<u>Module 14: Infectious Diseases Principles of ID, Pharm of selected Antibiotics Part 1</u>

Pharmacology of Antimicrobial Agents: General Treatment Principles

Objectives for Section

- Understand mechanisms of action of antimicrobial agents
- Describe MOST COMMON side effects of these agents
- Describe clinically important drug interactions that clinicians must be aware of
- List antimicrobial agents active against common pathogens and incorporate into treatment decisions
    - Empiric treatment and targeted therapy
- Describe common mechanisms of resistance in various microorganisms
    - Most importantly → incorporate this into therapeutic decisions!

A Plan of Attack for Learning Antimicrobials

- Learn categories into which organisms fit
    - Gram (-), Gram (+), "anaerobes"
- Pay attention to differences in "generations" of antimicrobials and why they were developed
- Bug-drug tables can be your friends
    - For each bug list important stats (i.e., Gram (+), seen in CAP, drug of choice is amoxicillin, etc.)
    - For each drug list important stats as well
- For each antimicrobial discussed
    - Class
    - Mechanism of Action
    - Spectrum of Activity
    - Broad (Gram + vs. Gram -) and specific (MRSA vs MSSA)
    - Important pharmacological Facts
    - e.g., Poor oral absorption, renal elimination
    - Major side effects and drug interactions

Major Clinically Important Bacteria

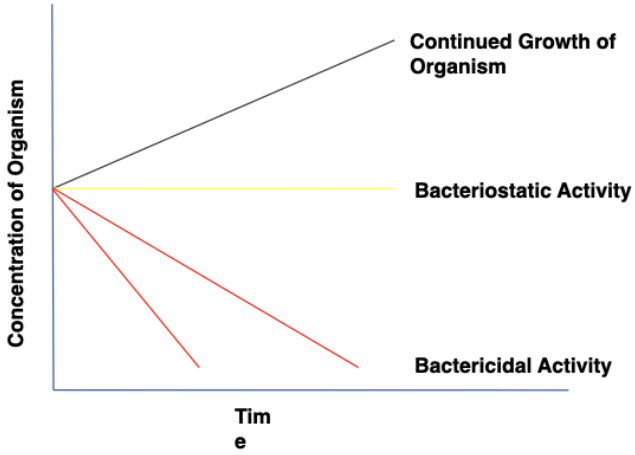
- Gram (+)
    - *Streptococcus spp.; S. aureus; Enterococcus spp.*
- Gram (-)
    - Enteric Gram-negatives (*Proteus spp., E.coli, K.pneumoniae*)
    - The "nasty" Gram-negatives (*P.aeruginosa, A.baumannii*)
    - Other nosocomial Gram negatives: Enterobacter, Citrobacter, and Serratia
- Anaerobes
- Common respiratory organisms (we'll get there!)
- *C.difficile*

Antimicrobial Terminology

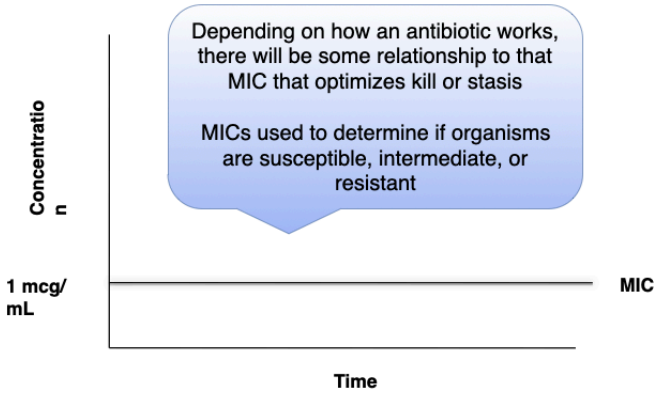
- Empiric vs. Definitive Therapy
    - Empiric → therapy before causative organism known; based off common pathogens
    - Definitive → once cultures and sensitivities back
- Bactericidal vs. Bacteriostatic
    - When exposed to antibiotic the number of bacteria decrease (cidal) or stay the same (static)
- Synergy
    - 1 + 1 = more than 2; or 1 + 0 = more than 1
    - Sports analogy: the team is better than the sum of its parts!
- Pharmacokinetics

    - “What the body does to the drug”
    - Absorption, distribution, metabolism, excretion
- Pharmacodynamics
    - “What the drug does to the body”
        - In the case of antimicrobials- to the bug at the site of action
    - Concentration-dependent or time-dependent killing
- Minimum inhibitory concentration (MIC)
    - The lowest concentration of the antimicrobial that inhibits growth (bacteriostatic effect) in the test tube

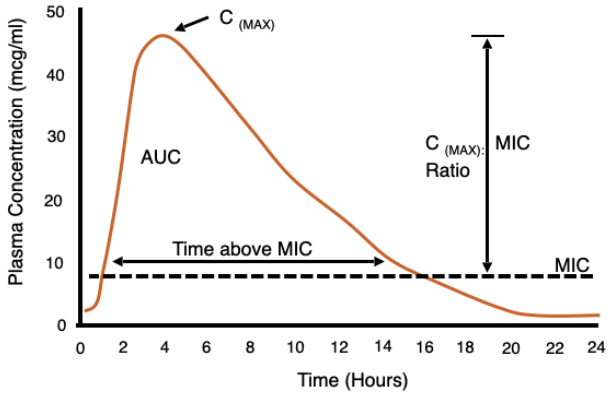
Bactericidal vs. Bacteriostatic



Minimum Inhibitory Concentration (MIC)



PK/PD Targets Associated with Efficacy



PK/PD Targets Associated with Efficacy

- T>MIC
  - B-lactams
  - Macrolides
  - Oxazolidinones
- AUC/MIC
  - Vancomycin
  - Fluoroquinolones
  - Tetracyclines
- Cmax/MIC
  - Aminoglycosides

Antimicrobial Susceptibility

- Susceptible
  - PK/PD targets are achievable, and you would expect common doses of the antimicrobial to lead to clinical success
- Intermediate
  - MICs are elevated for the organism toward the antimicrobial in question
  - One MIGHT see clinical success with dose-optimization strategies
- Resistant
  - PK/PD targets not obtainable- would not expect clinical success with the agent

Dose Optimization Strategies

- T > MIC
  - Extended or continuous infusions
- AUC/MIC
  - Optimize daily dose
- Cmax/MIC
  - High dose, extended interval dosing

