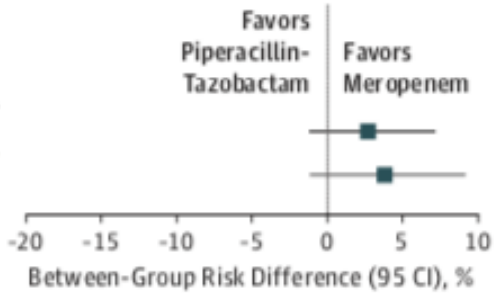
Secondary Outcomes

Figure 2. Secondary Outcomes

Measure of Success	Patients Meeting End Point, No./Total No. (%)		Between-Group Difference (95% CI)
	Piperacillin-Tazobactam	Meropenem	
Clinical and microbiological success at day 4[a]	121/177 (68.4)	138/185 (74.6)	-6.2 (-15.5 to 3.1)
Microbiological success at day 4	169/174 (97.1)	184/185 (99.5)	-2.3 (-6.1 to 0.4)



Measure of Failure	Patients Meeting End Point, No./Total No. (%)		Between-Group Difference (95% CI)
	Piperacillin-Tazobactam	Meropenem	
Microbiological relapse	9/187 (4.8)	4/191 (2.1)	2.7 (-1.1 to 7.1)
Secondary infection with multiresistant organism or *Clostridium difficile*	15/187 (8.0)[b]	8/191 (4.2)[c]	3.8 (-1.1 to 9.1)



[a] Clinical and microbiological success defined as survival, negative blood cultures, temperature of 38°C or less, and peripheral white blood cell count of less than or equal to 12 000/μL (to convert to $\times 10^9$/L, multiply by 0.001).

[b] Twelve patients with meropenem- or piperacillin-tazobactam–resistant organism and 3 with *Clostridium difficile* infection.

[c] Six patients with meropenem- or piperacillin-tazobactam–resistant organism and 2 with *Clostridium difficile* infection.

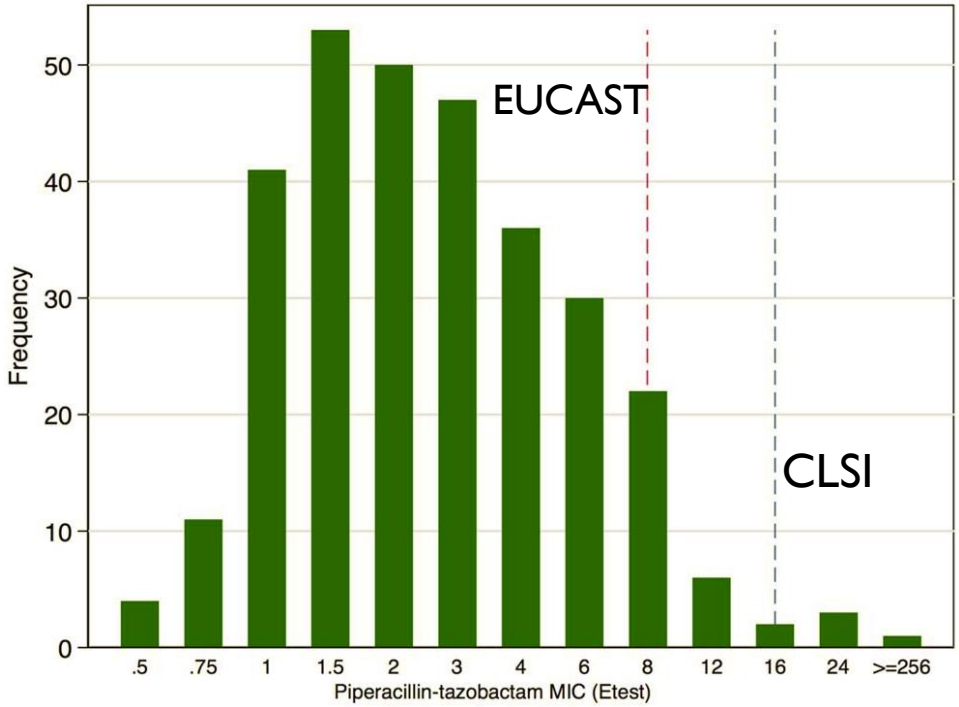
 Harris PNA, et al. JAMA. 2018 Sep 11;320(10):984-994.

Susceptibility

- Local: 100% of isolates were sensitive to both pip/tazo and meropenem

- E-Test Confirmation
  - EUCAST: 12 (3.9%) nonsusceptible
  - CLSI: 4 (1.3%) nonsusceptible

European Committee for Antimicrobial Susceptibility Testing (EUCAST)
Clinical and Laboratory Standards Institute (CLSI)



Harris PNA, et al. JAMA. 2018 Sep 11;320(10):984-994.

Discussion and Conclusion

- Limitations
  - Empiric therapy
    - Beta-lactam/beta-lactamase inhibitor
      - 39 (20.7) pip/tazo and 50 (26.2%) in meropenem group
    - Carbapenem
      - 26 (13.8%) vs 29 (15.2%), respectively
  - Carbapenem step down 38 (20.2%) in pip/tazo and 39 (20.4%) in meropenem group
  - Only 2 patients were enrolled from North America (Canada)
- Conclusion
  - Definitive treatment with piperacillin-tazobactam compared with meropenem did not result in noninferior 30-day mortality
    - These findings do not support use of piperacillin-tazobactam in this setting

Harris PNA, et al. JAMA. 2018 Sep 11;320(10):984-994.

