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Back to Basics : Get Smart About Antimicrobials II

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July 2022

Objectives

- Explain the concept of bactericidal vs. bacteriostatic antimicrobials
- Describe the difference between concentration dependent and time dependent antimicrobials
- Discuss the differences in spectrum of activity, characteristics and clinical usage of penicillins, cephalosporins, monobactam, carbapenems, etc.

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1.The Great Debate: Cidal vs. Static

Bactericidal	Bacteriostatic	Tolerance
>3 $\log_{10}$ kill in 24 hours	<3 $\log_{10}$ kill in 24 hours	----------
MBC/MIC $\leq$4	MBC/MIC >4	MBC/MIC $\geq$32

MBC=Minimal bactericidal concentration, MIC=Minimum inhibitory concentration

- Interplay of bug and drug
- Varies by organism and MIC

Craig W. Clin Infect Dis 1998;26:1-12
Pankey GA, *et al.* Clin Infect Dis 2004;38 (6):864-870
Kohanski M, *et al.* Nature Reviews Microbiology 2010:8:23-435

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Advantages/Disadvantages

- **Advantages**
  - Infections with rapid, lethal consequence
  - Reduction in selection of resistance
    - If bactericidal concentration is maintained
    - Clinical data lacking
  - Speed of response
    - Clinical data lacking

- **Disadvantages**
  - Rapid lysis of bacteria
    - Release of cell wall components
    - Release of endotoxin
    - Increase cytokine production systemically
    - Increase local inflammatory effects
  - Less effect on toxin production
    - May not decrease protein synthesis quickly

Pankey GA, *et al.* Clin Infect Dis 2004;38 (6):864-870

Bactericidal/static Antimicrobials

- **Bactericidal**
  - Aminoglycosides
  - Beta-lactams
  - Daptomycin
  - Quinolones (MSSA)
  - Quinupristin/dalfopristin (MSSA)
  - Vancomycin

- **Bacteriostatic**
  - Clindamycin
  - Linezolid
  - Macrolides
  - Rifampin
  - Tetracycline
  - Tigecycline
  - TMP/SMX

Pankey GA, *et al.* Clin Infect Dis 2004;38 (6):864-870

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What Infections Require Bactericidal Antimicrobials?

- Endocarditis
- Meningitis
- Neutropenic fever
- Osteomyelitis

Pankey GA, *et al.* Clin Infect Dis 2004;38 (6):864-870

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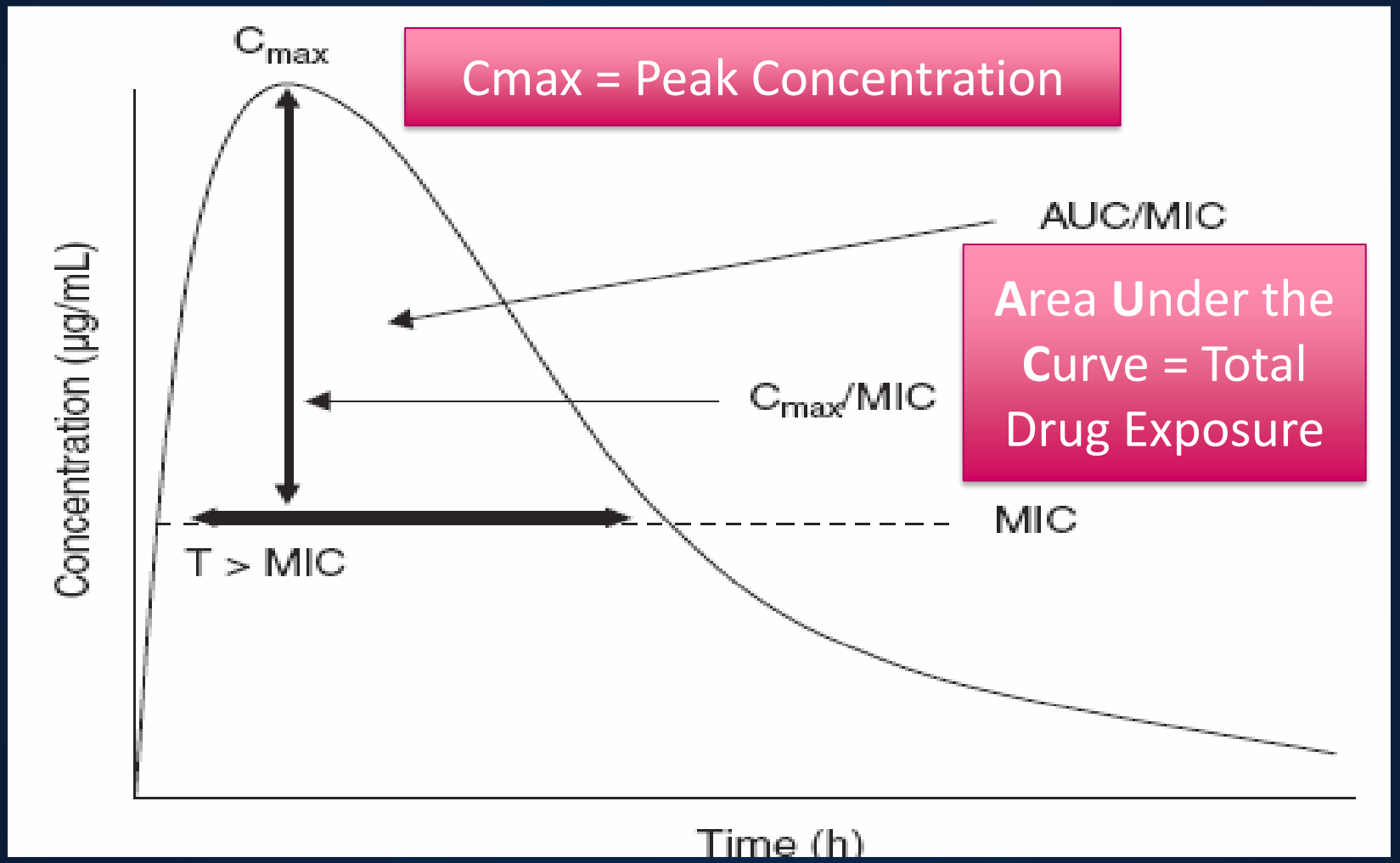
2. Key PD Predictors of Efficacy



DeRyke CA, *et al.* Drugs. 2006;66:1-14

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Classification

	Cmax/MIC	AUC/MIC	T>MIC
ABX	Aminoglycosides Fluoroquinolones Polymyxins	Azithromycin Fluoroquinolones Linezolid Daptomycin Tigecycline Vancomycin	Penicillins Cephalosporins Carbapenems Vancomycin
Organism kill	Concentration-dependent	Concentration/ Time-dependent	Time-dependent
Therapeutic goal	Maximize exposure	Maximize exposure	Optimize duration of exposure

Craig W. Clin Infect Dis 1998;26:1-12
DeRyke CA, *et al.* Drugs. 2006;66:1-14

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3. β- lactams Pharmacodynamics

- Key efficacy marker T>MIC
- Near-maximal bactericidal effect is typically observed when the *free drug* concentration exceeds the MIC (% f T>MIC) for

Drug Class	Bacteriostatic	Bactericidal
Cephalosporins	35-40%	60-70%
Penicillins	30%	50%
Carbapenems	20%	40%

- % attainment

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Drusano GL, *et al.* Nat Rev Microbiol. 2004;2:289-300

ß-lactams: Maximizing T>MIC

- Strategies to increase T>MIC
  - Select agent with lower MICs against given pathogen
    - Improve pharmacodynamic profile
  - Increase dosing frequency
    - Shorten interval (not increase dose) for greatest increase
    - Increase dose has little impact on T>MIC
  - Increase duration of infusion
    - Prolongs exposure- often can use less total drug

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Probability of Target Attainment Analysis for Piperacillin/tazobactam

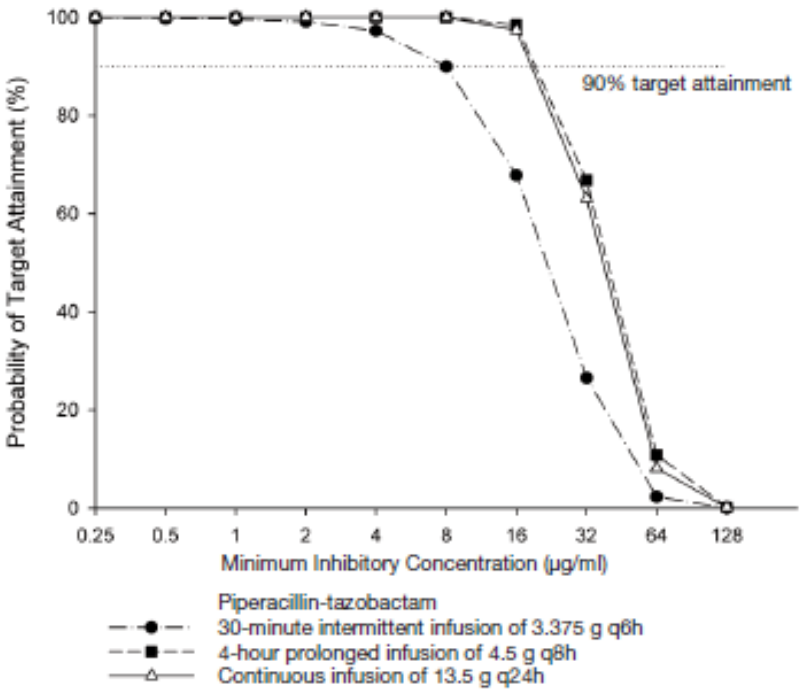

Figure 2. Probability of target attainment at doubling minimum inhibitory concentration dilutions for piperacillin-tazobactam regimens containing piperacillin 12 g/day.