Example: Susceptibility Profile

P. aeruginosa	MIC	Interpretation
Ceftazadime	32	R
Cefepime	2	S
Piperacillin/Tazobactam	32	I
Meropenem	0.5	S
Ciprofloxacin	2	R
Tobramycin	8	I
Amikacin	4	S

Steps for Selecting Antimicrobials

1. Have a working diagnosis
2. Know common pathogens for the expected infection
3. Also, patient specific factors (allergies, previous antibiotic exposure, end-organ disease, h/o drug-resistant pathogens
4. Obtain appropriate diagnostic information (including cultures)
5. Start empiric antimicrobials targeting most likely pathogens
6. Await diagnostics
7. Streamline therapy based off of culture information

Potential Resources

- Book version
    - Antibiotics Simplified (Gallagher and MacDougall)
        - There is an App for this now!!!
- Online version
    - www.idstewardship.com

Antimicrobial Stewardship

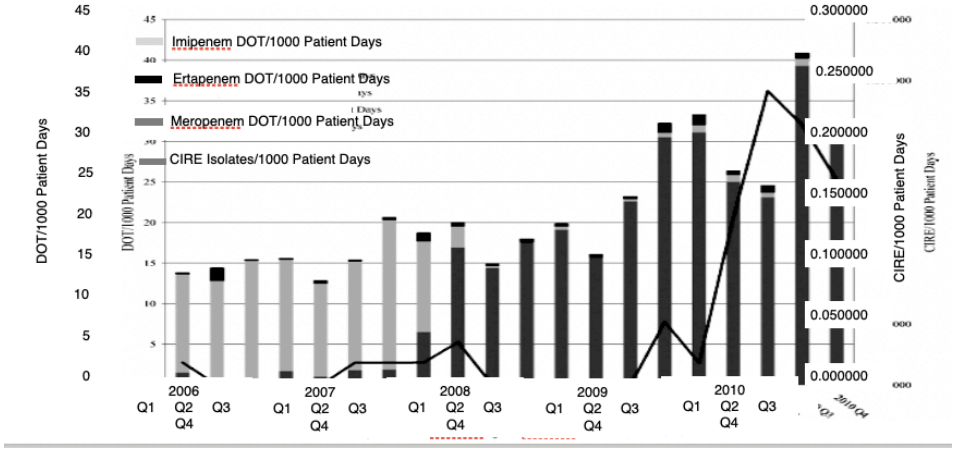
Antimicrobial Stewardship

- Optimize clinical outcomes of patients with infectious diseases
    - Optimize appropriate use of antimicrobials
        - Selection, dose, route, duration
- Minimize unintended consequences of antimicrobial use
    - Toxicity
    - Emergence of resistant pathogens
        - MRSA, VRE, MDR A. baumannii, P. aeruginosa
    - Selection of superinfections
        - C. difficile, candida spp.
    - Reduce antimicrobial expenditure

How Antibiotic Resistance Happens

1. There are lots of germs and a few are resistant to antibiotics.
2. When antibiotics kill bacteria causing illness, they also kill good bacteria protecting the body from infection.
3. The antibiotics-resistant bacteria grow and take over.
4. Some bacteria give their antibiotics resistance to other bacteria, causing more problems.

Carbapenem Usage and CRE



Impact of Previous Antibiotic Use on Resistance

Independent impact of any antibiotic exposure in the previous 90 days

	CRE vs. uninfected	ESBL vs. uninfected	CRE vs. ESBL	CRE vs. susceptible	CRE vs. all controls combined
Odds ratio (95% CI)	11.4 (2-64.3)	1.7 (0.7 – 4.1)	5.2 (1.4 – 19.4)	12.3 (3.3 – 45)	7.1 (1.9 – 25.8)

Every Antibiotic Counts….

	CIRE vs. CSE (n = 102)		CIRE vs. uninfected controls (n = 85)	
Number of antibiotic exposures	**Odds Ratio**	**95% CI**	**Odds Ratio**	**95% CI**
0	1	---	1	---
1	1.43	1.19 – 1.72	1.36	1.06 – 1.77
2	2.05	1.70 – 2.47	1.88	1.45 – 2.43
≥ 3	2.93	2.43 – 3.53	2.58	2.00 – 3.33

CIRE = Carbapenem intermeidate or resistant enterobacteriaceae;
CSE = Carbapenem susceptible enterobacteriaceae

And Every Day as Well….

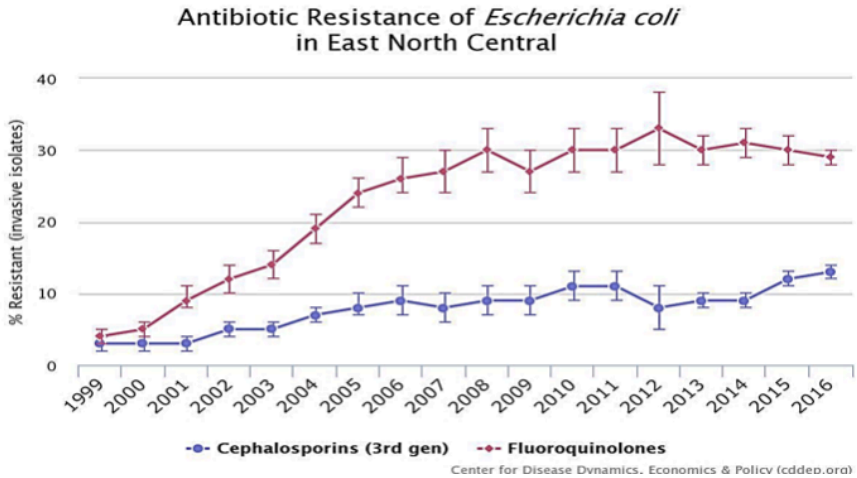
Antibiotic Exposures			Univariable Analysis		Multivariable Analysis
	Case patients (n=104)	Control subjects (n=104)	OR (95% CI)	P	OR (95% CI)
Receipt of any antibiotic	96 (92)	71 (68)	7.25 (2.55-20.62)	<.001	….
Days of antibiotic therapy	53.9 ± 52.4	14.4 ± 30.5	1.03 (1.02-1.05)	<.001	1.04 (1.01-1.06)