MDRO Risk Score

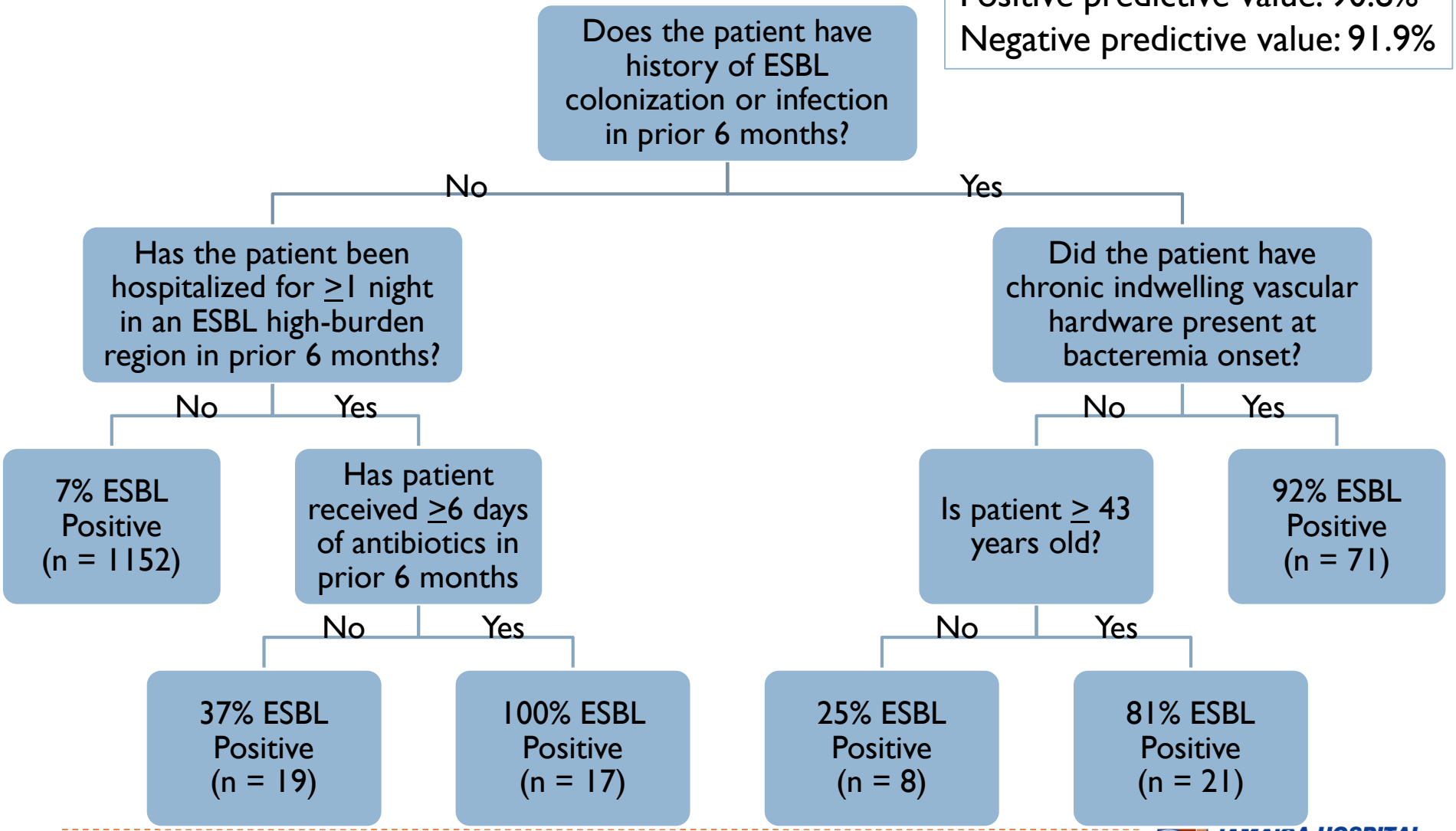
- Recent hospitalization for at least 48 hours during the preceding 90 days – 4 points
- Admission from a long-term care (LTC) facility – 3 points
- Chronic HD – 2 points
- Admitted to the ICU within 24 hours of evaluation in the ED – 1 point

- Maximum score of 10
  - Score >4 – high risk for MDRO

Shorr AF. Clin Infect Dis. 2012 Jan 15;54(2):193-8.

Empiric Therapy – ESBLs

Sensitivity: 51.0%
Specificity: 99.1%
κ value: 0.61
Positive predictive value: 90.8%
Negative predictive value: 91.9%



Goodman KE, et al. Clin Infect Dis. 2016 Oct 1;63(7):896-903.

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stration

[Image] http://www.keepcalmandposters.com/poster/5561852_keep_calm_and_be_aggressive

Don't Forget…

- Asymptomatic bacteriuria (ASB)
  - Patients without indwelling catheters is ≥10^5 colony-forming units (CFU)/mL (≥10^8 CFU/L) in a voided urine specimen **without signs or symptoms** attributable to UTI

Screening and treatment of ASB is **not** recommended for:	Screening and treatment of ASB is recommended for:
• Infants and children • Healthy premenopausal, nonpregnant women or healthy postmenopausal women • Functionally impaired older women or men residing in the community • Older residents of Long-term Care Facilities • Indwelling catheters • Spinal cord injury • Renal transplant recipients (>1 month post-op) • Non-renal solid organ transplant recipients	• Pregnant women • Endoscopic urologic procedures

- Treatment of ASB found to contribute to inappropriate antimicrobial use
  - Emergence of antimicrobial resistance

33 Nicolle LE, et al. Clin Infect Dis. 2019 May 2;68(10):1611-1615.
[Image] https://weheartit.com/entry/272426040

Carbapenems

- Agents
  - Ertapenem, meropenem, doripenem, imipenem/cilastatin
- MOA: inhibits bacterial cell wall synthesis
- Spectrum
  - Extended Spectrum Beta-Lactamase (ESBL)
  - *Pseudomonas*, except ertapenem
  - *Acinetobacter*, except ertapenem

The Sanford guide to antimicrobial therapy 2019 / editors, David N. Gilbert, M.D.,

Ceftazidime/avibactam (Avycaz®)

- 3rd generation cephalosporin/non–beta-lactam beta-lactamase inhibitor
  - Avibactam has activity against Ambler class A and C carbapenemases TEM, SHV, CTX-M, KPCs, AmpC, and certain OXA
  - Limited activity against class D OXA ß-lactamases
  - No activity against metallo-ß-lactamases
- MOA: inhibition of cell wall biosynthesis
  - Bactericidal
- Spectrum
  - Carbapenem-resistant Enterobacteriaceae (CRE)
  - Extended Spectrum Beta-Lactamase (ESBL)
  - MDR-*Pseudomonas*
  - Does NOT cover MDR-*Acinetobacter*
- Dose: ceftazidime 2 g/avibactam 0.5 g per vial
- Infused over 2 hours

35 [Image] https://www.avycaz.com
Avycaz® (ceftazidime/avibactam) [package insert]. Irvine, CA: Allergan USA, Inc.; 2018 Feb

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Ceftolozane/tazobactam (Zerbaxa®) AKA "tol/taz"

- "Novel" cephalosporin/beta-lactamase inhibitor
- MOA: Inhibition of cell wall biosynthesis
- Tazobactam: irreversible inhibitor of some beta-lactamases (certain penicillinases and cephalosporinases), binds covalently to some chromosomal and plasmid-mediated bacterial beta-lactamases
  - Inhibitor of PBPs of *P. aeruginosa* (PBP1b, PBP1c, and PBP3) and *E. coli* (e.g., PBP3)
  - Bactericidal
- Spectrum
  - Extended Spectrum Beta-Lactamase (ESBL)
  - MDR-*Pseudomonas*
  - Does NOT cover MDR-*Acinetobacter*
- Dose: ceftolozane 1 g/tazobactam 0.5 g per vial