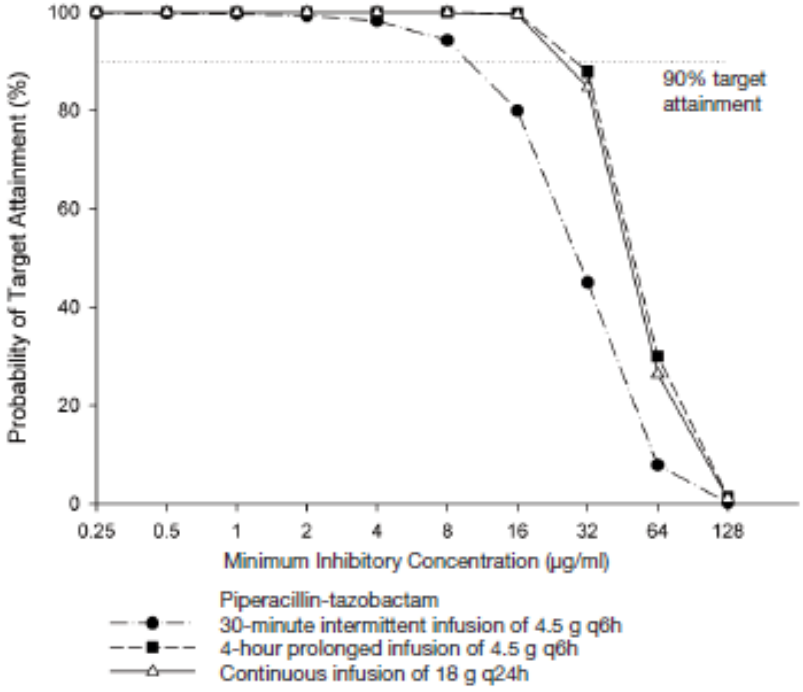

Figure 3. Probability of target attainment at doubling minimum inhibitory concentration dilutions for piperacillin-tazobactam regimens containing piperacillin 16 g/day.

Kim A, *et al*. Pharmacotherapy 2007; 27:11

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Extended Infusion

CrCl	Cefepime (ICUs)	
	Most Indications	**Meningitis, Neutropenic Fever, *P. aeruginosa***
≥ 60 mL/min	1 gm q8h or 2 gm q12h over 4 hrs	2 gm q8h over 4 hrs
> 30 mL/min	1 gm q8h or 2 gm q12h over 4 hrs	2 gm q12h over 4 hrs
≤ 30 mL/min	1 gm q24h over 30 min	1 gm q12h or 2 gm q24h over 30 min
HD	1 gm q24h or 2gm after HD* over 30 min *For stable patients or upon discharge for mild to moderate infections. This dosing strategy should NOT be used for patients require >1g/day of cefepime (ie. morbidly obese, severe sepsis, CNS infection, etc.). References: UptoDate, Perez K, etal. Am J Kidney Dis. 2012; 59(5):738-742.	1-2 gm q24h over 30 min
CRRT	2 gm q12h over 4 hrs	2 gm q12h over 4 hrs
	Piperacillin/tazobactam (All Units)	
CrCl	**All Indications**	
≥ 20 mL/min	4.5 gm q8h over 4 hrs	
< 20 mL/min or HD	4.5 gm q12h over 4 hrs	
CRRT	4.5 gm q8h over 4 hrs	
	Meropenem* (Selective Patient)	
CrCl	**Most Indications**	**Intermediate Sensitivity, Meningitis**
≥ 50 mL/min	1 gm q8h over 3 hrs	2 gm q8h over 3 hrs
26-49 mL/min	1 gm q12h over 3 hrs	2 gm q12h over 3 hrs
10-25 mL/min	500 mg q12h over 30 min	1 gm q12h over 30 min
< 10 mL/min or HD	500 mg q24h over 30 min	1 gm q24h over 30 min
CRRT	1 gm q12h over 3 hrs	2 gm q12h over 3 hrs

4. When to Use High Dose of Time-dependent Antimicrobials?

- Morbidly obese patients
- Penetration
- Neutropenic host
- Intermediately sensitive organism
- Altered pharmacokinetics

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5. IV to PO switch

- Ciprofloxacin
- Doxycycline
- Fluconazole
- Levofloxacin
- Metronidazole (q12h vs. q8h)
- Trimethoprim/sulfamethoxazole
- Linezolid
- Rifampin
- Voriconazole

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6. Consider the following when You Renally Adjust Antimicrobials

- CrCl, urine output
- Hemodialysis vs. continuous renal replacement therapy (CRRT)
- Severity of infection
- Site of infection
- Multi-drug or extensive-drug resistant organisms

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7. When Start Empiric Therapy, Consider the Following:

- Previous organisms identified and antibiotic susceptibility in the last 6 months
- Antibiotic exposures within the past 30 days
- Local susceptibility patterns for the most likely pathogen
- Adjust antimicrobial therapy based on the identity and susceptibility profile of the pathogen

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PENICILLINS

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Mechanism of Action

- Binds the penicillin-binding proteins (PBPs)
- Prevents cross-binding of the peptidoglycan polymers for cell wall formation
- Results cell wall weakening and lysing, leading to cell death.

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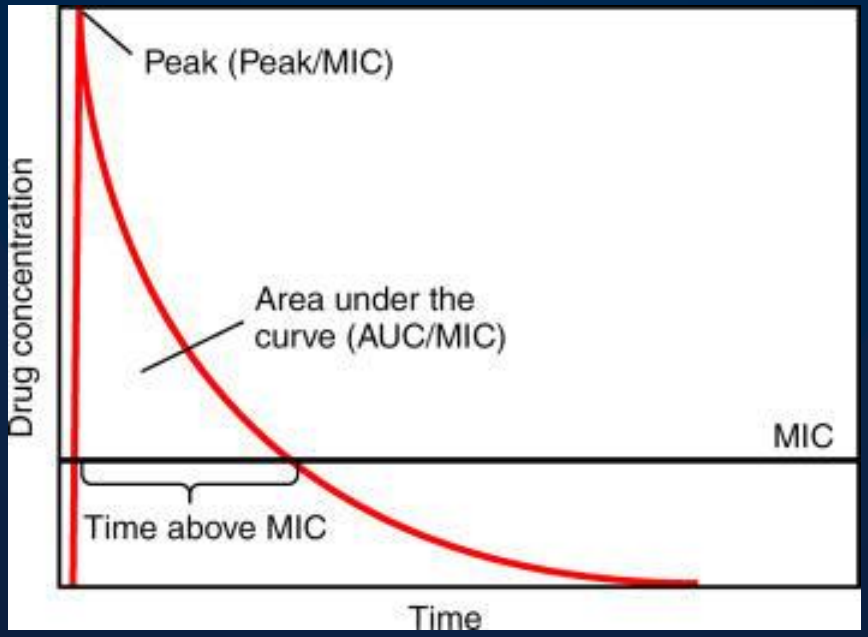
Pharmacokinetics

- Bactericidal
- Time-dependent killing
  - Time > MIC
  - Concentration > MIC for >50% of dosing interval



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Categories

- **Natural penicillins**
  - Penicillin G, penicillin V
- **Aminopenicillins**
  - Ampicillin, amoxicillin
- **Penicillinase-resistant penicillins**
  - Nafcillin, oxacillin, dicloxacillin, methicillin, cloxacillin
- **Carboxypenicillins**
  - Ticarcillin
- **Ureidopenicillins**
  - Piperacillin
- **Penicillin + beta-lactamase inhibitor**
  - Amoxicillin/Clavulanic acid
  - Ampicillin/Sulbactam
  - Ticarcillin/Clavulanic acid
  - Piperacillin/Tazobactam

The Natural Penicillins

- Penicillin G
  - Spectrum of activity
    - Gram +:
      - Staphylococci, many Streptococci, *E. faecalis*, and *L. monocytogenes, Actinomyces*
    - Gram -:
      - *N. meningitidis, N. gonorrhoeae*
    - Anaerobes:
      - *Peptostrepcoccus, clostridium* (not difficile)
    - Others:
      - *Treponema pallidum*

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Susceptibility of *S. pneumoniae*

Penicillin	N	% of Isolates		
Sterile Sites		**Susceptible**	**Intermediate**	**Resistant**
CSF or CNS involvement	24	71%	/	29%
No CNS involvement	26	92%	5%	8%
Non-Sterile Sites		**Susceptible**	**Intermediate**	**Resistant**
Parental Penicillin	32	75%	16%	9%
Oral Penicillin	32	25%	31%	44%

FDA Raises Breakpoints for *S. pneumoniae*

	Minimum Inhibitory Concentration (mcg/mL)		
	Susceptible (S)	Intermediate (I)	Resistant (R)
Updated	≤2	4	≥8
Previous	≤0.06 (Meningitis: remains unchanged)	0.12-1.0	≥2

IDSA News: volume 18, number 4, April 2008

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The Penicillinase-Resistant Penicillins

- Nafcillin, oxacillin, dicloxacillin (methicillin, cloxacillin)
  - Developed in response to the discovery of resistant *S. aureus*
  - Resistant to hydrolysis by lactamase produced by the staphylococci
  - Mainly used for penicillin-resistant *Staphylococcus* and *Streptococcus* species
  - Do not cover gram-negative, or anaerobic organisms

The Aminopenicillins

- Ampicillin, Amoxicillin
  - Spectrum of activity
    - Same activity as the natural penicillins
    - Improved coverage of gram-negative cocci and Enterobacteriaceae that do not produce β-lactamase
    - Effective against *L. monocytogenes*

Ampicillin	*E. faecalis*		*E. faecium*	
	N	% Susceptible	N	% Susceptible
Urine	208	98	47	13
Non-Urine	166	99	94	12

The Extended-Spectrum Penicillins

- Known as anti-*Pseudomonal* penicillins
- Carbenicillin (oral), ticarcillin, piperacillin
- Retain activity against gram-positive bacteria
- Extend activity against gram-negative bacteria
  - *Citrobacter*
  - *Enterobacter*
  - *Pseudomonas aeruginosa*
  - *Serratia*

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The Addition of β-Lactamase Inhibitors

- **Amoxicillin/Clavulanic acid**
- **Ampicillin/Sulbactam**
- **Piperacillin/Tazobactam**

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Ampicillin/Sulbactam

- Multi-drug resistant *A. baumannii* (54% sensitive, antibiogram 2020-2021)
- 3g of Unasyn= 2g of ampicillin + 1g of sulbactam
- 40 yrs old male in ICU with carbapenem resistant *Acinetobacter* (CRAB) bacteremia, normal renal function, what's the dose for unasyn?
  A. 3g IV q6h
  B. 9g (3g of sulbactam) IV q8h over 4 hours
  C. 27g (9g of sulbactam) IV q24h as a continuous infusion
  D. Call ID pharmacist
- 50 yrs old female with *Acinetobacter* UTI, can patient be discharged on augmentin if sensitive to unasyn?
  – Ans. **NO**

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Piperacillin/Tazobactam

- Extended spectrum beta-lactamase (ESBL)
  - ESBLs > 120 types (TEM-1, SHV-2, CTX-M-15…)
  - Chromosomally encoded or plasmid and transposon mediated (transferred from bacteria to bacteria)
- Inhibited by clavulanate
- Hydrolyze most penicillins, cephalosporins, and aztreonam
- Non-susceptibility to ceftriaxone (MIC≥2 mcg/mL)
- Carbapenems and cephamycins (cefoxitin, cefotetan) spared
- Organisms that produce ESBLs include: *E. coli, K. pneumoniae, K. oxytoca, P. mirabilis*…and more!