Impact of Antibiotic Resistance

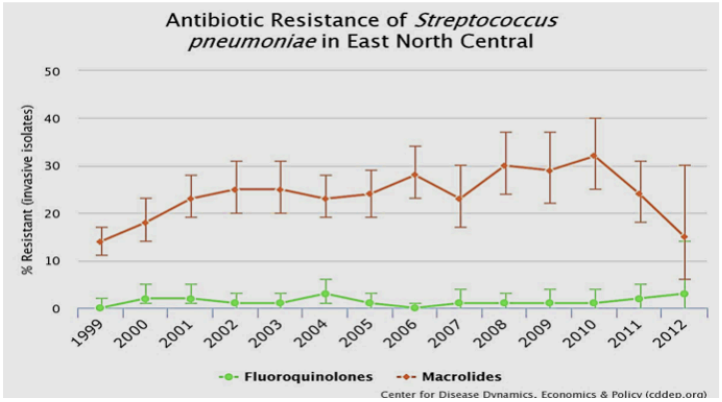
Infection	Increased Risk of Mortality (OR)	Attributable Length of Stay (days)	Attributable Cost ($)
MRSA bacteremia	1.9	2.2	6,916
MRSA surgical infection	3.4	2.6	13,901
VRE infection	2.1	6.2	12,766
Resistant Pseudomonas	3.0	5.7	11,981
Resistant Enterobacter	5.0	9	29,379

Total cost of antimicrobial resistance is estimated to be $30 billion annually

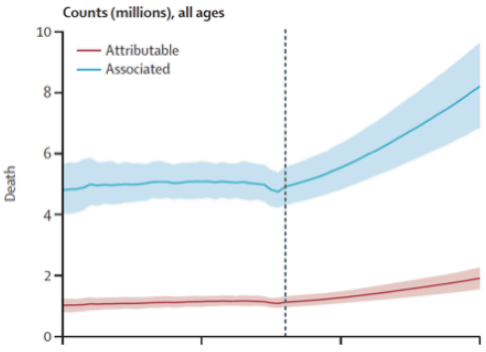
And Rates Are Increasing!



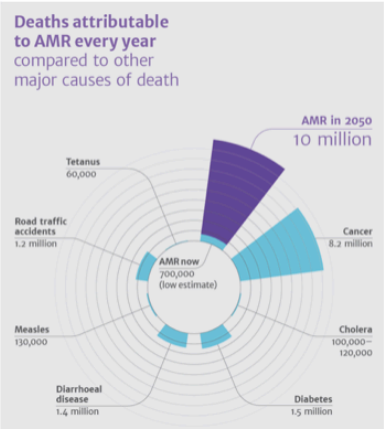
In The Community as Well…..



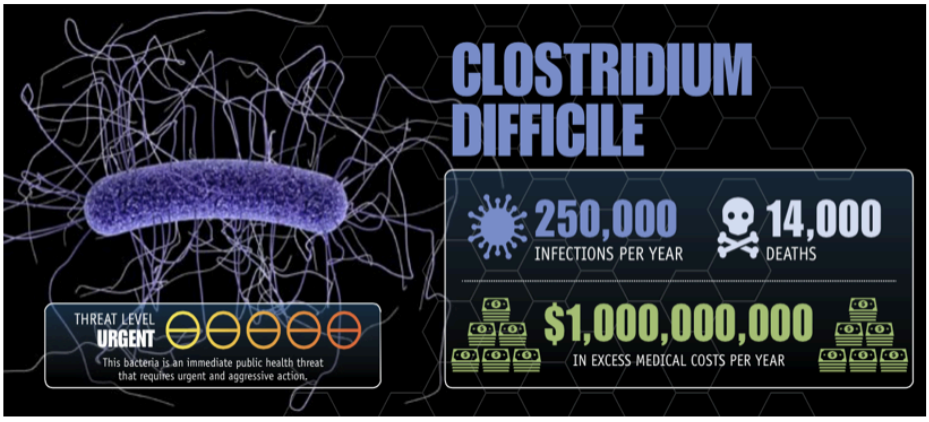
What Our Future Could Look Like



Lancet 2024; 404:1199-226



And Don't Forget About…..



Antibiotic Use and *C.difficile*

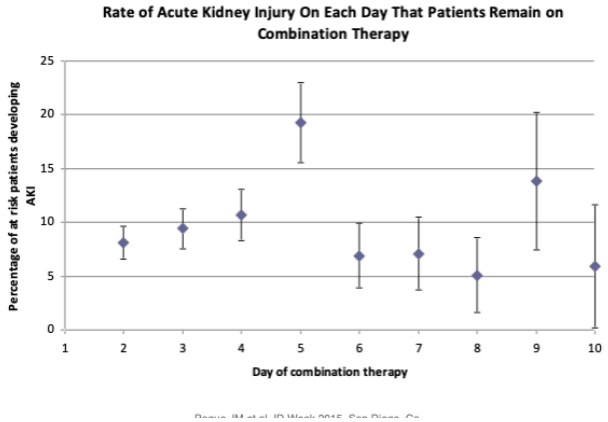
Antibiotic class	Odds Ratio	95% Confidence Interval
3rd gen cephalosporins	3.20	1.80 - 5.71
Clindamycin	2.86	2.04 – 4.02
2nd gen cephalosporins	2.23	1.47 – 3.37
Cefepime	2.14	1.47 – 3.52
Carbapenems	1.84	1.26 – 2.68
TMP-SMX	1.78	1.04 – 3.05
FQ's	1.66	1.17 – 2.35
BLBLIs	1.45	1.05 – 2.02

J. Antimicrob. Chemother. (2014) 69 (4): 881-891.
J. Antimicrob. Chemother. (2014) 69 (7): 1748-1754.

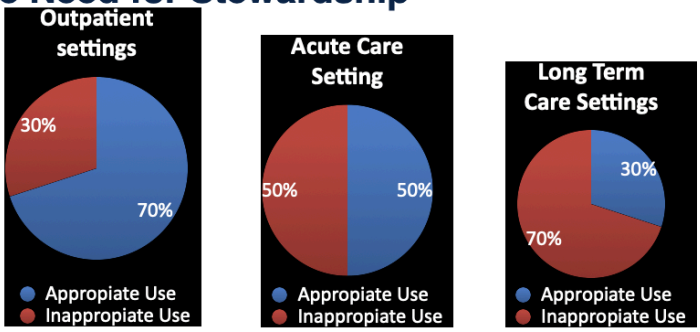
In a meta-analysis of 16 articles looking at impact of antimicrobial stewardship programs on incidence of *C difficile*…..