36 [Image] https://www.empr.com/drug/zerbaxa/

Zerbaxa® (ceftolozane/tazobactam) [package insert]. Whitehouse Station, NJ: Merck & Co, Inc.; 2018 Oct

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ASPECT-NP

Design

- Multicenter
- Randomized
- Controlled
- Double-blind
- Phase 3
- Non-inferiority trial

Intervention

- Treatment of patients with ventilated nosocomial pneumonia (VNP)
- Ceftolozane/tazo 3g IV q8hr
- Meropenem 1g IV q8hr

Inclusion Criteria

- Intubated and mechanically ventilated adults (≥18 years of age)
- Diagnosed with VAP or vHABP

Exclusion

- Gram-positive on Gram stain
- Gram-negative pathogen resistant to study drug
- >24 hours of gram-negative therapy for nosocomial pneumonia within 72 hours of study drug
- Immunosuppression or neutropenia
- Hemodialysis

Kollef, M et al. ASPECT-NP: a randomized, double-blind, phase III trial comparing efficacy and safety of ceftolozane/tazobactam versus meropenem in patients with ventilated nosocomial pneumonia (VNP). ECCMID. Paper poster #P1917

ASPECT-NP – Results

Endpoint	C/T n/N (%)	Meropenem n/N (%)	% Treatment Difference (95% CI)[a]
28-day all-cause mortality (ITT)	87/362 (24.0%)	92/364 (25.3%)	1.1 (-5.13, 7.39)[b]
VAP	63/263 (24.0%)	52/256 (20.3%)	-3.6 (-10.74, 3.52)[c]
vHAP	24/99 (24.2%)	40/108 (37.0%)	12.8 (0.18, 24.75)[c]
Clinical cure at TOC (ITT)	197/362 (54.4%)	194/364 (53.3%)	1.1 (-6.17, 8.29)[b]
VAP	147/263 (55.9%)	146/256 (57.0%)	-1.1 (-9.59, 7.35)[c]
vHAP	50/99 (50.5%)	48/108 (44.4%)	6.1 (-7.44, 19.27)[c]
Clinical cure at TOC (CE)	139/218 (63.8%)	143/221 (64.7%)	-1.3 (-10.21, 7.67)[b]
VAP	105/159 (66.0%)	111/172 (64.5%)	1.5 (-8.72, 11.62)[c]
vHAP	34/59 (57.6%)	32/49 (65.3%)	-7.7 (-24.99, 10.60)[c]

- Endpoints
  - Primary: 28-day all-cause mortality (10% non-inferiority margin)
  - Secondary: clinical response at test-of-cure (7-14 days after end-of-therapy) (12.5% non-inferiority margin)
- Legend
  - C/T: Ceftolozane/tazobactam
  - TOC: test of cure
  - VABP: ventilator-associated bacterial pneumonia
  - vHABP: ventilated hospital-associated bacterial pneumonia

Kollef, M et al. ASPECT-NP: a randomized, double-blind, phase III trial comparing efficacy and safety of ceftolozane/tazobactam versus meropenem in patients with ventilated nosocomial pneumonia (VNP). ECCMID. Paper poster #P1917

ASPECT-NP – Microbiology

Pathogen	Ceftolozane/tazo (n = 264)	Meropenem (n = 247)	% Treatment Difference (95% CI)
Gram-negative pathogen	259 (98.1%)	240 (97.2%)	
Pseudomonas aeruginosa	63 (23.9%)	65 (26.3%)	
mITT Eradication	47/63 (74.6%)	41/65 (63.1%)	11.5 (-4.51-26.72)
ME Eradication	23/29 (79.3%)	21/38 (55.3%)	**24.0 (1.11-43.01)**
MDR	24 (9.1%)	11 (4.5%)	
XDR	10 (3.8%)	5 (2.0%)	
ESBL + Enterobacteriaceae	84 (31.8%)	73 (29.6%)	
mITT Eradication	56/84 (66.7%)	52/73 (71.2%)	-4.6 (-18.56 -9.93)
ME Eradication	33/45 (66.7%)	27/39 (69.2%)	-2.6 (-21.59-17.14)

Microbiological intention to treat: (mITT): received ≥1 dose of study treatment and ≥1eligible culture

Microbiologically evaluable (ME): MITT who adhered to protocol, had evaluable clinical response at test-of-cure visit (7-14 days after end-of-therapy)

Kollef, M et al. ASPECT-NP: a randomized, double-blind, phase III trial comparing efficacy and safety of ceftolozane/tazobactam versus meropenem in patients with ventilated nosocomial pneumonia (VNP). ECCMID. Paper poster #P1917, Mini-oral ePoster #O0302

ASPECT-NP

- Conclusion
  - Ceftolozane/tazobactam 3-gram dose regimen is non-inferior to meropenem for the treatment of nosocomial pneumonia
  - Similar rates of microbiologic eradication for nosocomial pneumonia caused by ESBLs
  - Higher rates of microbiologic eradication for nosocomial pneumonia caused by *Pseudomonas* in ME group

Kollef, M et al. ASPECT-NP: a randomized, double-blind, phase III trial comparing efficacy and safety of ceftolozane/tazobactam versus meropenem in patients with ventilated nosocomial pneumonia (VNP). ECCMID. Paper poster #P1917. Mini-oral ePoster #O0302

Meropenem/vaborbactam (Vabomere™)

- Carbapenem/beta-lactamase inhibitor
- MOA: inhibition of cell wall biosynthesis
  - Vaborbactam: non-suicidal beta-lactamase inhibitor that protects meropenem from degradation by certain serine beta-lactamases such as KPC
    - Does not have any antibacterial activity
  - Bactericidal
- Spectrum
  - Carbapenem-resistant Enterobacteriaceae (CRE)
  - Extended Spectrum Beta-Lactamase (ESBL)
  - MDR-Pseudomonas
  - Does NOT cover MDR-*Acinetobacter*
- Infused over 3 hours
- Dose: meropenem 1 g/vaborbactam 1 g per vial

[image] https://www.drugtopics.com/sites/default/files/Vabomere.png
Vabomere™ (meropenem/vaborbactam) [package insert]. Lincolnshires, IL: Melinta Therapeutics, Inc.; 2018 April

Imipenem/cilastatin/relebactam (Recarbrio™)