Paterson DL, *et al*. Clinical Microbiology Reviews 2005;18(4): 657-86.

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MERINO 1 Trial

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)

- Noninferiority, parallel group, RCT in 9 countries (2014-2017)
- Inclusion criteria
  - Adult patients
  - >1 positive blood culture with *E. coli* or *Klebsiella* spp. testing nonsusceptible to ceftriaxone but susceptible to piperacillin/tazobactam
    - Piperacillin/tazobactam 4.5g q6h for 4-14 days (n=187)
    - Meropenem 1g q8h for 4-14 days (n=191)
- Primary outcome
  - All-cause mortality at 30 days

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

MERINO1 Results

	30-d Mortality, No./Total No. (%)		Risk Difference, % (1-Sided 97.5% CI)[a]	*P* Value for Noninferiority
	Piperacillin-Tazobactam	Meropenem		
Primary analysis	23/187 (12.3)	7/191 (3.7)	8.6 (−∞ to 14.5)	.90
Per-protocol analysis	18/170 (10.6)	7/186 (3.8)	6.8 (−∞ to 12.8)	.76
Subgroup analyses[b]				*P* Value for Interaction
UT vs non-UT source				
UT	7/102 (6.9)	4/128 (3.1)	3.7 (−∞ to 10.7)	.44
Non-UT	16/85 (18.8)	3/63 (4.8)	14.1 (−∞ to 24.5)	

Avoiding piperacillin/tazobactam for the treatment of invasive ESBL-*Enterobacterales* infection

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

IDSA Guidance on the Treatment of Antimicrobial-Resistant Gram-Negative Infections: Version 1.0

Published by IDSA, 3/7/2022

A Focus on Extended-Spectrum β-lactamase Producing Enterobacterales, Carbapenem-Resistant Enterobacterales, and *Pseudomonas aeruginosa* with Difficult-to-Treat Resistance

Type of Infection	Therapy of Choice
Cystitis	Nitrofurantoin, Bactrim, Aminoglycoside, Fosfomycin (E. coli only), Piperacillin/tazobactam (if clinically improving)
Pyelonephritis/cUTI	Quinolones, Bactrim, Aminoglycoside, Piperacillin/tazobactam (if clinically improving), Carbapenem
Outside of Urinary Track	Carbapenem (Oral step-down)

Montefiore Antimicrobial Stewardship Program (ASP) Implementation

- Proposal (coming soon):
  - If ceftriaxone nonsusceptible— *"This organism may produce extended-spectrum ESBLs. Piperacillin/tazobactam can be used for non-bacteremic urinary tract infections. Contact ID or ASP for guidance."*

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CEPHALOSPORINS

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Classification

- First generation
  - Cefadroxil, cefazolin, cephalexin
- Second generation
  - Cefaclor, cefotetan, cefoxitin, cefprozil, cefuroxime, loracarbef
- Third generation
  - Cefdinir, cefditoren, cefixime, cefoperazone, cefotaxime, cefpodoxime, ceftazidime, ceftibuten, ceftizoxime, ceftriaxone
- Fourth generation
  - Cefepime
- Fifth generation
  - Ceftaroline (Teflaro)
- Newer cephalosporin
  - Ceftolozane/tazobactam (Zerbaxa), Ceftazidime/avibactam (Avycaz)
- Newest addition
  - Cefiderocol (Fetroja)

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Characteristics of Cephalosporins

- Parentally administered cephalosporins
  - Relative short half-lives: 0.5-2 hrs
    - Dosing frequency: q8h
    - Exception: ceftriaxone (half-life: 8 hrs)

Type of Infection	Dosing/Frequency
Common infection (i.e. CAP, UTI, etc.)	1g IV q24h
Endocarditis/osteomyelitis	2g IV q24h
Enterococcal endocarditis synergy w/ ampicillin	2g IV q12h
Meningitis	2g IV q12h

  - Elimination: renal excretion
    - Ceftriaxone, cefoperazone: dual elimination (biliary/renal excretion), **NO RENAL ADJUSTENT NECESSARY**

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Spectrum of Activity (gram +)

- *Staphylococcus*
  - 1st generation > 4th generation > 3rd generation > 2nd generation
  - 5th generation
- *Streptococcus*
  - 1st-5th generations
- Do not cover *Enterococcus, Listeria, MRSA (except ceftaroline)*

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Spectrum of Activity (gram -)

- 1st generation-**PECK(S)**
  - *Proteus, E. coli, Klebsiella, Salmonella?*
- 2nd generation-**HEN PECK(S)**
  - *Proteus, E. coli, Klebsiella, Salmonella?*
  - *Hemophilus, Enterobacter, Neisseria*
  - *Bacteroides* (cefoxitin, cefotetan)
- 3rd generation-**A HEN PECKSS**
  - *Proteus, E. coli, Klebsiella, Serratia, Salmonella*
  - *Acinetobacter, Hemophilus,* ***Enterobacter****, Neisseria*
  - *P. aeruginosa* (cefoperazone, ceftazidime)

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Journal of Antimicrobial Chemotherapy (2004) **54**, 173–177
DOI: 10.1093/jac/dkh282
Advance Access publication 18 May 2004

JAC

Relationship between ceftriaxone use and resistance to third-generation cephalosporins among clinical strains of *Enterobacter cloacae*

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[1]Service d'Hygiène Hospitalière et d'Epidémiologie Moléculaire, Centre Hospitalier Universitaire Jean Minjoz, Besançon, France; [2]Preventive Medicine Unit, Hospital Vega Baja, Orihuela, Spain

Received 17 October 2003; returned 10 February 2004; revised 3 March 2004; accepted 10 April 2004

Objective: To investigate the potential correlation between the use of extended-spectrum cephalosporins (ESCs) and resistance to this antibiotic class among clinical isolates of *Enterobacter cloacae* in a university-affiliated hospital.

Materials and methods: Data on antimicrobial resistance and antimicrobial use concerning *E. cloacae* and ESCs were collected over a 4 year period. Various statistical tools were used to explore the potential relationship.

Results: From 1999 to 2002, the proportion of *E. cloacae* isolates resistant to ESCs increased from 24.3% to 29.6%. ($P = 0.04$), and the quantity of ESCs prescribed and given did not change. Within the subclass constituted by first-line ESCs, the proportion of ceftriaxone increased from 64.3% to 77.6% and the proportion of cefotaxime decreased accordingly, from 35.7% to 22.4%. Statistical analyses showed that *E. cloacae* resistance to ESCs correlated with ceftriaxone use regardless of the other ESCs. For every defined daily dose of ceftriaxone per 1000 patient days used in our hospital, resistance of *E. cloacae* isolates to ESCs increased by 1.36%.

Conclusion: This study demonstrates a specific correlation between ceftriaxone use and the development of resistance in *E. cloacae* clinical isolates. The high biliary elimination of ceftriaxone compared with other ESCs may be responsible for a greater impact of this antibiotic on the digestive flora.

- Amp C- plasmid-mediated or chromosomally hyperproduced
- Avoid ceftriaxone to treat *Enterobacter* associated infection

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Spectrum of Activity (gram -)

- 4th generation
  - *Proteus, E. coli, Klebsiella, Serratia, Salmonella*
  - *Acinetobacter, Hemophilus, Enterobacter, Neisseria*
  - *P. aeruginosa*
  - *Inducible* β-lactamase producing organism **(SPICE/SPACE or HECK-Yes)**
    - ***S****erratia*
    - ***P****seudomonas*
    - **I**ndo positive *Proteae*
      - *Proteus*
      - *Providencia*
      - *Morganella*
    - *Acinetobacter*
    - ***C****itrobacter*
    - ***E****nterobacter*

- **H**afnia alvei
- **E**nterobacer cloacae
- **C**itrobacter freundii
- **K**lebsiella (Enterobacter) aerogenes
- **YE**r**S**inia enterocolitica

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2022 Enterobacterales MIC Breakpoints

Piperacillin/ tazobactam

Cefepime

Meropenem

Interpretive Categories and MIC Breakpoints, µg/mL				Comments
S	SDD	I	R	
≤ 8/4	16/4		≥ 32/4	**(21) Breakpoints for susceptible are based on a dosage regimen of 3.375-4.5 g administered every 6 h as a 30-minute infusion. Breakpoints for SDD are based on a dosage regimen of 4.5 g administered every 6 h as a 3-h infusion or 4.5 g administered every 8 h as a 4-h infusion**
≤ 2	4-8	-	≥ 16	(28) The breakpoint for susceptible is based on a dosage regimen of 1 g administered every 12 h. The breakpoint for SDD is based on dosage regimens that result in higher cefepime exposure, either higher doses or more frequent doses or both, up to approved maximum dosage regimens. See Appendix E for more information about breakpoints and dosage regimens. Also see the definition of SDD in the Instructions for Use of Tables section.
≤ 1	-	2^	≥ 4	(46) Breakpoints are based on a dosage regimen of 1 g administered every 8 h.

- MERINO 2 trial
- Cystitis, low inoculum
- Cefepime MIC 4-8 can harbor ESBL

CLSI. M100, Ed. 32nd: 2022

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The CEPHALOSPORIN WITH MRSA COVERAGE

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Ceftaroline (Teflaro)

- **5th generation**
  - Approved by FDA-October 2010
  - Indications:
    - Acute bacterial skin & skin structure infections
    - Community-acquired bacterial pneumonia
  - Bactericidal against *S. aureus* due to its affinity for PBP2a and against *S. pneumoniae* due to its affinity for PBP2x.
  - Not active against Gram-negative bacteria producing ESBLs from the TEM, SHV or CTX-M families, serine carbapenemases (such as KPC), class B metallo-beta-lactamases, or class C (AmpC cephalosporinases)
  - Protein binding: 20%
  - Elimination: 88% renally excreted

Steeed ME, *et al*. Pharmacotherapy 2010;30-375.
Crithcley BD, *et al*. J Antimicrob Chemother 2010;65:(S4):iv9-16).