Risk Ratio 0.48 (0.38 – 0.62)

It Isn't Just About Resistance



The Need for Stewardship



Putting this into practice: Always Remember our Mission

- Optimize clinical outcomes of patients with infectious diseases
- Minimize unintended consequences of antimicrobial use

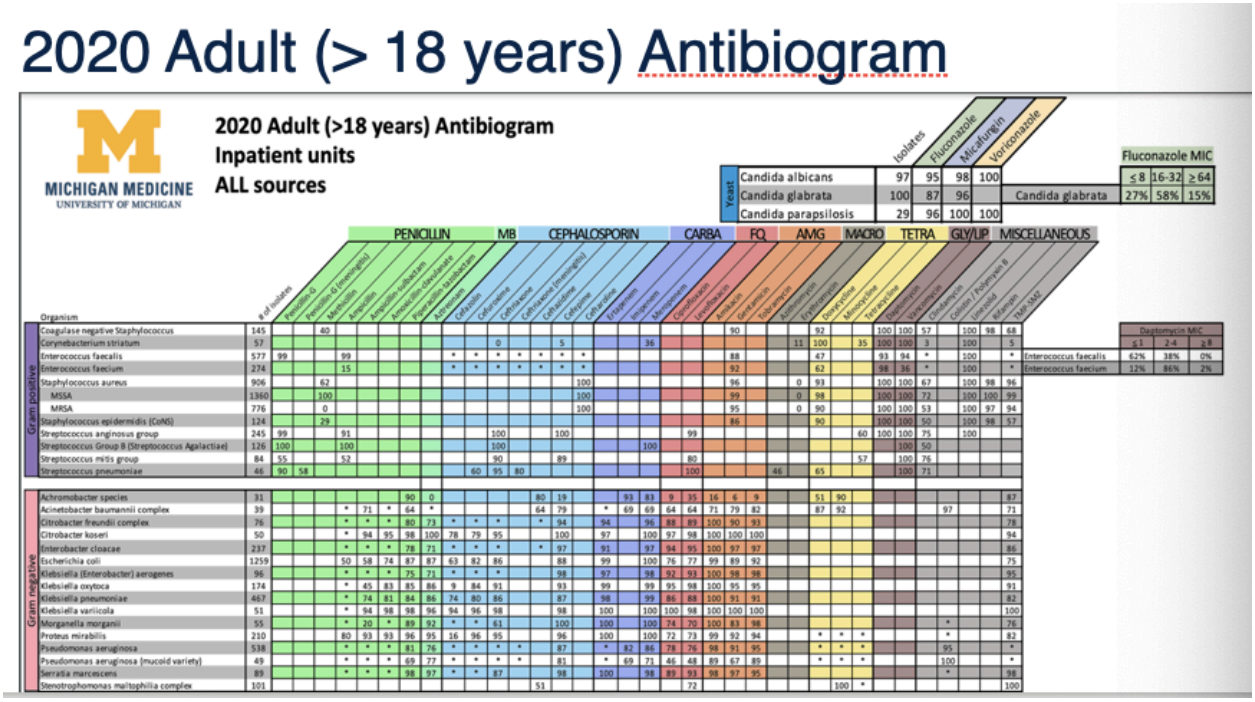
Improving Outcomes: Always Primary Goal

- Decreasing time to appropriate therapy is one of the most important modifiable risk factors for mortality in infected patients
- The sicker the patient is, the more important it is to get them on active therapy ASAP
- Appropriate therapy is good, optimal therapy is better!

Empiric Therapy Guidelines will be Institution Specific (But should be similar)

- For every disease there are certain organisms that are most likely pathogen
- Antibiograms describe local susceptibilities of those pathogens
- Empiric therapy guidelines will incorporate local susceptibility, disease severity, and formulary considerations
- Do NOT neglect patient specific factors

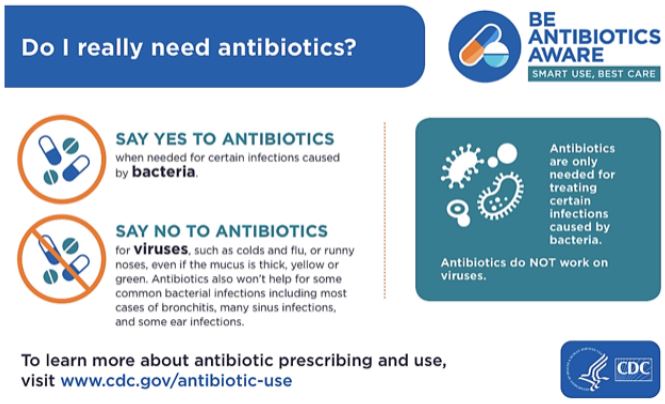
2020 Adult (> 18 years) Antibiogram



Balancing Appropriateness And Overuse

Hospital-Acquired and Ventilator Associated Pneumonia (HAP and VAP)			
	Recommended	Recent Piperacillin-tazobactam or Cefepime Exposure within 90 Days (>/= to 48-72 hours)	Anaphylactic reactions to β-lactam (i.e., hives, angioedema)
HAP in floor patient admitted ≥ 48 hours	Cefepime* 2gm IV every 8 hours plus vancomycin* IV PTD	Meropenem* 1gm IV every 6 hours plus vancomycin* IV PTD	Aztreonam* 2gm IV every 8 hours* plus vancomycin* IV PTD
VAP or HAP in ICU patient admitted ≥ 48 hours	Cefepime* 2gm IV every 8 hours plus vancomycin* IV PTD plus tobramycin* IV PTD	Meropenem* 1gm IV every 6 hours plus vancomycin* IV PTD plus tobramycin* IV PTD	Aztreonam* 2gm IV every 8 hours* plus vancomycin* IV PTD plus tobramycin* IV PTD