- Carbapenem/renal dehydropeptidase inhibitor/diazabicyclooctane beta lactamase inhibitor
- MOA: inhibition of cell wall biosynthesis by binding to PBP 2 and PBP 1B in Enterobacteriaceae and *Pseudomonas aeruginosa*
  - Relebactam: protects imipenem from degradation by certain serine beta lactamases such as SHV, TEM, CTX-M, *Enterobacter cloacae* P99 (P99), *Pseudomonas*-derived cephalosporinase (PDC), and KPC
    - Does not have any antibacterial activity
- Spectrum
  - Carbapenem-resistant Enterobacteriaceae (CRE)
  - Extended Spectrum Beta-Lactamase (ESBL)
  - MDR-*Pseudomonas*
  - Does NOT cover MDR-*Acinetobacter*
- Dose: imipenem 0.5 g/cilastatin 0.5 g/relebactam 0.25 g per vial

Recarbrio™ (imipenem/cilastatin/relebactam) [package insert]. Whitehouse Station, NJ: Merck & Co., Inc.; 2019 July

Polymyxins

- Polymyxin B vs colistin (AKA Polymyxin E, Colistimethate)
- MOA: binds to phospholipids, alters permeability, and damages the bacterial cytoplasmic membrane permitting leakage of intracellular constituents
- Recommend to use in combination with another agent
  - Increased mortality when used as monotherapy

- Spectrum
  - Gram-negative bacilli (generally)
    - *Acinetobacter baumannii*
    - *Pseudomonas aeruginosa*
    - *Klebsiella pneumoniae*
    - *Klebsiella aerogenes*
    - *Escherichia coli*
    - Carbapenem-resistant Enterobacteriaceae (CRE)
    - Extended Spectrum Beta-Lactamase (ESBL)

- Intrinsic resistance
  - *Providencia spp.*
  - *Proteus spp.*
  - *Serratia spp.*
  - *Morganella spp.*
  - *Burkholderia spp.*

Tsuji BT. Pharmacotherapy. 2019 Jan;39(1):10-39.

Polymyxins

Polymyxin B

- Use for systemic invasive infections
- 4% renally eliminated
  - No renal dose adjustments
  - Less nephrotoxic than colistin
- Loading dose: 2.0–2.5 mg/kg (TBW)

Colistin

- Use for treatment of UTI
- Prodrug
- Dosed in colistin base activity (CBA)
- Loading dose: 300 mg of CBA
  - AUC goal of 2 mg/L
  - https://clincalc.com/colistin/

44 Tsuji BT. Pharmacotherapy. 2019 Jan;39(1):10-39.
[Image] https://weheartit.com/entry/272426040

RESTORE-IMI 1

Objective

- To evaluate imipenem/relebactam for the treatment of imipenem-nonsusceptible infections

Design

- Randomized (2:1), controlled, double-blind, international, phase 3 trial of hospitalized patients with hospital-acquired/ventilator associated pneumonia (HAP/VAP), complicated intraabdominal infection (cIAIs), or complicated urinary tract infection (cUTIs), caused by imipenem-nonsusceptible pathogens

Inclusion Criteria

- Hospitalized, adult patients (aged ≥18 years)
- Requiring treatment for HAP/VAP, cIAIs, or cUTIs caused by imipenem-nonsusceptible pathogens

Exclusion Criteria

- APACHE II score >30
- Renal dysfunction: CrCL <15 mL/min, requiring hemodialysis/peritoneal dialysis
- Concomitant systemic/inhaled agents active against Enterobacteriaceae, *Pseudomonas* spp., and gram-negative anaerobic bacilli
- Prior colistin-based therapy
- Pulmonary obstructions (eg, lung cancer) in HAP/VAP; and complete obstruction of any portion of the urinary tract in cUTI

 Motsch J, et al. Clin Infect Dis. 2019 Aug 10. pii: ciz530.

RESTORE-IMI 1

Intervention

- Imipenem/relebactam 500 mg/250 mg every 6 hours plus placebo (IMI/REL)
- Imipenem/relebactam plus colistimethate sodium IV (IMI/COL)
  - Colistimethate sodium loading dose: 300 mg colistin base activity (CBA), followed by maintenance doses up to 150 mg CBA q12hr

Outcomes

- Primary: overall response in the microbiologic modified intent-to-treat (mMITT) population
  - HAP/VAP: 28-day all-cause mortality
  - cIAI: day 28 clinical response
  - cUTI: composite clinical and microbiologic response at early follow-up visit
- Secondary
  - Day 28 clinical response (mMITT population)
  - 28-day all-cause mortality mMITT population)
  - Treatment-emergent nephrotoxicity

Motsch J, et al. Clin Infect Dis. 2019 Aug 10. pii: ciz530.

RESTORE-IMI 1 – Demographics

Characteristic	IMI/REL (n = 21)	IMI/COL (n = 10)
Age ≥ 65 years	6 (28.6%)	5 (50%)
APACHE II Score >15	7 (33%)	2 (20%)
Primary diagnosis		
HAP	1 (4.8%)	1 (10%)
VAP	7 (33.3%)	2 (20%)
cUTI (urinary tract abnormalities)	5 (23.8%)	3 (30%)
cUTI (pyelonephritis)	6 (28.6%)	2 (20%)
cIAI	2 (9.5%)	2 (20%)
Bacteremia		
Yes	1 (4.8%)	1 (10%)
No	5 (23.8%)	2 (20%)
Unknown	15 (71.4%)	7 (70%)

47 Motsch J, et al. Clin Infect Dis. 2019 Aug 10. pii: ciz530.

RESTORE-IMI 1 – Microbiology

Pathogen	IMI/REL (n = 21)	IMI/COL (n = 10)
Citrobacter freundii	1 (4.8%)	0 (0%)
Enterobacter cloacae	1 (4.8%)	0 (0%)
Klebsiella oxytoca	0 (0%)	1 (10%)
Klebsiella pneumoniae	3 (14.3%)	1 (10%)
Pseudomonas aeruginosa	16 (76.2%)	8 (80%)

β-lactamases	IMI/REL (n = 21)	IMI/COL (n = 10)
Class A: SHV-1, SHV-11	2 (9.5%)	1 (10%)
Class A: TEM	7 (33.3%)	3 (30%)
Class A: CTX-M	7 (33.3%)	4 (40%)
Class A: SHV-28	1 (4.8%)	0 (0%)
Class A: KPC	4 (19%)	1 (10%)
Class C: PDC*	16 (76.2%)	8 (80%)
Class D: OXA-48	0 (0%)	1 (10%)

Chromosomal AmpC - *Pseudomonas*-derived cephalosporinase (PDC)

 Motsch J, et al. Clin Infect Dis. 2019 Aug 10. pii: ciz530.