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CLSI Breakpoint Changes for 2019

S. aureus	Old	New
Ceftaroline	S: ≤ 1	S: ≤ 1
	I: 2	SDD: 2-4
	R: ≥ 4	R: ≥ 8

- S (susceptible): **600mg IV q12h**
- SDD (susceptible-dose-dependent) or persistent bacteremia: **600mg IV q8h**

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Role of Ceftaroline

- Salvage therapy for deep-seated MRSA infection
  - Failed vancomycin or daptomycin
  - Combination of daptomycin + ceftaroline
- Consolidation therapy
  - i.e. *MRSA* bacteremia + *E. coli* UTI
- Long term use: monitor neutrophil count – especially for q8h dosing

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The New Anti-Gram-Negative Cephalosporins

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β-lactamases According to the Ambler Classification System

Ambler Class	Enzyme Type	Common Bacterial Species	Examples
A	Narrow-spectrum	*E. coli, Klebsiella spp.*	Staphylococcal penicillinase, TEM-1, TEM-2, SHV-1
A	Extended-spectrum	*Enterobacteriaceae, P. aeruginosa, Acinetobacter spp., Kluyvera spp.*	SHV-like, CTX-like, KLUG-like
A	Serine **carbapenembases**	*Klebsiella spp.*	**KPC**-like, IMI-like
B	Metallo-β-lactamases, **carbapenemases**	*S. maltophilia, P. aeruginosa, B. fragilis, A. baumannii*	**VIM**-like, **IMP**-like, **NDM**-like, GIM, SPM, SIM
C	Extended-spectrum, cephalosporinases	*Enterobacter spp., Klebsiella spp., Citrobacter freundii, E. Coli*	**AmpC**, p99, ACT-like, CMY-like MIR-like
D	**Carbapenemases**	*P. aeruginosa, E. coli, A. baumannii*	**OXA**-like

Bush K, *et al*. Antimicrob Agents Chemother 2010;54:969-976.
Liscio JL, *et al.* Int Antimicrob Agents 2015;46:266-271.

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β-lactamase and β-lactamase Inhibitor 101

Class	Example	Cefepime	Pip/tazo	Carbapenems	Aztreonam	Avibactam	Vaborbactam	Relebactam
A	**ESBL**	-	✔ (?)	✔	-	✔	✔	✔
	KPC	-	-	-	-	✔	✔	✔
B	**MBLs (**NDM, VIM, IMP**)**	-	-	-	✔	-	-	-
C	**AmpC**	✔	-	✔	-	✔	✔	✔
D	**OXA (**23, 48, 58**)**	-	-	-	-	✔	-	-

MBL: Metallo-β-lactamases

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	Ceftolozane/tazobactam (Zerbaxa)	Ceftazidime/avibactam (Avycaz)
FDA Approval Date	December 2014	February 2015
Company	Cubist -> Merck	Actavis/Allergan -> Pfizer
Cephalosporin Generation	Ceftolozane: a novel 3rd generation	Ceftazidime: 3rd generation (1985)
FDA Approved Indications	Complicated intra-abdominal infection (with metronidazole)	Complicated intra-abdominal infection (with metronidazole)
	Complicated urinary track infection	Complicated urinary track infection
	HABP/VABP	HABP/VABP
Spectrum of Activities	Gram positive organisms • Streptococcus • Staphylococcus (limited)	Gram positive organisms • Minimal
	Gram negative organisms • Class A (TEM, SHV, CTX-M) • Class C (AmpC) • **Increased activity against resistant *P. aeruginosa isolates* (including XDR strains)** • Not active against MBLs (NDM-1, IMP, VIM), carbapenmases	Gram negative organisms • Class A (TEM, SHV, CTX-M) • Class C (AmpC) • Class D (OXA) β-lactamases • **Carbapenemase-producing isolates** • Not active against MBLs (NDM-1, IMP, VIM) • Minimal activity against Acinetobacter
	Anaerobes • Limited activity for *Bacteroides fragilis*	Anaerobes • Limited activity for *Bacteroides fragilis*

Liscio JL, *et al*. Int Antimicrob Agents 2015;46:266-271.

The New Anti-gram-negative Cephalosporins

	Enterobacteriaeceae	Pseudomonas aeruginosa	Bacteroides fragilis
Ceftolozane/tazobactam			
Susceptible	≤ 2/4	≤ 4/4	≤ 8/4
Intermediate	4/4	8/4	16/4
Resistant	≥ 8/4	≥ 16/4	≥ 32/4
Ceftazidime/avibactam			
Susceptible	≤ 8/4	≤ 8/4	N/A
Intermediate	N/A	N/A	N/A
Resistant	≥ 16/4	≥ 16/4	N/A

N/A, not available

Liscio JL, *et al*. Int Antimicrob Agents 2015;46:266-271.

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The New Anti-gram-negative Cephalosporins

- Ceftolozane/tazobactam

CrCl (ml/min)	Regimen (each dose infuse over 1 hour)
>50	1.5g IV q8h
30-50	750mg IV q8h
15-29	375mg IV q8h
HD	Loading dose 750mg IV x1, 150mg IV q8h
CRRT	1.5g IV q8h

- Ceftazidime/avibactam

CrCl (ml/min)	Regimen (each dose infuse over 2 hours)
> 50	2.5g IV q8h
31-50	1.25g IV q8h
<30, HD	0.94g IV q12h
CRRT	1.25-2.5g IV q8h

For pneumonia: 3g IV q8h

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Challenging Case

- 42 years old male with no PMH was involved in a bus accident in Bangladesh in February 2018.
- He sustained a degloving injury of the right upper arm and open elbow fracture, with multiple skin grafting procedures, has been receiving long term antibiotics: Imipenem/colistin x 1-2 months + eventually switched to oral antibiotics x 3 weeks.
- Early May, he presented to hospital with significant arm pain. He was off antibiotics for 3 weeks at this point.
  - Able to move fingers without decrease in sensation
  - Fevers for 2 weeks at home, but afebrile upon admission
  - He went to OR for debridement and cultures were collected

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Audience Poll Question

So….concern about carbapenem resistant Enterobacteriaceae (CRE). How would you treat the CRE?

A. Polymyxin B
B. Polymyxin B + meropenem (extended infusion)
C. Ceftazidime/avibactam
D. Meropenem/vaborbactam
E. Imipenem/relebactam
F. None of above

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Back to our patient…

- Carbapenemase-producing *K. pneumoniae*
  - *NDM-1 detected!!*
  - *OXA-48 detected!!*
- ESBL
  - blaCTX-M-15 *detected!!*

Antibiotic	Interpretation (MIC, mcg/ml)
Amikacin	R (>32)
Aztreonam	R (64)
Ceftazidime/avibactam	R (>265)
Meropenem	R (>8)
Polymyxin B	S (0.05)
Tigecycline	I (3.0)
Chloramphenicol	R
Meropenem/vaborbactam	R (>16/8)
Imipenem/relebactam	R (>32)

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Audience Poll Question

How would you like to adjust treatment now?

A. Polymyxin B
B. Polymyxin B + meropenem (extended infusion)
C. Polymyxin B + tigecycline
D. Tigecycline + meropenem (extended infusion)
E. Ceftazidime/avibactam + aztreonam
F. Cefiderocol

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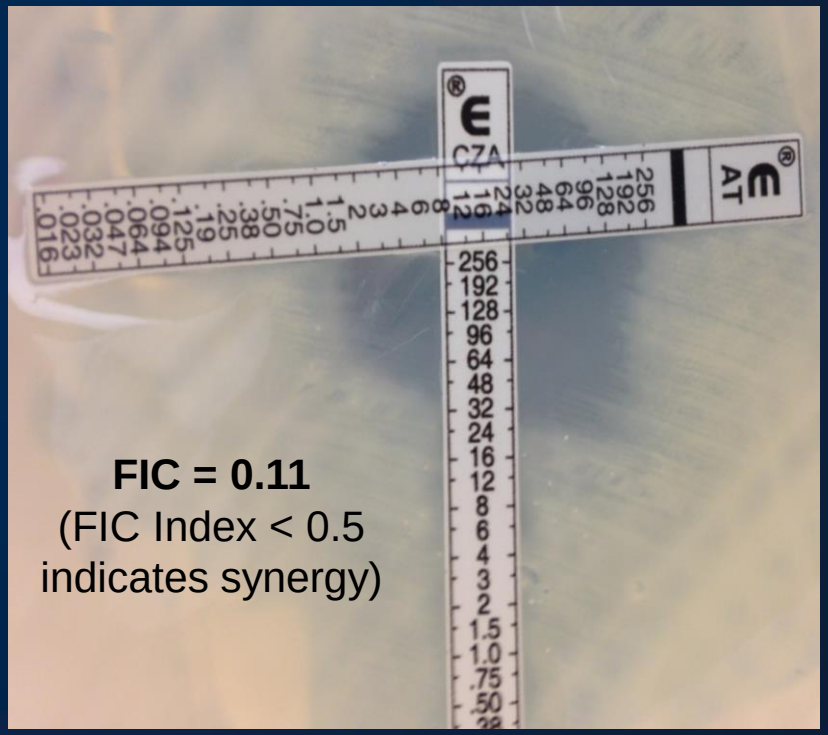
Back to our patient…

- Carbapenemase- producing *K. pneumoniae*
  - *NDM-1 detected!!*
  - *OXA-48 detected!!*
- ESBL
  - blaCTX-M-15 *detected*

- Synergy testing by microbiology lab

Cross Etest at MIC



FIC = 0.11
(FIC Index < 0.5 indicates synergy)

FIC, fractional inhibitory concentration

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Synergy Testing Results

Antibiotic Tested	Interpretation (FIC Index)*
Ceftazidime/avibactam + aztreonam	Synergy (0.11)
Tigecycline + meropenem	Indifference (2)
Meropenem + polymyxin B	Indifference (2)
Polymyxin B + tigecycline	Indifference (4)
Aztreonam + ampicillin/sulbactam	Indifference (2)