Part Two: Limiting Unnecessary Use



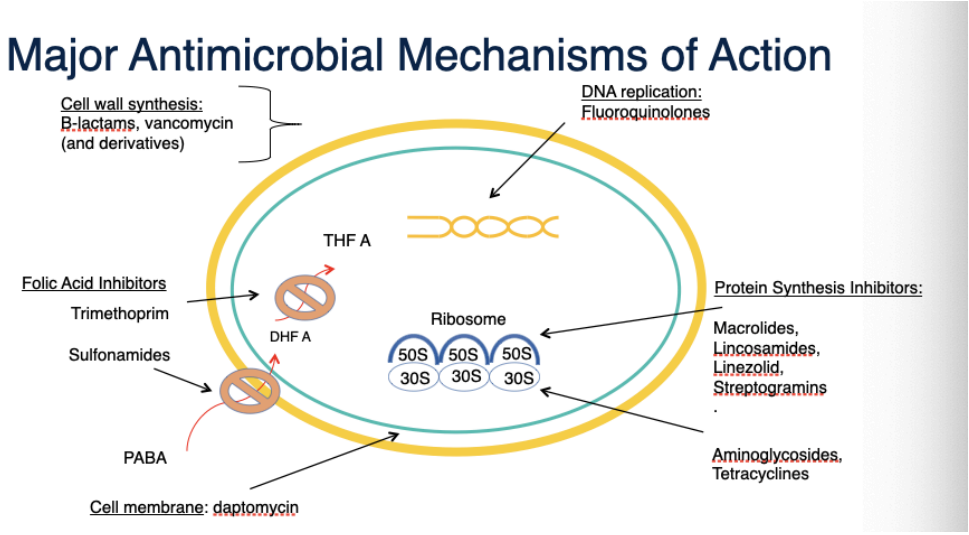
Asymptomatic Bacteriuria

- The number one cause of inappropriate antimicrobial usage in the hospital
- Refers to a positive urine culture in the absence of symptoms
    - Altered mental status alone is not diagnostic for UTI
    - Pyuria represents non-specific inflammation of the genitourinary tract and occurs in many patients with indwelling urinary catheters (and others)
- Pyuria accompanying asymptomatic bacteriuria is NOT an indication for treatment
- Asymptomatic bacteriuria should only be treated when it has a benefit for the patient
    - Pregnancy, Undergoing urological procedure (TURP)
- Treatment of asymptomatic bacteriuria
    - Does NOT improve patient outcomes
    - Is associated with increases in adverse events, C. difficile infection, development of antimicrobial resistance, and INCREASES in recurrent urinary tract infections

Other Key Stewardship Interventions

- Limit broad spectrum antibiotic use
    - De-escalation
- Duration of therapy
    - “Shorter is better”
- Dose optimization and TDM

Beta-lactams: Penicillins

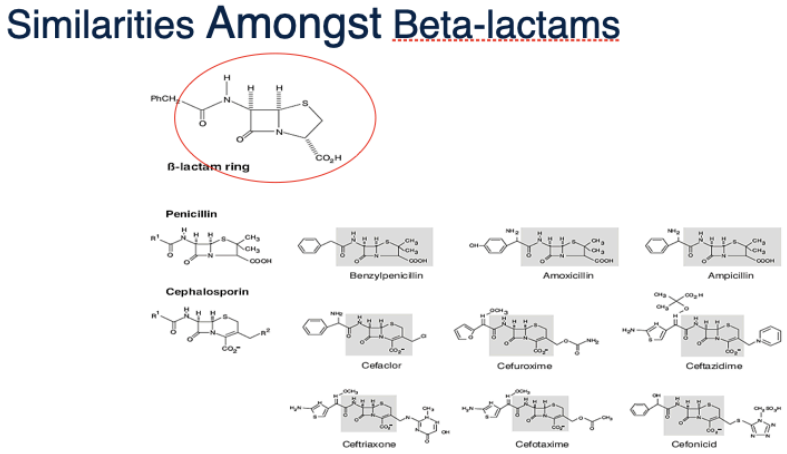


Major Mechanisms of Antimicrobial Resistance

- Antimicrobial modifying enzymes
    - B-lactamases
- Target site alterations
    - Penicillin Binding Protein alterations
- Decreased concentrations in cell
    - Efflux Pumps
    - Outer membrane Porin Down-regulation

Beta-lactams

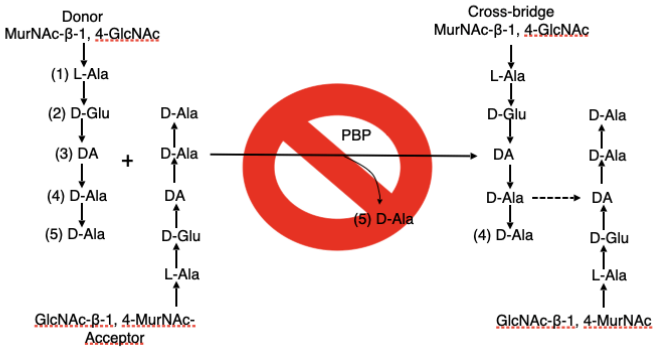
- Most used antimicrobial class
    - First line for a variety of infections, particularly in the hospital setting
- First available in the 1940's with the introduction of penicillin
- Several different classes and generations with a similar structure and mechanism of action
    - Penicillins, Cephalosporins, Carbapenems, Monobactams



- Mechanism of action
    - Inhibition of final step of cell wall synthesis
    - Block the cross-linking of the peptidoglycan

        - Cross-linking essential for structural integrity of the cell
    - The enzymes that carry this process (transpeptidation) out are called penicillin-binding proteins (PBPs)
- Easy to remember: Penicillins (and all beta-lactams) bind to PBPs and block transpeptidation
    - Not lethal itself, but starts a process that will lead to rapid cell death

Beta-lactams MOA



- Bactericidal
- Time-dependent antimicrobials
    - Optimize time concentrations are above the MIC
        - Extended or continuous infusions
- Most well-studied and relatively non-toxic agents
    - Most indications we use these agents if we can
- Caveat: We will go over clinically relevant indications for each agent, however, de-escalating based on culture results to the narrowest spectrum of these agents with activity is also appropriate (and encouraged!)

Penicillin

- Spectrum of activity
    - Streptococci
        - *S. pyogenes, S. viridans, S. pneumoniae*
    - Enterococci
        - *E. faecalis*
    - *Treponema pallidum*
    - Mouth anaerobes
        - Varying activity due to presence of B-lactamases

Benzathine Penicillin

- A long-acting depot preparation
- Must be given IM
    - Causes a slow steady release of the drug
    - Gives a low-level concentration for a long period of time
- Only appropriate for organisms the are very susceptible (very low MIC values)
    - Syphilis

The Bacteria QUICKLY Strike Back: The B-lactamase

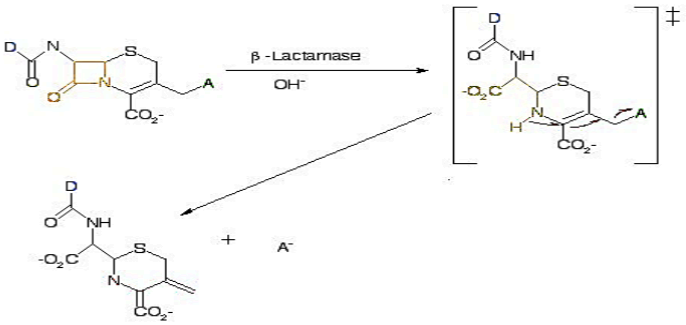


Figure 1. The β-lactamase enzyme reacting with the substrate, hydrolyzing the cephalosporin ring (in orange), and generating an intermediate structure (in brackets). The intermediate structure then rearranges to products where the donor and acceptor are separated. Adapted from Ziokarnik *et al.*, 1998.