RESTORE-IMI 1 – Results

	IMI/REL (n = 21)		Colistin + IMI (n = 10)		Unadjusted Difference	Adjusted Difference[a]	
Endpoint	n	% (95% CI)[b]	n	% (95% CI)[a]	%	%	90% CI
Primary endpoint							
Favorable overall response[c]	15	71.4 (49.8, 86.4)	7	70.0 (39.2, 89.7)	1.4	–7.3	(–27.5, 21.4)
Hospital-acquired bacterial pneumonia/ ventilator-associated bacterial pneumonia	7/8	87.5 (50.8, 99.9)	2/3	66.7		20.8	
Complicated intraabdominal infection	0/2[d]	0.0	0/2[e]	0.0		0.0	
Complicated urinary tract infection	8/11	72.7 (42.9, 90.8)	5/5	100.0 (51.1, 100.0)		–27.3 (–52.8, 12.8)	
Secondary endpoints							
Favorable clinical response (day 28)	15[f]	71.4 (49.8, 86.4)	4[g]	40.0 (16.7, 68.8)	31.4	26.3	(1.3, 51.5)
28-day all-cause mortality	2	9.5 (1.4, 30.1)	3	30.0 (10.3, 60.8)	–20.5	–17.3	(–46.4, 6.7)
Treatment-emergent nephrotoxicity[h]	3/29	10.3 (2.8, 27.2)	9/16	56.3 (33.2, 76.9)		–45.9 (–69.1, –18.4)	

 Motsch J, et al. Clin Infect Dis. 2019 Aug 10. pii: ciz530.

Discussion and Conclusion

- Discussion
  - Similar efficacy between arms
  - Less nephrotoxicity in IMI/REL arm
  - IMI/REL-treated patients had higher clinical response rates and lower 28-day mortality
- Limitations
  - Small sample size
  - Colistin vs. Polymyxin B
- Conclusion
  - IMI/REL is a suitable treatment option for gram-negative infections, including those caused by carbapenem-nonsusceptible pathogens
  - IMI/REL may be preferable to colistin-based therapy for the treatment of these pathogens

Motsch J, et al. Clin Infect Dis. 2019 Aug 10. pii: ciz530.

Ambler Class vs. Combo Agents

Ambler Class	Beta-lactamase Type	Enzyme Examples	Common Bacteria	Ceftaz /avi	Cefto /tazo	Mero/ vabor	Imip/ rele
A	Penicillinases	CTX-M, KPC, SHV, TEM	*E. coli, Klebsiella, Enterobacteriaceae, Pseudomonas*	Yes	Partial	Yes	Yes
B	Metallo-beta-lactamases	IMP, NDM, VIM	*Pseudomonas, Acinetobacter*	No	No	No	No
C	Cephalo-sporinases	AmpC	*Enterobacter, Citrobacter, Proteus, Serratia, Pseudomonas*	Yes	Partial	Yes	Yes
D	Oxacillinases	OXA	*Acinetobacter, E. coli, Pseudomonas*	Yes	No	No	No

A Comparison of Avycaz, Vabomere, and Zerbaxa [Internet] IDStewardship [updated 24 July 2019] [Image] https://weheartit.com/entry/272426040
Recarbrio™ (imipenem/cilastatin/relebactam) [package insert]. Whitehouse Station, NJ: Merck & Co., Inc.; 2019 July

Aminoglycosides

- Gentamicin, tobramycin, amikacin
- MOA: interferes with bacterial protein synthesis by binding to 30S ribosomal subunit resulting in a defective bacterial cell membrane
- Concentration dependent (time independent) kinetics
  - Goal peak 8-10x MIC of organism
  - Recommend extended interval dosing (higher peaks)
- Should be used in combination with a second agent
  - Could be considered for monotherapy for UTIs
- Nephrotoxicity and ototoxicity
- Spectrum
  - Carbapenem-resistant Enterobacteriaceae (CRE)
  - Extended Spectrum Beta-Lactamase (ESBL)
  - MDR-*Pseudomonas*
  - *Acinetobacter* (amikacin only)

52 Gentamicin. Lexicomp Online, Lexi-Drugs, Hudson, Ohio: Wolters Kluwer Clinical Drug Information, Inc.; 2013; March 3, 2019.

Fosfomycin (Monurol®) – Remember Me?

- Phosphonic acid derivative
  - Produced by *Streptomyces* spp.
- MOA: inhibits bacterial wall synthesis by inactivating the enzyme pyruvyl transferase
  - Bactericidal
- Treatment of UTI only
  - Low oral bioavailability
- Activity against KPC and New Delhi metallo-ß-lactamases
- Spectrum
  - Carbapenem-resistant Enterobacteriaceae (CRE)
  - Extended Spectrum Beta-Lactamase (ESBL)
  - MDR-Pseudomonas
  - Does NOT cover Acinetobacter
- Pipeline – IV formulation

53 Monurol® (fosfomycin) [package insert]. Madison, NJ: Allergan USA, Inc.; 2018 April

Tigecycline (Tygacil®)

- Glycylcycline
- MOA: Inhibits protein synthesis by binding to the 30S ribosomal subunit
- Recommended in combination with other agents
- High dose: 100 mg IV q12hr
- Lipophilic
  - Extensive tissue distribution: gallbladder, lung, and colon
  - Avoid in bacteremia and UTIs

- BBW: an increase in all-cause mortality has been observed in a meta-analysis of phase 3 and 4 clinical trials in tigecycline-treated patients versus comparator

- Spectrum
  - Carbapenem-resistant Enterobacteriaceae (CRE)
  - Extended Spectrum Beta-Lactamase (ESBL)
  - *Acinetobacter*

Tigecycline. Lexicomp Online, Lexi-Drugs, Hudson, Ohio: Wolters Kluwer Clinical Drug Information, Inc.; 2013; March 3, 2019.