FIC, fractional inhibitory concentration
MIC, minimum inhibitory concentration
*FIC index=$\frac{\text{Drug A MIC in combination}}{\text{Drug A MIC alone}} + \frac{\text{Drug B MIC in combination}}{\text{Drug B MIC alone}}$
FIC index interpretation: synergy < 0.5, indifference 0.5 to 4, antagonistic >4

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Aztreonam + Ceftazidime/avibactam

- Aztreonam has in vitro activity against NDM (metallo-β-lactamase)
- The potent activity of combination therapy may be mediated by the preservation of aztreonam activity by avibactam.
  - ESBL likely to cause aztreonam resistance in the absence of avibactam
  - Avibactam is active against OXA-48

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Mittal J, et al. *BMJ Case Rep* 2018. pii: bcr-2018-225440. doi:10.1136/bcr-2018-225440

Case Reports

Cases	Number of Patient	Organism	Type of Infection	Regimen	Outcome
Shaw E, et al (Spain)	10	*K. pneumoniae* (NDM-1, OXA-48, CTX-M-15	HAP, cUTI, bacteremia, intra-abdominal infection	Ceftazidime/ avibactam + Aztreonam	60% cure rate (2 recurrence)
Davido B, et al (France)	2	*K. pneumoniae* (NDM-1, OXA-48) *P. aeruginosa* (NDM-1, AmpC)	Bacteremia, pneumonia	Ceftazidime/ avibactam + Aztreonam	Cured
Marshall S, et al (U.S.)	1	*E. cloacae* (NDM-1) *K. pneumoniae* (ESBL)	Bone/joint infection post a total hip arthroplasty	Ceftazidime/ avibactam + Aztreonam	Cured

HAP: hospital acquired pneumonia, cUTI: complicated urinary tract infection

Shaw E, et al. *J Antimicrob Chemother* 2018;73:1104-1106
Davido B, et al. *Antimicrob Agents Chemother* 2017;61:e01008-17
Marshall S, et al. *Antimicrob Agents Chemother 2017; 61;e02243-16*

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Lesson Learned

- Infections with CRE are challenging to manage as they are often requiring combination therapy
- There are minimal clinical data on effective regimens for treatment of osteomyelitis due to CRE
- Rapid molecular diagnostics and synergy testing are valuable resources to assist with the management of CRE infections
- Be cognizant of the risk of CRE infection due to international travel

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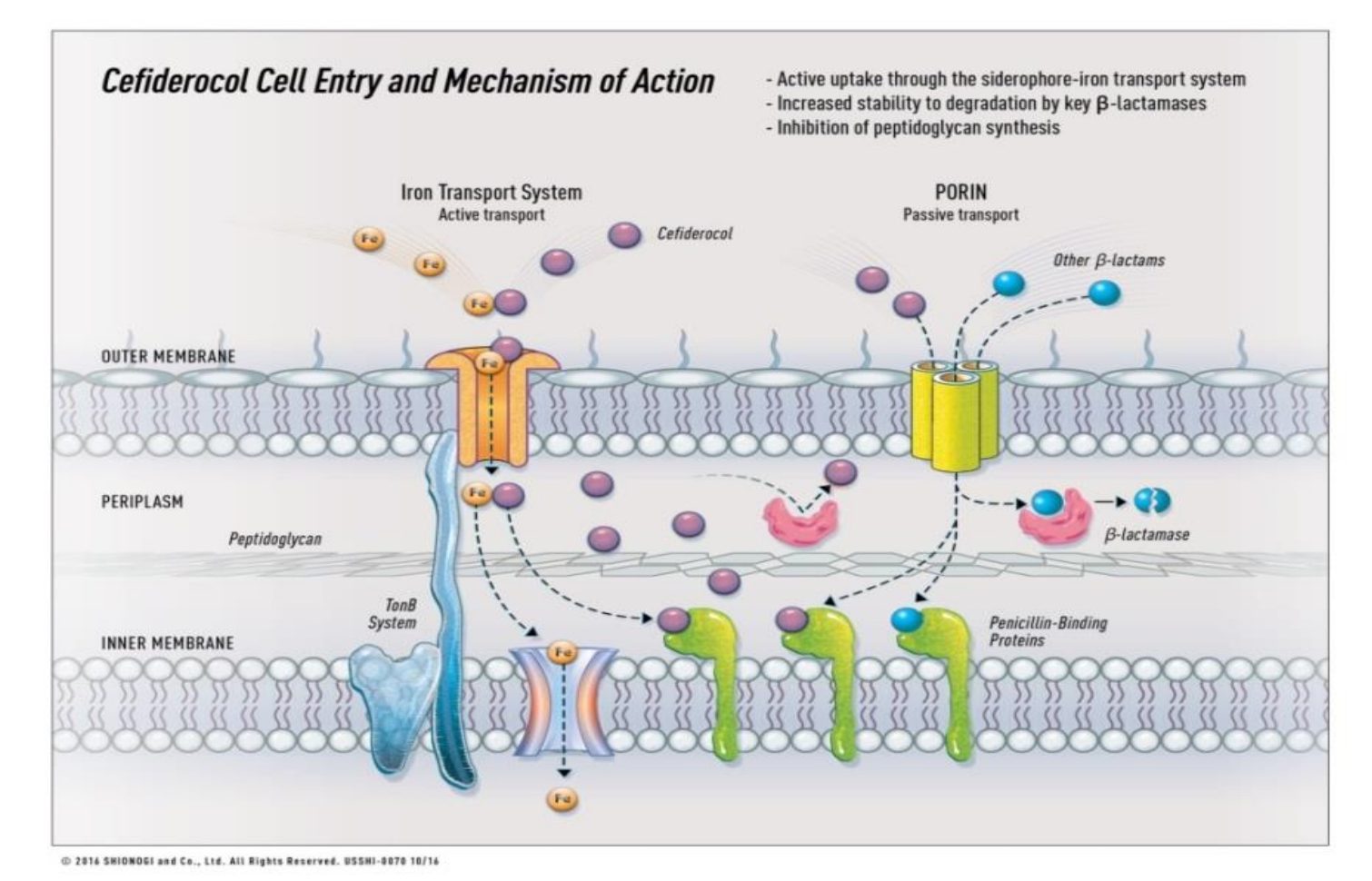
Cefiderocol

Cefiderocol- a Siderophore Cephalosporin



A. Ito et al. AAC 2016;60:7396

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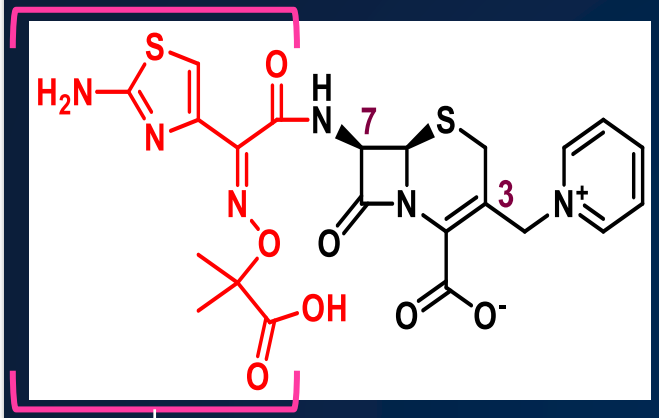
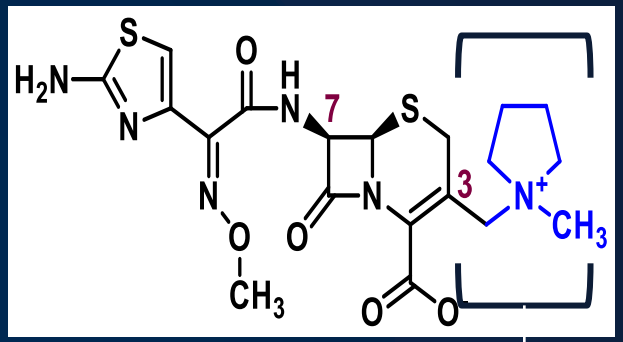
Cefiderocol Structure Activity Relationship

C-7 side chain
enhances stability against β-lactamases

C-3 side chain
prevents recognition by β-lactamases (eg, metallo β-lactamases)



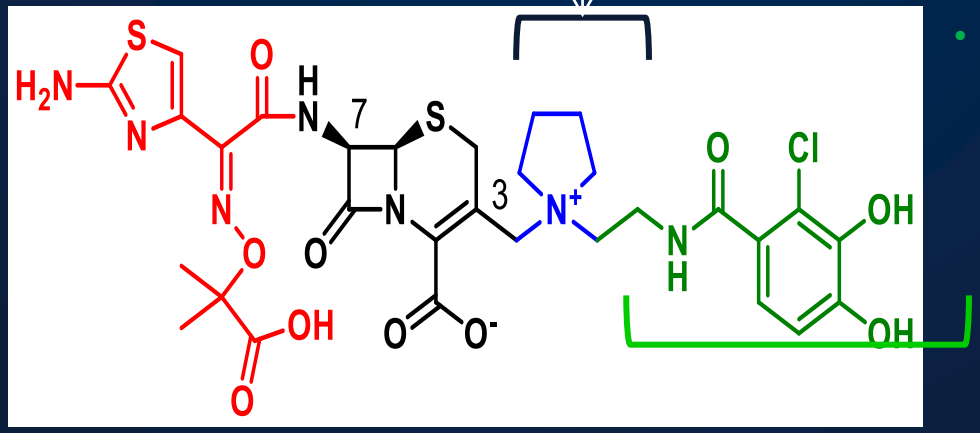
Ceftazidime



Cefepime

Catechol moiety

- Additional stability against β-lactamases
- Binds to free iron



Cefiderocol

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Cefiderocol

- Approval year: 2019
- Broadest coverage (Class A, B, C, D)
- More stable: ESBL, KPC, NDM, VIM, IMP, Oxa-type
- Overcome porin channel mutations and efflux pump overproducers (Pseudomonas)

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Cefiderocol

- Cover *P. aeruginosa*, all resistant *Enterobacteriaceae* including *A. baumannii*, *S. maltiphilia, Burkholderia*
- *No gram-positive or anaerobic activity*
- Increased mortality in clinical trials with *A. baumanii* associated infection
- Resistant developed after a few doses has been reported

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Cefiderocol

Breakpoints			
	S	**I**	**R**
Enterobacteriaceae	≤4	8	≥16
P. aeruginosa	≤4	8	≥16

	Cefiderocol
Dose	2g IV q8h over 3 hrs
Renal Adjustment	CrCl <60 ml/min CrCl ≥120 ml/min – 2g IV q6h

Last Last Last Resort ABX!!---call your ID pharmacist

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MONOBACTAM

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Aztreonam

- Single beta-lactam core
- Structure looks like ceftazidime
  - In vitro activity similar is 3rd generation cephalosporins
- Narrow spectrum
  - No activity against gram positive or anaerobic bacteria
- Distribution
  - Achieve therapeutic level in lung, bronchial secretion, bone, bile, liver, CSF w/ inflamed meninges, synovial fluid, prostate, etc.
- When do we use it?
  - Patient with penicillin allergy
  - Primarily used against gram-negative aerobic bacteria including *P. aeruginosa*

Brogden RN, *et al.* Drugs 1986;31(2):96-130.
Westley-Horton, *et al.* Am J Med Sci 1991;302(1):46-49.