Beta-lactamases

- Enzymes which are secreted by the organism that hydrolyze beta-lactam antibiotics
    - Literally thousands of different enzymes identified
    - Penicillinases, cephalosporinases, carbapenemases
    - Most do not hydrolyze all beta-lactams….but some do!
- Most common mechanism of beta-lactam resistance in Gram–negative bacilli
    - Less common in Gram-positive organisms

S. aureus and Penicillin

- Initially penicillin was the drug of choice (DOC) for S. aureus
- Even prior to the introduction of penicillin on to the market, Staph created a penicillinase
- Today- a relative rarity to see penicillin-susceptible S aureus (PSSA)
    - 20-30% of isolates

Penicillin: Still has Utility to this Date!

- Syphilis
    - DOC for all stages, great efficacy, resistance not seen
- Necrotizing fasciitis
    - *S. pyogenes*
- Dental coverage
- Definitive therapy for many streptococcal infections
    - Endocarditis, pneumonia, amongst others

The Empire Strikes Back: Penicillinase–Resistanct Penicillins

- Nafcillin, Methicillin, Oxacillin, Dicloxacillin
- “Antistaphylococcal penicillins”
    - Designed to overcome penicillinase
    - Most common utilized: Nafcillin or Oxacillin
    - Methicillin not clinically used, BUT important for nomenclature
        - MSSA or MRSA
- Treatment of MSSA, also has streptococcal activity
    - Lacks Gram (-), enterococcus, anaerobic activity

Staph gets the last laugh: PBP Alterations

- Recall that PBPs are the binding site for B-lactams
- PBPs with decreased affinity for B-lactams can occur
    - In *S. aureus* this is a PBP2 → PBP2A alteration

    - This PBP can carry out transpeptidation even in presence of beta-lactams
    - MRSA (Methicillin RESISTANT)
- Confers resistance to all** b-lactams
- Treatment options to be discussed later

Aminopenicillins

- **Am**picillin (IV) and **Am**oxicillin (PO)
- Spectrum of importance: HELPS bugs
    - **H**. influenzae
    - **E**. faecalis
    - **L**. monocytogenes
    - **P**. mirabilis
    - **S**almonella and **S**higella
        - Penicillin susceptible **s**treptococci as well
- Clinical Presentation
    - Enterococcal infections
        - Only bacteriostatic against *e. faecalis*, limited activity against *e. Faecium*
        - For life-threatening, deep-seeded enterococcal infections (e.g., endocarditis, osteomyelitis) used in combination with either ceftriaxone or gentamicin for synergy
    - Meningitis
        - High dose ampicillin added when concerned for listeria
    - Streptococcal infections
    - Respiratory tract infections
    - B-lactamases can limit the widespread utility

Piperacillin

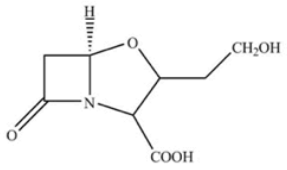
- Expands the coverage of ampicillin to include *P. aeruginosa*
- Clinical pearl 1
    - If enterococcus in susceptible to ampicillin, it is also susceptible to piperacillin
- Clinical pearl 2
    - Piperacillin/tazobactam (will discuss shortly) offers no advantage over piperacillin for *P. aeruginosa*
- Not commercially available by itself in the US any longer

Penicillins Activity Against Gram (-) Organisms and Anaerobes

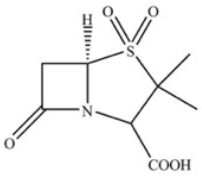
- Despite numerous modifications, penicillins are very susceptible to b-lactamase mediated hydrolysis by many aerobic Gram (-) organisms and anaerobes
    - This makes empiric therapy impractical in many disease states
- So, remember….. we needed to come up with a way to get around **b-lactamases** produced by **Gram (-) bacilli** and **anaerobes**

The Solution: Penicillin/Beta-lactamase inhibitor (BLI) Combinations

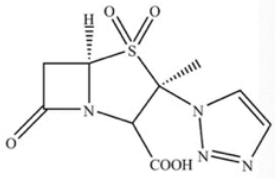
Our Heroes



Clavulanic Acid



Sulbactam



Tazobactam

- The Products
    - Amoxicillin/Clavulanic Acid (Augmentin) – PO
    - Ampicillin/sulbactam (Unasyn) – IV
    - Piperacillin/Tazobactam (Zosyn) – IV
    - In general – what the BLI bring to the table
        - Greater Gram (-) and anaerobic activity
        - MSSA
- Where do these agents fit in?
    - Amoxicillin/Clavulanic Acid and Ampicillin/Sulbactam
        - Empiric regimens for broad coverage in community-based infections
            - Caution: Increased resistance in Gram (-) to ampicillin/sulbactam
        - Good option for respiratory tract infections
            - Sinus, otitis, oral infections when treated with antibiotics
        - Can be an option for skin infections when MRSA is not a concern
        - Sulbactam and Acinetobacter infections
            - Sulbactam/Durlobactam
    - Piperacillin/tazobactam
        - Empiric, broad spectrum therapy for nosocomial infections

Penicillins: Common Adverse Events

- Allergic reactions
    - Can range from mild rash to anaphylaxis
    - NOT related to beta-lactam ring, but rather side chains important distinction when discussing “cross-reactivity” with other beta-lactams
- Acute interstitial nephritis
    - Can be seen with all agents, most common with methicillin class
        - Long term use of penicillinase resistant penicillins associated with high rates of acute kidney injury
- Bone marrow suppression
    - Rare (thrombocytopenia, neutropenia) can be seen with long courses

A Word About Drug Allergies

Type	Manifestations	Timing
Type I (IgE mediated)	Anaphylaxis, urticaria, angioedema, bronchospasm	Minutes to hours after exposure
Type II (cytotoxic)	Anemia, thrombocytopenia, leukopenia	Variable
Type III (immune complex)	Serum sickness, vasculitis, fever, rash, arthralgia	1 – 3 weeks after exposure
Type IV (delayed, cell mediated)	Contact sensitivity, maculopapular skin rashes, Can be more serious: SJS/TEN	2 - 7 days after drug exposure

- Seizures
    - Concern only when high doses/non renally adjusted doses given
- Gastrointestinal
    - Particularly with clavulanic acid!