Sulbactam

- β-lactamase inhibitor
  - Inhibits Ambler class A enzymes
  - Binds to *A. baumannii* PBP1 and PBP3
    - Activity against *Acinetobacter*

- Only available in the US as ampicillin/sulbactam (Unasyn®)

- Recommended dose of sulbactam = 9 g/day
  - Ampicillin/sulbactam dose = 27 g/day
  - Consider ampicillin/sulbactam dosing of 3g IV q4hr
    - 6g of sulbactam/day

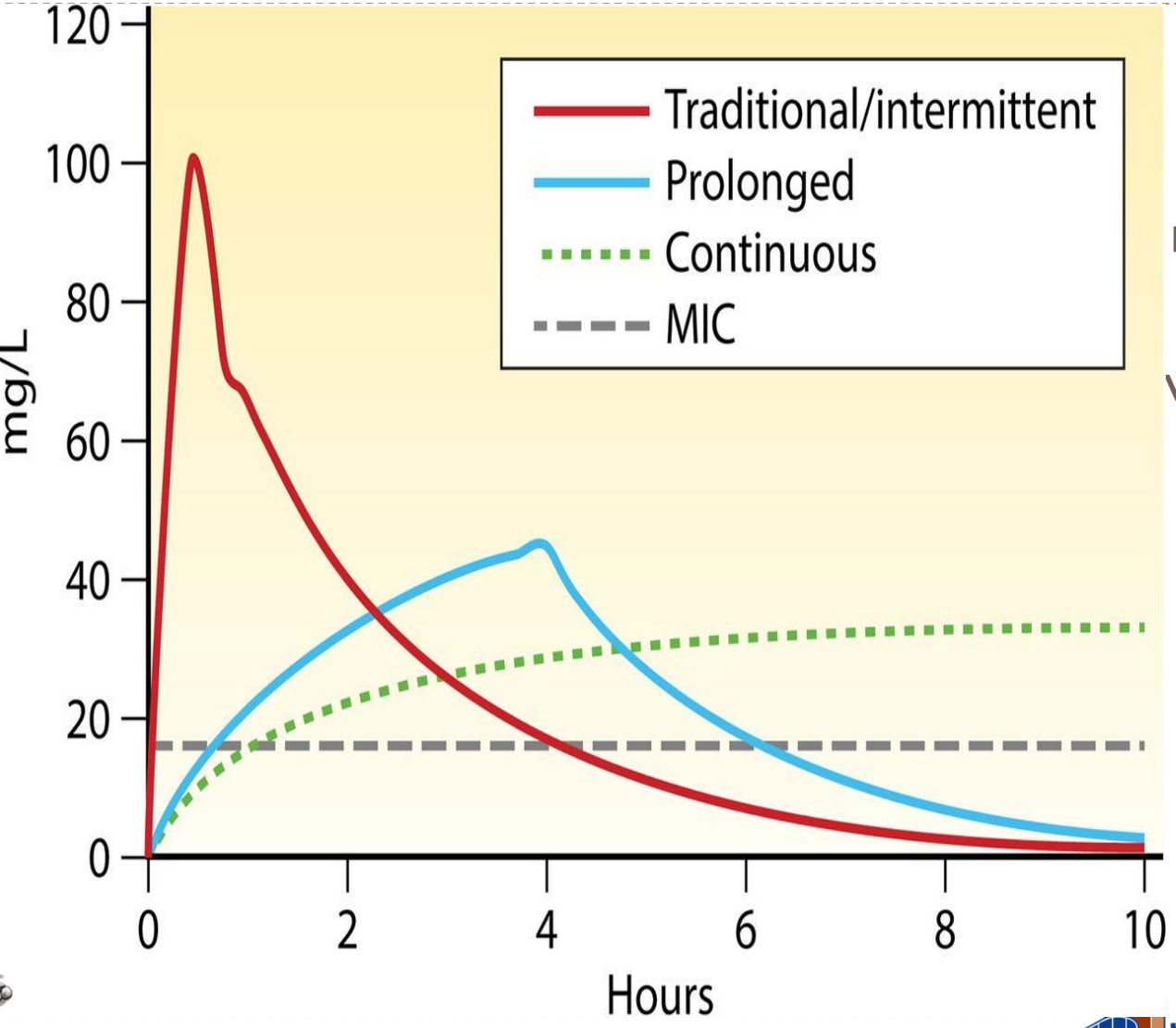
Penwell WF, et al. Antimicrob Agents Chemother. 2015 Mar;59(3):1680-9.
Fraimow H, et al. Crit Care Clin. 2013 Oct;29(4):895-921.
Ampicillin and Sulbactam. Lexicomp Online, Lexi-Drugs, Hudson, Ohio: Wolters Kluwer Clinical Drug Information, Inc.; 2013; March 7, 2019.