Adult Antibiogram 2020-2021

	Aztreonam	Ciprofloxacin
A. baumannii	0%	46%
E. cloacae	66%	81%
E. coli	82%	63%
K. pneumoniae	80%	80%
P. aeruginosa	67%	78%

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CARBAPENEMS

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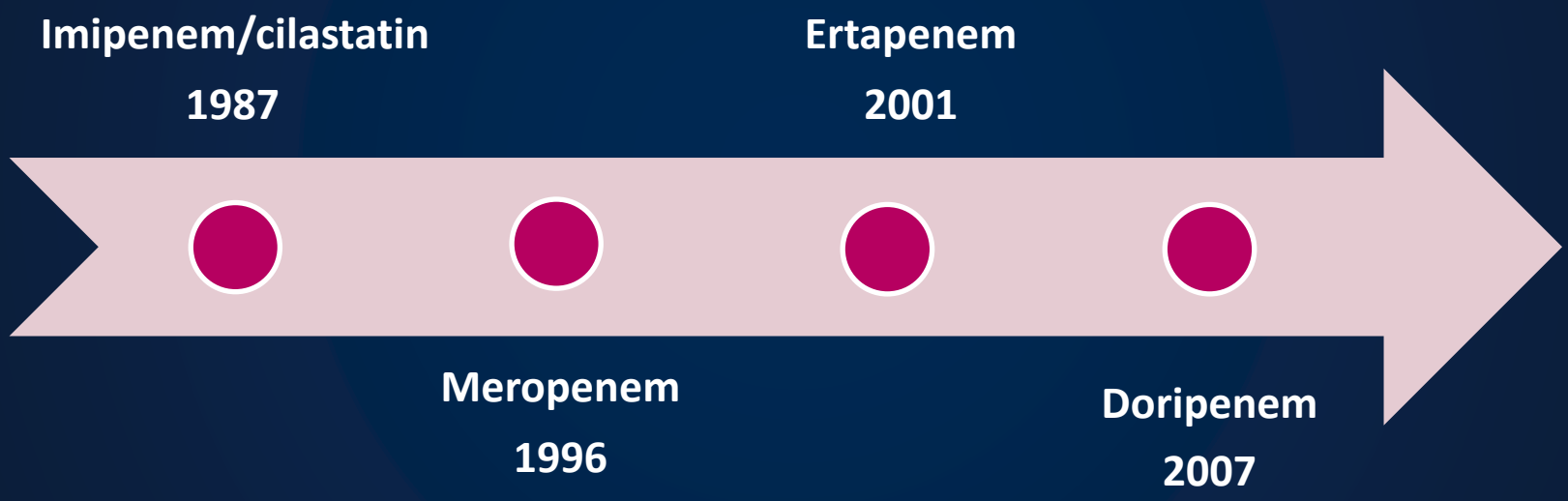
Timeline of Carbapenems



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FDA Approved Indications

	Imipenem	Meropenem	Ertapenem	Doripenem
Intra-abdominal Infection	√	√	√	√
Urinary Tract Infection			√	√
Skin and Skin Structure Infection	√	√	√	
Lower Respiratory Tract infection	√			
Community Acquired Pneumonia			√	
Bacterial Meningitis		√		
Gynecologic/pelvic Infection	√		√	
Prophylaxis of Colorectal Surgery			√	

Zhanel GG, *et al*. Drugs 2007;67(7):1027-1052

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Spectrum of Activity

Bacteria	Imipenem		Meropenem		Ertapenem		Doripenem	
	MIC 50	MIC 90	MIC 50	MIC 90	MIC 50	MIC 90	MIC 50	MIC 90
MSSA	≤ 0.5	≤ 0.5	0.12	0.12	0.12	0.25	0.06	0.06
MRSA	32	32	16	32	8	> 32	16	16
S. pyogenes	≤ 0.08	≤ 0.08	≤ 0.08	≤ 0.08	≤ 0.08	≤ 0.08	≤ 0.08	≤ 0.08
S. pneumoniae	≤ 0.08	≤ 0.08	≤ 0.08	≤ 0.08	0.015	0.015	≤ 0.08	≤ 0.08
E. faecalis	1	4	8	16	8	16	4	8
E. faecium	> 8	> 8	> 16	> 16	> 16	> 16	> 16	> 16
Acinetobacter	0.25	0.25	0.25	1	4	> 8	0.25	1
E. cloacae	0.5	2	0.03	0.06	≤ 0.015	0.06	0.03	0.06
E. coli (ESBL)	≤ 0.5	≤ 0.5	0.03	0.06	< 0.06	0.25	0.03	0.06
K. pneumoniae (ESBL)	0.5	1	0.03	0.12	< 0.06	0.5	0.06	0.12
P. aeruginosa	1	> 8	0.5	16	> 8	> 8	0.5	8
Bacteroides	0.25	0.5	0.12	0.5	0.25	0.5	0.5	1

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Zhanel GG, *et al*. Drugs 2007;67(7):1027-1052

Pharmacokinetic Parameters

Drug	IV Dose (g)	Cmax (mg/L)	AUC (mg.h/L)	T1/2 (h)	Vd (L/kg)	% Protein Binding	% Excreted Unchanged	Dosing interval
Imipenem	0.5	30-35	42.2	1	0.23-0.31	20	60-70	q8h-q6h
	1	60-70	186					
Meropenem	0.5	26	27.3-32.4	1	0.23-0.35	2	70	q8h-q6h
	1	50-60	66.9-77.5					
Ertapenem	1	154.9	572.1	3.8	8.2	92-95	44	q24h
Doripenem	0.5	20.2	44.1	0.93	16.8L	8.9	75	q8h-q6h

Zhanel GG, *et al*. Drugs 2007;67(7):1027-1052

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Adverse Effects

- Percent overall incidence of adverse events (drug-related adverse events) in clinical practice

Adverse Event	Imipenem (n=1802)	Meropenem (n=5026)	Ertapenem (n=1152)	Doripenem (1338)
Diarrhea	3.1 (1.4)	5.0 (2.3)	9.2 (5.6)	6-12%
Nausea/vomiting	7.4 (3.2)	4.9 (1.4)	10.4 (4.7)	4-12%
Headache	2.9 (0.6)	1.9 (0.4)	6.8 (2.3)	3-16%
Phlebitis	1.6 (1.3)	1.7 (1.1)	1.6 (1.0)	2-8%
Pruritus	1.6 (0.9)	1.0 (0.4)	1.0 (0.5)	1-3%
Rash	2.3 (1.3)	3.3 (1.4)	2.3 (1.1)	1-6%

Zhanel GG, *et al*. Drugs 2007;67(7):1027-1052

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Role in Therapy

- Infection associated with multidrug-resistant gram negative organisms

- Imipenem, meropenem, doripenem
  - Severe nosocomial and polymicrobial infections

- Ertapenem
  - Mild to moderate ESBL infections
  - Outpatient intravenous therapy
  - Not for *Pseudomonas* or *Acinetobacter* associated infections
  - Combine with cefazolin for MSSA?

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Meropenem/vaborbactam

- Approval year: 2017
- Components
  - Meropenem
    - Stable against ESBL, AmpC
  - Vaborbactam
    - Beta-lactamase inhibitor
    - Stable against KPCs
- No increased anti-pseudomonal activity compared to meropenem alone
- **Targeted pathogen: KPC producing organisms**
- **More potent vs. ceftazidime/avibactam against KPCs**

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Meropenem/vaborbactam

Breakpoints			
	S	**I**	**R**
Enterobacteriales	≤4/4	8/4	≥16/4

Meropenem/vaborbactam (1:1)	
Dose	• 4g IV q8h • Infuse over 3 hr
Renal Adj	**eGFR** <50 ml/min

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Imipenem/cilastatin/relebactam

- Approval year: 2019
- Components:
  - Imipenem/cilastatin
    - Carbapenem with DHP-1 inhibitor
  - Relebactam
    - Structurally related to avibactam
- **Targeted pathogen: KPC producing organisms**
- **May be active against carbapenem-resistant *P. aeruginosa***

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Imipenem/cilastatin/relebactam

Breakpoint			
	S	**I**	**R**
Enterobacteriaceae	≤1/4	2/4	≥4/4
P. aeruginosa	≤2/4	4/4	≥8/4

	Imipenem/cilastatin/relebactam
Dose	1.25g IV q6h over 30 min
Renal adj	CrCl <90 ml/min

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Summary of Antibiotic Activities

Activity against...	Ceftazidime/ avibactam	Meropenem/ vaborbactam	Imipenem/ relebactam
KPC	+	+	+
Concerns for on-therapy resistance development	Yes, D179Y mutation in KPC-3	Less likely	Less likely
Gram positive	-	+	+
Anaerobic	-	+	+
Carbapenem-resistant *P. aeruginosa*	+	-	+
OXA-48	+	-	-

Summary of Antibiotic Activities

Antibiotic	ESBL	CRE (KPC)	CRE (MBL)	CR-*Pseudomonas*	MDR *Acinetobacter*
IMI/REL	+	+	-	+/-	-
MER/VAB	+	+	-	-	-
CAZ/AVI	+	+	-	+/-	-
TOL/TAZ	+	-	-	+	-
Eravacycline	+	+	+/-	-	+
Cefiderocol	+	+	+	+	+