Penicillins: Drug Interactions

- Minimal
- Probenecid
    - Gout medication, can block renal secretion and prolong half-life
- Nafcillin is a CYP3A4 inducer
    - Warfarin, Calcium Channel Blockers, Calcineurin inhibitors
- Vancomycin + Piperacillin/tazobactam
    - Increases AKI with vancomycin (unknown mechanism)

Anti-pseudomonal Drugs

- Piperacillin
- Piperacillin/tazobactam

Cephalosporins

An Overview

- Structurally similar to the penicillins and share the same MOA
- Listed in generations – which is great for learning and studying purposes
    - Novel cephalosporin +/- BLI combinations do NOT fit cleanly in the generation evolution and need to be thought of outside of that
- Clinical pearl: Despite good Gram (+) coverage, the entire class lacks reliable enterococcal activity
- Similar ADE profile to penicillins with a few notable exceptions

1st Generation Cephalosporins

- **Cephalexin (PO), Cefazolin (IV), Cefadroxil (PO)**
- Gram (+) activity
    - Good versus staphylococcus (MSSA) – emerging Drug of Choice (DOC)
    - Good versus most streptococcus (variable against pneumococcus)
    - Makes for nice skin coverage if MRSA not a concern
- Gram (-) activity
    - Generally poor
    - Has activity against “PEK” organisms – maybe
        - Proteus, *E. coli, K. pneumoniae*
        - Unreliable empirically for Gram (-) (but good de-escalation agent!)

        - More likely to be active against community isolates, appropriate empirically for mild-moderate UTI
- Anaerobic
    - Lacks clinically significant anaerobic activity

2nd Generation Cephalosporins

- Cefaclor, cefuroxime ("respiratory second generation")
    - Gram (+) improved S. pneumoniae
    - Gram (-) a little better
        - Enhanced activity against *H. influenzae, M. catarrhalis*
        - No anaerobic or *P. aeruginosa* activity
    - Clinical utility: respiratory tract infections
- Cefotetan, cefoxitin ("GI 2nd generation" or cephamycins)
    - Same as above except addition of **good anaerobic activity**
    - Major use: Community acquired intraabdominal infections or surgical prophylaxis

Cephalosporins: Spectrum of Activity

Generation	1st	2nd (resp)	2nd (GI)
Gram (+)	Good	Good	Good
Gram (-)	Weak	Better	Better
P. aeruginosa	None	None	None
Anaerobes	None	None	Good

3rd Generation

- **Ceftriaxone, Cefotaxime – IV; Cefixime, Cefpodoxime – PO**
- Gram (+)
    - Excellent *S. pneumoniae*
        - Enhanced potency important for meningitis
    - Variable MSSA
- Gram (-)
    - Excellent in vitro activity against most nosocomial GNB of interest
        - Enhanced activity against PEK
        - Rising rates of ESBLs compromising activity
    - No activity against *P. aeruginosa* or anaerobes
    - CAUTION: Enterobacter, Citrobacter, *K. aerogenes*
- What's ESBL Now?
    - ESBL = **E**xtended **S**pectrum **B**eta-**L**actamase
    - Most commonly seen in *E. coli* and *K. pneumoniae*
        - Can be transferred to other Enterobacteriaceae
    - Ability to hydrolyze extended spectrum b-lactams
        - 3rd and 4th generation cephalosporins
    - If present – isolate considered resistant to penicillins, cephalosporins, and aztreonam
        - A few of the novel agents (will discuss) restore activity
    - Most are also resistant to non-B-lactam drugs
    - **Carbapenems are the drug of choice**

- Ceftazidime
    - 3rd generation cephalosporin (IV)
    - Gram (+)
        - DECREASED staph and strep
    - Gram (-)
        - Adds *P. aeruginosa*
- 3rd Generation Cephalosporin Clinical Uses
    - Ceftriaxone
        - DOC (by many, not UM) for Community Acquired Pneumonia (CAP)
            - Enhanced activity against *S. pneumoniae* and reliable activity against beta lactamase producing *H. influenzae* and *M . Cattarhalis*
        - DOC for empiric meningitis (*S. pneumoniae and N. meningitidis*)
        - Intra-abdominal infections (+ metronidazole)
        - Urinary tract infections
    - Oral 3rd generations cephs may be used for PO step down therapy for some of these indications
- 3rd Gen Cephalosporin Clinical Pearl
    - *Enterobacter spp., K. aerogenes*, and *C. freundii*
    - All of these have a chromosomal b-lactamase (called “ampC- like”) that can be selected for during therapy
    - Initially the lab will say that the isolate is susceptible to 3rd generation cephalosporins
    - If treated with 3GC the b-lactamase may be selected for, which will confer resistance, and the patient may worsen
    - Take home: Generally, avoid for serious infections due to these organisms
        - Cefepime or carbapenems are the DOC

Cephalosporins: Spectrum of Activity (cont.)

Generation	1st	2nd (resp)	2nd (GI)	3rd	Ceftazidime
Gram (+)	Good	Good	Good	↑ SP ↓ MSSA	↓ SP ↓ MSSA
Gram (-)	Weak	Better	Better	Good	Good
P. aeruginosa	None	None	None	None	Yes
Anaerobes	None	None	Good	None	None

4th Generation: Cefepime

- Gram (+)
    - Activity against streptococci and staphylococci
- Gram (-)
    - Excellent against nosocomial organisms
    - Enterobacter, *K. aerogenes, C. freundii*
    - *P. aeruginosa*
    - Unreliable against ESBL (avoid)
- Anaerobic
    - No relevant activity

Cephalosporins: Spectrum of Activity (cont.)

Generation	1st	2nd (resp)	2nd (GI)	3rd	Ceftazidime	Cefepime
Gram (+)	Good	Good	Good	↑ SP ↓ MSSA	↓ SP ↓ MSSA	Good
Gram (-)	Weak	Better	Better	Good	Good	Good
P. aeruginosa	None	None	None	None	Yes	Yes
Anaerobes	None	None	Good	None	None	None

Ceftaroline and Ceftobiprole (IV only)

- Ceftaroline
  - "Advanced generation cephalosporin"
  - Binds to PBP2, PBP2A, and PBP2X
    - MRSA, enhanced *S. pneumoniae* activity
  - Gram (-) activity falls in between that of a 2nd and 3rd generation cephalosporin
    - No *P. aeruginosa*
- Ceftobiprole
  - Also active against MRSA, expanded Gram-negative coverage to include some *P. aeruginosa* activity
- Clinical role still being defined…. Refractory MRSA infections