Administration:
Extended or Continuous Infusion Beta-Lactams

- Ratio
  - Tim
  - Tim
    max
  - Goa
    imp

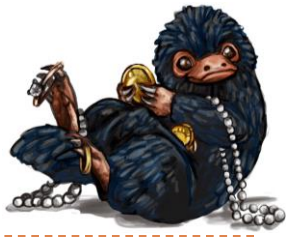
near-

vity and

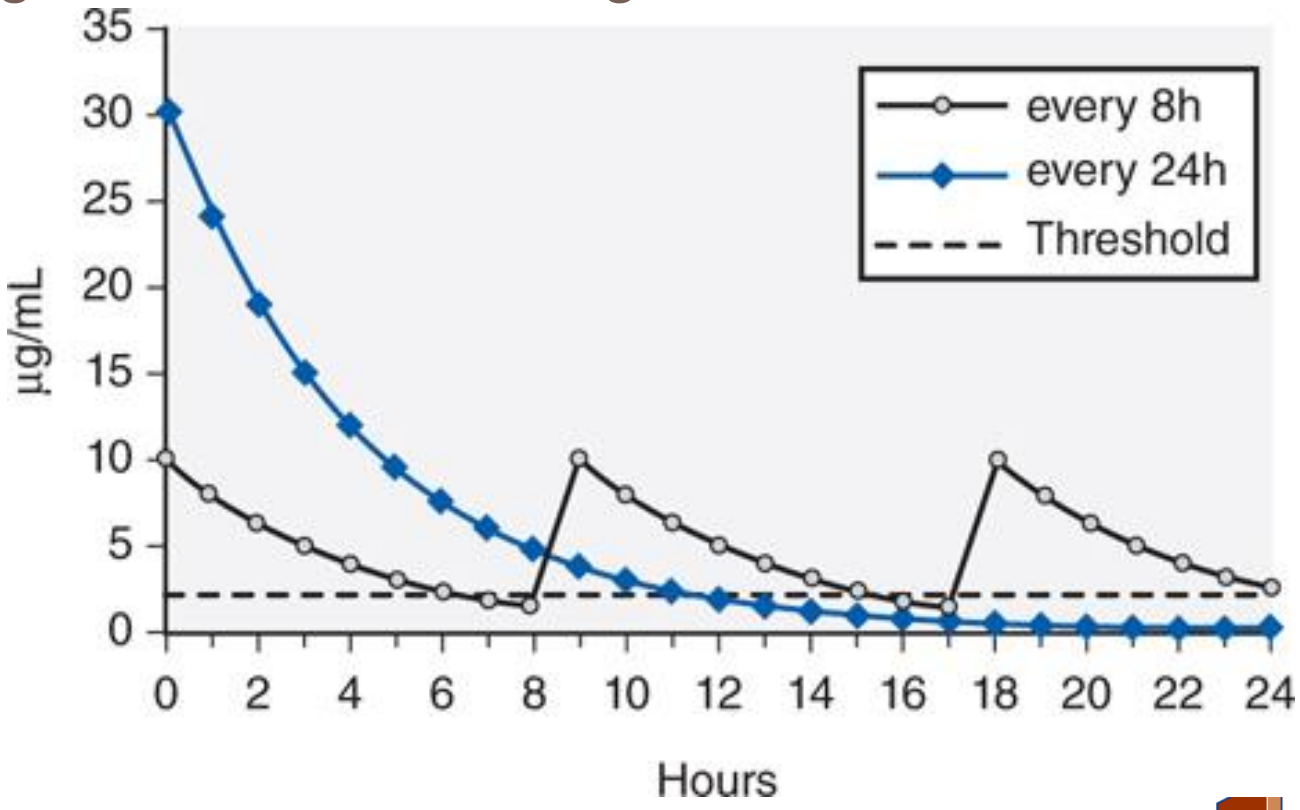


[Image] https://cmr.asm.org/content/29/4/759
[Image] https://weheartit.com/entry/272426040

Administration: Extended Interval Aminoglycosides



- Rationale
  - Concentration dependent pharmacokinetics
  - Target: 8-10x MIC of the organism



[Image] https://www.google.com/url?sa=i&rct=j&q=&esrc=s&source=images&cd=&cad=rja&uact=8&ved=2ahUKEwjzsYqBmvrgAhVPL
AKHRu_AAsQjRx6BAgBEAU&url=https%3A%2F%2Fbasicmedicalkey.com%2Faminoglycosides-
4%2F&psig=AOvVaw10_i0w52dBpdCg7ssAg6SJ&ust=1552397613174947
[Image] https://weheartit.com/entry/272426040

Case

- 70 year old female presents to the ED from local nursing home with CC of fever and rigors
- PMH:
  - Subarachnoid hemorrhage status post trach/vent and PEG
  - Stage IV sacral ulcers
  - Diabetes mellitus type 2
  - COPD
  - Epilepsy
  - *Klebsiella pneumoniae* ESBL bacteremia (2 months prior)
  - *Proteus mirabilis* ESBL pneumonia (2 months prior)

Case

- Work up
  - Blood cultures
  - Sputum
  - Urine culture
  - Respiratory viral panel

Lab	Reference Range	Result
WBC	4.8-10.8 K/mcL	32.9
Lactate	0-2 mmol/L	4.35
Procalcitonin	0-0.09 mcg/mL	9.68
Temperature		102.8°F

What antimicrobial therapy would you initiate?

What antimicrobial therapy would you initiate?

Case

- Patient received 1x dose of vancomycin 1g and pip/tazo 3.375g in the ED
- Admitting team initiated meropenem 2g IV q8hr
- ID was consulted
  - Change to ceftolozane/tazobactam 1.5 g IV q8hr
    - History of ESBL organisms
    - Seizure history
- Microbiology
  - Blood cultures reveal GNR after 15.5 hours
  - Sputum Gram stain revealed GNR

Microbiology Results – Blood

Klebsiella pneumoniae-CRE	
Amikacin	>32 R
Ampicillin	>16 R
Ampicillin/sul	>16 R
Aztreonam	>16 R
Cefazolin	>16 R
Cefepime	>16 R
Cefotaxime	>32 R
Ceftazidime	>16 R
Cefuroxime	>16 R
Ciprofloxacin	>2 R
Ertapenem	>1 R
Gentamicin	<=4 S
Imipenem	>8 R
Levofloxacin	>4 R
Meropenem	>8 R
Pip/tazo	>64 R
Trimeth/sulfa	<=2/38S

- Sent to NYC DOH
  - MALDI-TOF
  - Carbapenemase positive
    - KPC

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Microbiology Result – Sputum

Klebsiella pneumoniae-CRE	
Amikacin	<=8 S
Ampicillin	>16 R
Ampicillin/sul	>16 R
Aztreonam	>16 R
Cefazolin	>16 R
Cefepime	>16 R
Cefotaxime	>32 R
Ceftazidime	>16 R
Cefuroxime	>16 R
Ciprofloxacin	>2 R
Ertapenem	>1 R
Gentamicin	8 I
Imipenem	>8 R
Levofloxacin	>4 R
Meropenem	>8 R
Pip/tazo	>64 R
Trimeth/sulfa	<=2/38 S

Proteus mirabilis-ESBL	
Amikacin	<=8 S
Ampicillin	>16 R
Ampicillin/sul	<=8/4
Aztreonam	16 R
Cefazolin	>16 R
Cefepime	>16 R
Cefotaxime	>32 R
Ceftazidime	<=1S
Cefuroxime	>16 R
Ciprofloxacin	>2 R
Ertapenem	0.5 S
Gentamicin	> 8 R
Levofloxacin	4 I
Meropenem	<=0.5 S
Pip/tazo	<=16 S
Trimeth/sulfa	>2/38 R

Case

- Based on these culture results, would you change therapy? If yes, to what?

JAMAICA HOSPITAL MEDICAL CENTER

Based on these culture results, would you change therapy? If yes, to what?

ESBL

Drug	Dose	Infusion	Cost/day (WAC)
Meropenem	1-2 g IV q8hr	Extended infusion – 3 hours	$174.00
Ertapenem	1g IV q24hr	0.5 hour	$117.07
Ceftazidime/avibactam	2.5 g IV q8hr	2 hours	$1,076.43
Meropenem/vaborbactam	4g IV q8hr	3 hours	$990.00
Imipenem/relebactam	500 mg/250 mg IV q6hr	0.5 hours	TBD
Ceftolozane/tazobactam	1.5-3 g IV q8hr	1 hour	$352.82-651.64
Tigecycline	100 mg IV q12hr	1 hour	$626.00
Fosfomycin (UTI only)	3 g PO q72hr x 3 days	N/A	$86.92
Nitrofurantoin monohydrate	100 mg PO BID	N/A	$6.00