IMI/REL: imipenem/relebactam; MER/VAB: meropenem/vabobactam; CAZ/AVI: ceftazidime/avibactam; TOL/TAZ: ceftolozane/tazobactam

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Cost Comparison

Antibiotics	Regimen	Cost Per Day
Ceftazidime/avibactam	2.5g IV q8h	$818.01
Ceftrolozane/tazobactam	1.5g IV q8h	$248.72
Cefiderocol	2g IV 8h	**$1058.8**
Eravacycline	70kg, 70mg IV q12h	$196
Imipenem/relebactam	1.25g IV q6h	$1102.1
Meropenem	500mg IV q6h	$59.35
Meropenem/vabobactam	4g IV q8h	**$989.71**
Polymyxin B	1 million unit IV q12h	$30

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CYCLIC LIPOPEPTIDE

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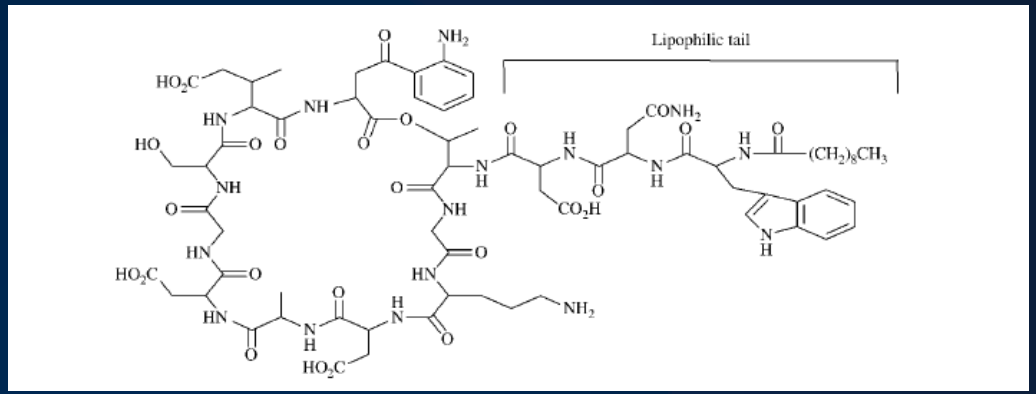
Daptomycin (Cubicin)

- Cyclic lipopeptide
- Bactericidal
- Concentration-dependent
- PD predictor of efficacy
  - AUC/MIC
- Exhibits PAE



Steenbergen JN, *et al*. J Antimicrob Chemother 2005;55:283-288.
Schriever CA, *et al*. Am J Health-Syst Pharm 2005;62:1145-1158.

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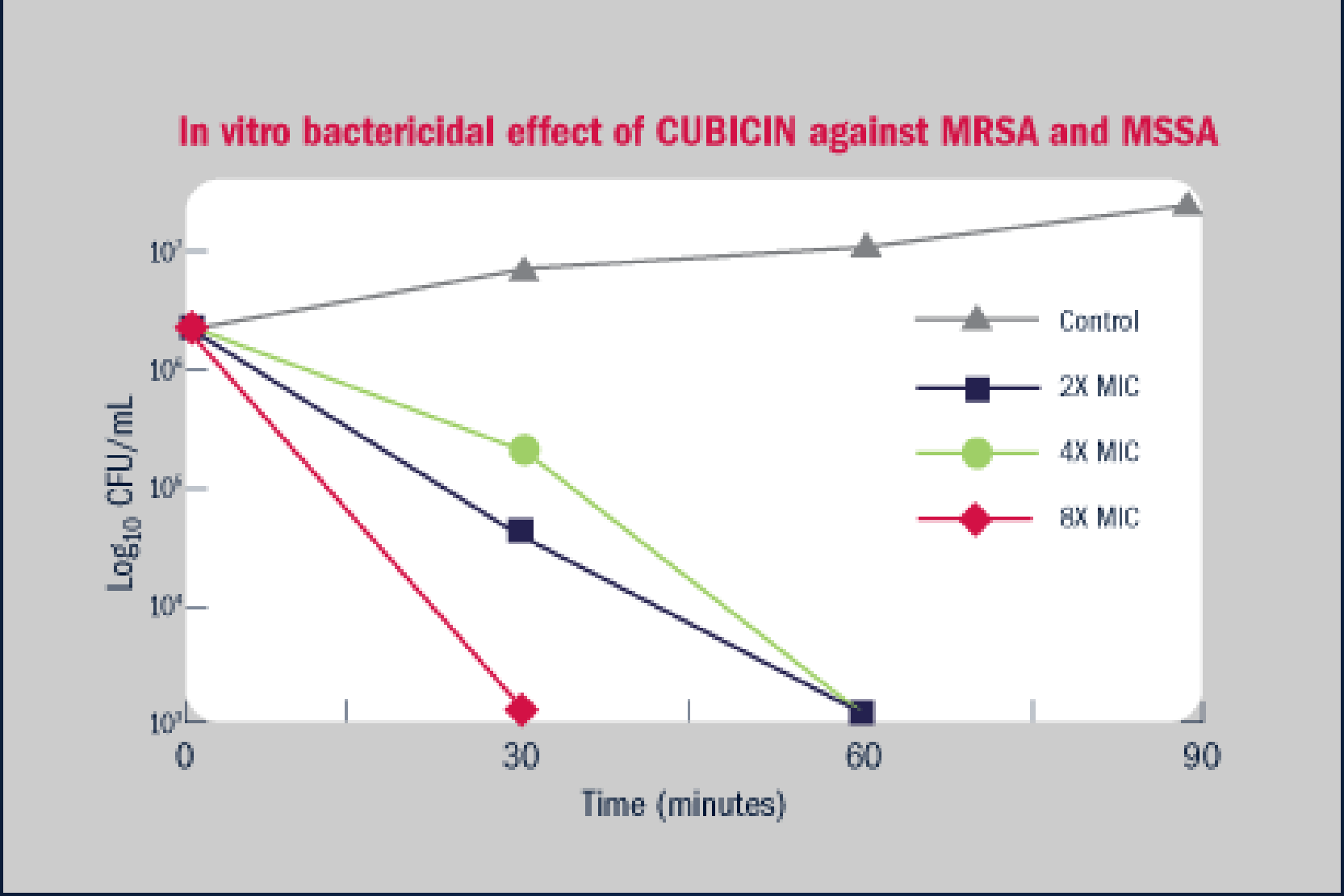
Time-kill Study of Daptomycin Against MRSA



1. CUBICIN® (daptomycin for injection) full prescribing information. Lexington, Mass: Cubist Pharmaceuticals, Inc

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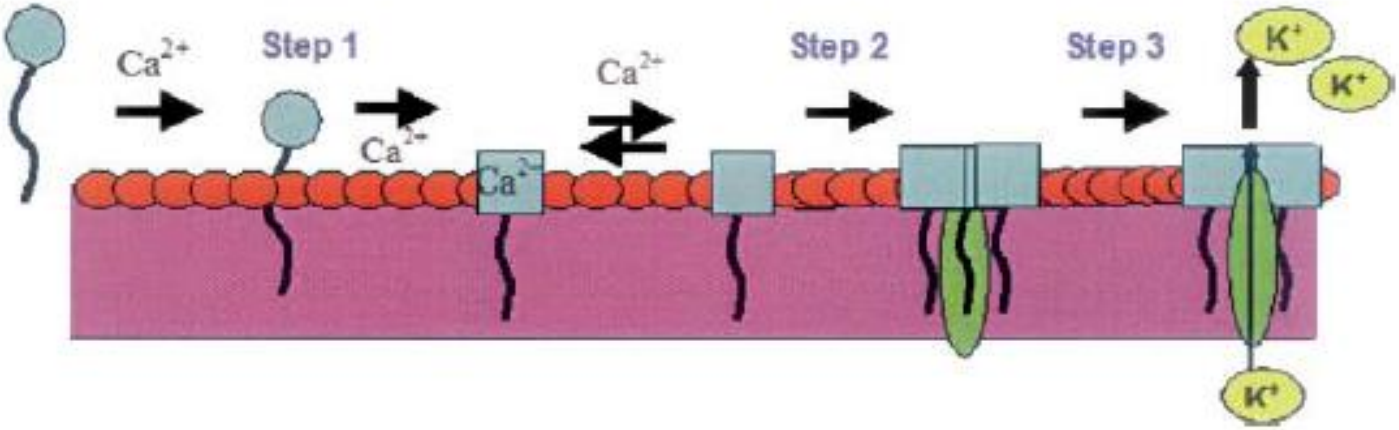
Mechanism of Action



- Binds to the bacterial cell membrane
- Causes rapid depolarization of membrane potential without cell lysis
- Loss of membrane potential leads to inhibition of protein, DNA, RNA synthesis, resulting in bacterial cell lysis

Schriever CA, *et al*. Am J Health-Syst Pharm 2005;62:1145-1158.
Steenbergen JN, *et al*. J Antimicrob Chemother 2005;55:283-288.

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Activity of Selected Antibiotics Against Gram-positive Isolates

Organism	Daptomycin	Oxacillin	Vancomycin	Linezolid	Quinupristin/Dalfopristin
S. aureus			(MIC90 mcg/mL)		
MS	0.13-1.0	0.5	1.0	2.0-4.0	0.25-1.0
MR	0.13-1.0	>8.0	1.0-2.0	2.0-4.0	0.25-1.0
VI	0.5-1.0	NA	8.0	1.0-2.0	NA
IHV	2.0	>8.0	S	S	S
VR	0.5	>64.0	>16.0	NA	NA
E. faecalis					
VS	1.0-2.0	>32.0	2.0-4.0	2.0	8.0
VR	2.0-4.0	>32.0	>64.0	2.0	16.0
E. faecium					
VS	2.0-4.0	>32.0	1.0-2.0	2.0	2.0-4.0
VR	4.0	32.0	>64.0	2.0	1.0-2.0
S. pyogenes	0.06-1.0	NA	0.25-.05	1.0	<0.12
S. agalactiae	0.13-0.25	NA	0.25-0.5	1.0	0.25
Viridan streptococci	0.5-1.0	NA	0.5-1.0	1.0	1.0

MS=methicillin susceptitble, MR=methicillin resistant, VI=intermediate resistant to vancomycin, NA=not assayed, VS=vancomycin susceptible, IHV=intermediate heteroresistance to vancomycin, VR=vancomycin resistant,

Schriever CA, *et al*. *Am J Health-syst Pharm. 2005, 62:1145-1158.*

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Daptomycin Tissue Penetration

Tissue	Species	Maximal Concentrations (% to serum)
Blister fluid	Human	27.6 mcg/mL (68%)
Blood clot-tissue	Rat, Rabbit	3.5 mcg/g (73%)
Peritoneal tissue	Rat	11.8 mcg/mL (35%)
Lung	Mouse, rat	5 mcg/mL (10%)
Bal-ELF	Mouse, rat, sheep	1 mcg/mL (2%)
CSF	Rabbit	5.2 mcg/mL (6%)

Steenbergen JN, *et al*. J Antimicrob Chemother 2005;55:283-288.