Ceftolozane/Tazobactum

- Cephalosporin + BLI combination that came to market in 2014
- Limited Gram (+) activity
  - Unreliable against both *S. aureus* and *S. pneumoniae*
- Claim to fame is its Gram (-) activity, notably against *P. aeruginosa*
  - Often retains good activity even when all traditional anti-pseudomonal agents have documented resistance
- Addition of tazobactam expands activity against Enterobacteriaceae, including ESBLs

Ceftazidime/Avibactum

- Approved in 2015, avibactam is the first of its kind, non-b-lactam BLI
- Restores the activity of ceftazidime against many bacteria producing b-lactamase and/or carbapenemases
  - Most notably it inhibits the KPC enzyme
    - Stands for *K. pneumoniae* carbapenemase – number one cause of carbapenem resistance in *Enterobacteriaceae* in the USA
  - Also inhibits ESBL, ampC, restoring ceftazidime activity
  - Can also enhance *P. aeruginosa* activity

Cefiderocol

- Approved in 2020
- Siderophore-cephalosporin
  - Uses Iron uptake pathway to get high concentrations at site of action, enhanced activity against resistant pathogens
- Highly active against many resistant Gram (-) pathogens
  - *P. aeruginosa*

    - *A. baumannii*
    - CRE, ESBL, ampC
    - *S. maltophilia*
- Underwhelming clinical trial results
- Role currently ill defined, but option when resistance to all others

Antipseudomonal Antibiotics

- Piperacillin
- Piperacillin/tazobactam
- Cefepime
- Ceftazidime
- Ceftolozane/Tazobactam
- Ceftazidime/avibactam
- Cefiderocol

Cephalosporin Side Effects

- Similar to Penicillins AND
- Ceftriaxone can cause biliary sludging
    - Most relevant in neonates – relative contraindication in this population
    - Keep this ADE in mind in adult patients if imaging suggests sludging and patient is symptomatic or if unexplained rises in liver function tests or pancreatic enzymes
    - Can theoretically occur in urethra as well
- Cephalosporins with a methylthiotetrazole (MTT) side chain can cause hypothrombinemia and disulfiram reactions in patients taking alcohol
    - Cefotetan, cefetazole, cefoperazone
- Cefepime and encephalopathy

Cephalosporin Cross-Reactivity

- Historic "book answer" was 5 – 15% if penicillin allergy
- However, recent evidence demonstrates "cross-reactivity" w/ cephalosporins negligible (<1-2%) if structurally unrelated side chains

(+) Known cross-reactive (X) Similar or same side chain	Penicillin	Amoxicillin	Ampicillin	Cephalexin	Cefazolin	Cefuroxime	Cefoxitin	Ceftriaxone	Cefotaxime	Ceftazidime	Cefepime	Cefiderocol	Aztreonam
Penicillin		+	+	+									
Amoxicillin	+		+	+									
Ampicillin	+	+		X									
Cephalexin	+	+	X										
Cefazolin													
Cefuroxime							X	X	X		X		
Cefoxitin						X							
Ceftriaxone						X			X		X		
Cefotaxime						X		X			X		
Ceftazidime												X	X
Cefepime						X		X	X				
Cefiderocol										X			X
Aztreonam										X		X	

Carbapenems and Aztreonam

Carbapenems

- Products: Imipenem-cilistatin, meropenem, doripenem, and ertapenem
- Broadest spectrum agents we have
    - Gram (+) activity including MSSA (no MRSA)
    - Gram (-) activity including many resistant organisms
    - Anaerobic activity excellent (not *C. difficile*)
- Literature suggests "cross-reactivity" with penicillins anywhere between 1- 50 (!!) %
    - Best evidence puts this at <1% (think similar to structurally unrelated cephalosporins)
- Group 1 Carbapenem
    - Ertapenem
    - Narrower spectrum
    - Take the coverage of the other carbapenems and the "holes" of ertapenem can be remembered by the acronym APE
        - *Acinetobacter, Pseudomonas, E. faecalis*
    - As it is narrower spectrum often considered DOC for ESBL, ampC infections
        - Also, once daily option!
- Group 2 Carbapenems
    - Imipenem, Meropenem, Doripenem
    - Great Gram (-) coverage
        - ESBL
        - *P. aeruginosa* (including some that are resistant to piperacillin/tazobactam, cefepime, ceftazidime)
        - *A. baumannii*
            - Activity has decreased over the past two decades (resistance ~50%)
        - Clinical utility: Empiric and/or definitive therapy for multi-drug-resistant organisms

Meropenem/Vaborbactam

- Came to market in 2017
- Vaborbactam
    - Boronic acid based BLI
    - What you need to know: Inhibits KPC and restores the activity of meropenem
    - This is the only real utility of this drug (and it does it very well!)

Imipenem/Relepactam

- Came to market in 2019
- Relebactam
    - Broad spectrum non-beta-lactam beta-lactamase inhibitor (same class as avibactam)
    - Inhibits KPC – restores imipenem activity
    - Also enhances activity of imipenem against *P. aeruginosa* (and this is where you are most likely to see this agent used)

Side Effects and Drug Interactions: Think Seizures

- Seizures are the side effect clinicians are most concerned about with the carbapenems
- Based off old imipenem data/experience
    - May be related to cilistatin (dihydropeptidase inhibitor added to imipenem to increase half-life)
- More of a concern with high dose or imipenem
    - Clinically we see it sometimes with ertapenem
- Carbapenem drug interaction
    - Valproic Acid → increased elimination and subtherapeutic levels of VPA

        - Recommend alternative therapy!!

Aztreonam

- Only commercially available agent in the monobactam class (IV only)
- Gram (-) activity ONLY
    - Included *P. aeruginosa*
    - No ESBL activity
- Claim to fame - generally thought to not have ANY cross reactivity with penicillins
- Place in therapy is for empiric (and sometimes definitive) Gram (-) coverage when patient has life threatening PCN allergy
    - Generally, can (and should) avoid aztreonam though

Anti-pseudomonal Agents

- Piperacillin
- Piperacillin/Tazobactam
- Cefepime
- Ceftazidime
- Ceftolozane/Tazobactam, Ceftazidime/Avibactam
- Cefiderocol
- Imipenem, Meropenem, Doripenem
    - NOT ertapenem
- Meropenem/Vaborbactam, Imipenem/Relebactam
- Aztreonam

B-lactams: Clinical Pearl on Renal Dosing

- Nearly every B-lactam is eliminated renally and requires renal dose adjustment
- Exceptions
    - Ceftriaxone (only cephalosporin)
    - Penicillinase-resistant Penicillins (e.g., nafcillin)