CRE

Drug	Dose	Infusion	Cost/day (WAC)
Ceftazidime/avibactam	2.5 g IV q8hr	2 hours	$1,076.43
Meropenem/vaborbactam	4g IV q8hr	3 hours	$990.00
Imipenem/relebactam	500 mg/250 mg IV q6hr	0.5 hours	TBD
Gentamicin, Tobramycin	5-7 mg/kg IV q24hr (extended interval)	2 hours	$17.01
Amikacin	15 mg/kg IV q24hr (extended interval)	2 hours	$23.20
Tigecycline	100 mg IV q12hr	1 hour	$626.00
Polymyxin B	2.5 mg/kg/day divided q12hr	1.5 hours	$44.00
Colistin	Defer to https://clincalc.com/colistin/	0.5 hours	$90.00
Fosfomycin (UTI only)	3 g PO q72hr x 3 days	N/A	$86.92

Pseudomonas aeruginosa

Drug	Dose	Infusion	Cost/day (WAC)
Ceftazidime/avibactam	2.5 g IV q8hr	2 hours	$1,076.43
Meropenem/vaborbactam	4 g IV q8hr	3 hours	$990.00
Imipenem/relebactam	500 mg/250 mg IV q6hr	0.5 hours	TBD
Ceftolozane/tazobactam	1.5-3 g IV q8hr	1 hour	$352.82-651.64
Meropenem	1-2 g IV q8hr	Extended infusion – 3 hours	$174.00
Cefepime	2 g IV q8hr	Extended infusion – 4 hours	$29.40
Piperacillin/tazobactam	4.5 g IV infused over 60 minutes once, then 4.5 g IV q8hr	Extended infusion – 4 hours	$41.19

Pseudomonas aeruginosa, cont.

Drug	Dose	Infusion	Cost/day (WAC)
Gentamicin, Tobramycin	5-7 mg/kg IV q24hr (extended interval)	2 hours	$17.01
Amikacin	15 mg/kg IV q24hr (extended interval)	2 hours	$23.20
Polymyxin B	2.5 mg/kg/day divided q12hr	1.5 hours	$44.00
Colistin	Defer to https://clincalc.com/colistin/	0.5 hours	$90.00
Fosfomycin (UTI only)	3 g PO q72hr x 3 days	N/A	$86.92

Acinetobacter

Drug	Dose	Infusion	Cost/day (WAC)
Meropenem	2 g IV q8hr	Extended infusion – 3 hours	$174.00
Cefepime	2 g IV q8hr	Extended infusion – 4 hours	$29.40
Ampicillin/sulbactam	3g IV q6hr*	0.5 hours	$36.00
Levofloxacin	750 mg IV/PO daily	1.5 hours	IV $6.90 PO $0.50
Amikacin	15 mg/kg IV q24hr (extended interval)	2 hours	$23.20
Polymyxin B	2.5 mg/kg/day divided q12hr	1.5 hours	$44.00
Colistin	Defer to https://clincalc.com/colistin/	0.5 hours	$90.00

- *Defer to ID for higher dosing: 3g IV q4hr

Fraimow H, et al. Crit Care Clin. 2013 Oct;29(4):895-921.

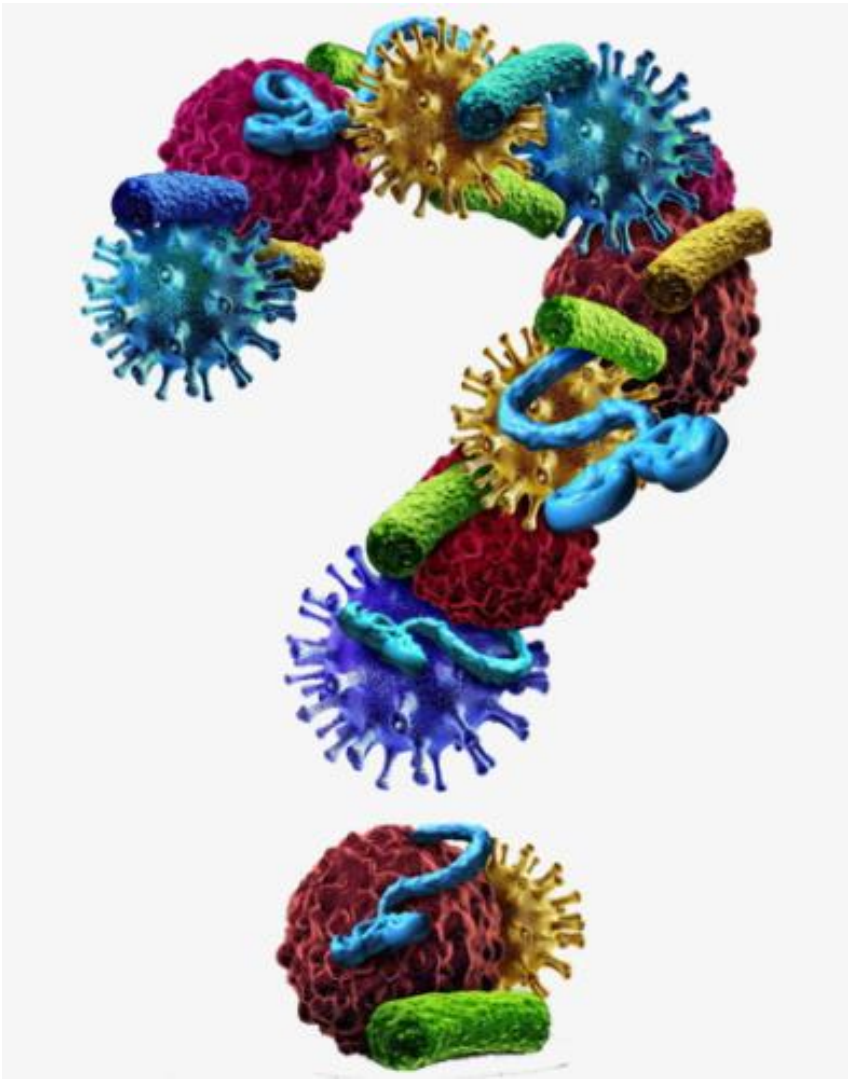
Pipeline

- IV fosfomycin
  - CRE, ESBL, MDR-*Pseudomonas*
  - Dose: 6 g IV q8hr
  - Phase 3 studies for UTI
- Aztreonam/avibactam
  - Mononactam/beta-lactamase inhibitor
- Cefiderocol
  - Siderophore cephalosporin
  - CRE and ***Acinetobacter***

Conclusion

- Gram negative resistance is rising
  - Emphasizes the importance of antimicrobial stewardship and appropriate duration of therapy
  - Avoid overuse of empiric carbapenems to prevent additional carbapenem resistance
- Molecular testing plays a role in drug selection
- New drugs in the pipeline to treat XDRO pathogens
- ASB recommendations still apply for MDROs

Questions



[Image] https://png.pngtree.com/element_origin_min_pic/16/12/04/b91eeeb333ef4de574696eb271f79275.jpg

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