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Place in Therapy

- FDA approved indications
  - Complicated infection of skin and/or subcutaneous tissue
  - *S. aureus* bacteremia, including right-sided endocarditis
- Off-label usage
  - Osteomyelitis, septic arthritis, prosthetic joint (+/- bacteremia)
    - Osteomyelitis-63% cure, 19% improved [CORE-Cubicin Outcomes Registry and Experience (CORE) database]
- Do Not use for the treatment of pneumonia!!

Arbeit RD, *et al*. Clin Infect Dis 2004;38:1673-81.
Fouler VG, et al. N Engl J Med 2006;355:654-665.
Lamp K, *et al*. The American Journal of Medicine 2007;120 (10A):S13-S20.

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Safety and Tolerability from cSSTIs Clinical Trial

	No. (%) of patients	
Adverse event	**Daptomycin group (n=534)**	**Comparator group (n=558)***
Nausea	31 (5.8)	53 (9.5)
Headache	29 (5.4)	30 (5.4)
Diarrhea	28 (5.2)	24 (4.3)
Rash	23 (4.3)	21 (3.8)
Vomiting	17 (3.2)	21 (3.8)
Abnormal liver function test results	16 (3.0)	9 (1.6)
Elevated serum CPK level	15 (2.8)	10 (1.8)

*Comparator agents was either vancomycin 1g IV q12h or a
Semisynthetic penicillin (nafcillin, oxacillin, cloxacillin or flucloxacillin) 4-12g/day given in divided doses

Arbeit RD, *et al*. Clin Infect Dis 2004;38:1673-81.

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Dose Recommendation

CrCl	*S. aureus* Bacteremia, Including Right-Sided Endocarditis[1]	Complicated Skin Infections[1]	Enterococcal/persistent MRSA bacteremia[2, 3, 4,]
>30 ml/min	6 mg/kg IV daily	4 mg/kg IV daily	8mg/kg, 10mg/kg……
< 30 ml/min including HD/PD	6 mg/kg IV q48h	4 mg/kg IV q48h	

1. Daptomycin package insert.
2. Moise PA, *et a*l. Ann Pharmacother 2009;43:1211-1219.
3. Kullar R, *et a*l. Pharmacotherapy 2011;31(6):527-536.
4. Casapao AM, *et al*. Antimicrob Agent and Chemother 2013;57(9):4190-4196.

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CLSI Breakpoint Changes for 2019

Enterococcus	Old	New
Daptomycin	S: ≤ 4	S: ≤ 1
	Non-susceptible: > 4	SDD: 2-4
		R: ≥ 8

- S (susceptible): **6mg/kg**
- SDD (susceptible-dose-dependent) or persistent bacteremia: **8-12mg/kg**
- **Dose based on actual body wt (morbidly obese patient: adjusted wt)**

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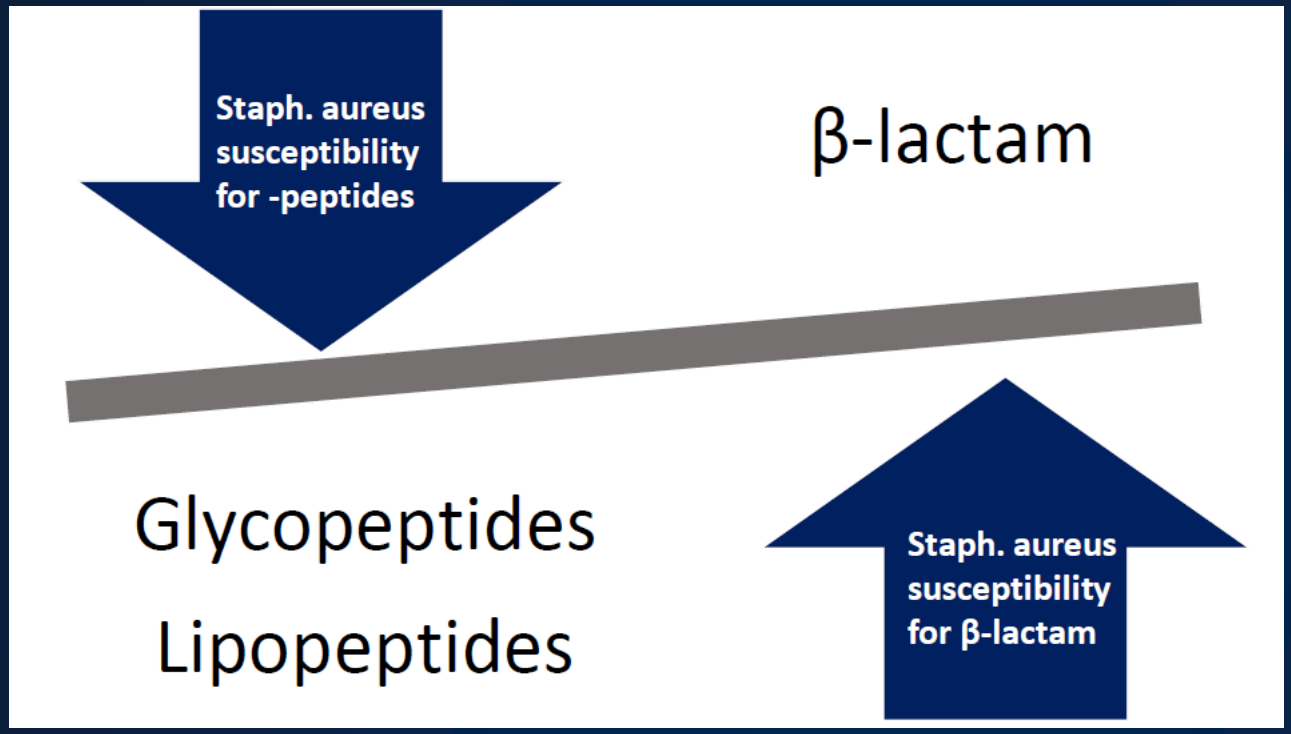
Combination Therapy with Daptomycin and β-lactam antibiotics



- **High Dose Daptomycin Combination with β-lactam:**
  - **Greater bactericidal activity**
  - **Avoid development of resistance**
  - **"See-Saw Effect"-enhance binding of daptomycin to cell wall**

Macrocyclic Antibiotic

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Fidaxomicin: Dificid's® Difficult Path

- First new therapy approved for CDI in decades at time of approval
- Macrocyclic antibiotic
- Highly active in vitro against *C. difficile* (MIC_{90} 0.125 mcg/ml)
- Desirable properties as an anti-CDI agent
  - Minimal systemic absorption (<5 ng/ml)
  - More limited effects on other colonic flora vs. vancomycin or metronidazole
- Similar cure rates vs vancomycin with lower recurrence rates
- Cost and limited data initially made place in therapy more difficult

Clin Infect Dis 2012;55(Suppl 2):S132 – S142
Clin Infect Dis 2012;55(Suppl 2):S121 – S126

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Strengths and Limitations by Agent

	Metronidazole	Oral Vancomycin	Fidaxomicin
Systemic Absorption	↑	↓	↓
Intracolonic Levels	↓	↑	↑
Ability to disrupt gut flora	↑	↑	↓
Collateral Damage	±	±	↔
Side Effects	±	±	±
Relative Cost	$	$ - $$	$$$
Rate of Recurrence	Both with 20 – 30% recurrence rate		↓ in non-NAP1 ribotypes

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	CDI Treatment Guideline (Inpatient)	
Initial Episode	**Vancomycin** 125mg po q6h x 10 days	**OR** **Fidaxomicin** 200mg po q12h x 10 days for patients meeting one of the following criteria: • Age ≥ 65 years <u>with</u> WBC ≥15,000 cells/mL *or* significant acute renal impairment • Solid organ or bone marrow transplant • Currently receiving or received chemotherapy or immune modulating agent within past 30 days • HIV with CD4 <u>≤</u>200 • Cirrhosis
	Metronidazole 500mg po q8h x 10-14 days if above agents are unavailable	
First CDI Recurrence	**Vancomycin** 125mg po q6h x 10 days	**OR** **Fidaxomicin** 200mg po q12h x 10 days ***or*** 200mg po q12h x 5 days followed by 200mg q48h x 20 days for patients meeting one of the following criteria: • Age ≥ 65 years • Solid organ or bone marrow transplant • Currently receiving or received chemotherapy or immune modulating agent within past 30 days • HIV with CD4 <u>≤</u>200 • Cirrhosis
Multiple CDI Recurrences	**Vancomycin taper:** 125mg po q6h x 10 days followed by tapering over 6 weeks: Week 1: 125mg po q8h Week 2: 125mg po q12h Week 3: 125mg po q24h Week 4: 125mg po q48h Weeks 5, 6: 125mg po every 3 days	**OR** **Fidaxomicin** 200mg po q12h x 10 days ***or*** 200mg po q12h x 5 days, then followed by q48h x 10 doses (20 days)
	Obtain ID or GI consult, consider fecal microbiota transplantation (FMT). FMT offers highest chance of cure compared to other available treatments.	
Fulminant CDI *(hypotension, shock, ileus, or mega-colon)*	***Vancomycin*** 500 mg po/NG/PEG q6h (duration as per ID consult) **If ileus or reduced gut motility due to shock:** **Add** metronidazole 500 mg *IV* q8h +/-vancomycin 500mg q6h in 100ml NS via rectal tube, clamp rectal tube for 1 hour **Obtain STAT Surgical and ID consults. Avoid fidaxomicin alone or combination with other agents**	

Use antibiotics wisely,
don't make superbug!!
Save antibiotics for future
generations to come!!!

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