ANTIBIOTICS REVIEW

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ANTIBACTERIALS

I. BETA-LACTAMS = PCNs, Cephalosporins, Carbapenems, Monobactam(Aztreonam)
- Cell wall inhibitors: bind PBPs (Penicillin-binding proteins) in cell membrane and inhibit cell wall crosslinking à bactericidal.
- Main side effects: Hypersensitivity reactions including anaphylaxis, Rashes, Bone marrow suppression, Interstitial Nephritis, GI (nausea, diarrhea, and C.diff) interstitial nephritis, GI (nausea, diarrhea, and C.diff), seizures (mainly with high doses in renal failure)

- As a general rule, if pathogen is susceptible and patient non-allergic, **beta-lactams are the preferred drug for most situations due to high efficacy and cidal nature**.
- **Most oral beta-lactams have poor bioavailability and achieve low serum concentrations**, making them poor choices for serious or deep seated infections (Amoxicillin has the best bioavailability).
- No beta-lactams has activity vs MRSA (except Ceftaroline), and none have activity vs atypical intracellular organisms (i.e. Legionella, Mycoplasma, Chlamydia).
- Beta-lactams exhibit **time-dependent killing**, meaning that efficacy depends on the amount of time the drug concentration is above the MIC.
- The **SPICE-A organisms** (Serratia, Pseudomonas/Providencia, Indole-positive Proteus, Citrobacter, Enterobacter, and Acinetobacter) have inducible, chromosomal beta-lactamases (AmpC) that may not be detected on initial susceptibility testing, but can lead to resistance while on therapy to all beta-lactams **except carbapenems**. Cefepime and Piperacillin/Tazobactam can be used with caution as well.

Overview of Beta-Lactam Allergies:

- Rash occurs in up to 5% of patients receiving PCN, but **the overall rate of anaphylaxis to PCN is <1/10,000.**
- **Among all patients with reported PCN allergy, ~85-90% will tolerate PCN** (either never truly allergic, or resolution of remote prior allergy).
- **Clinical cross-reactivity with cephalosporins and carbapenems is very low: of those with a positive PCN skin test, ~ 2% will have a cephalosporin reaction, and <1% will have a carbapenem reaction**.
- **There is no cross-reactivity between PCN and Aztreonam;** however, cross-reactivity between Aztreonam and Ceftazidime has been reported (due to an identical side chain).

- Skin testing is useful to evaluate for potential Type I (IgE-mediated) allergic reaction (only 10-15% of those with reported allergy will have positive skin test). Skin test has ~50% positive predictive value à give alternate drug, do graded challenge, or desensitize. **Skin test has very a high negative predictive value: >98% will tolerate PCN, but not 100% à give 10% "test" dose and observe for 1 hour prior to full dose.**
- If skin testing unavailable and beta-lactam is preferred, decision depends on prior type of reaction and how recently it occurred. If >10 years ago, and/or not characteristic of IgE, give cephalosporin or carbapenem (<1% of anaphylaxis). If recent and/or features of IgE reaction, can give cephalosporin or carbapenem by graded challenge. If probable history of anaphylaxis, desensitize.

A. PENICILLINS

1. Penicillin G (IV) or V (PO)
Spectrum: Many strains of Streptococci **(Drug of choice for Group A Strep - universally PCN sensitive**), minority of Staphylococci (most are resistant) and some Enterococcus, most oral anaerobes, Syphilis (universally PCN sensitive).
Used for: Strep throat and other infections due to Group A Strep, Syphilis (for neurosyphilis or pregnant women, must desensitize to PCN), bacteremia/endocarditis due to PCN sensitive Streptococcus, Enterococcus, or Staph aureus **(<10% of S.aureus strains are PCN-sensitive),** and more. For most situations, generally start with broader antibiotics until pathogen and susceptibilities identified.

2. Aminopenicillins- Ampicillin (IV), **Amoxicillin** (PO)
Spectrum: some Gram positives (Strep, Enterococcus, Listeria) but **NOT MSSA**, and limited Gram negative coverage. Notable gram negative holes include Klebsiella, Moraxella, and SPICE A organisms.
Used for: Upper respiratory infections, sinusitis, otitis media, cellulitis, Listeria infections, UTI's, early Lyme disease (alternative to Doxycycline), and more.

- **Drug of choice for Enterococcal infections if susceptible** (E.faecalis generally susceptible, E.faecium usually not). Used with aminoglycosides for synergy for Enterococcal endocarditis.
- **Amoxicillin is the best-absorbed beta lactam** (75-90% bioavailability). Little role for oral ampicillin due to inferior absorption vs Amoxicillin.

3. Anti-Staphylococcal Penicillins - Methicillin / Nafcillin / Oxacillin (IV), **Dicloxacillin** (PO)
Spectrum: MSSA, and with activity vs strep.
Used for: **Drug of choice for MSSA infections** (unless PCN sensitive, which is rare). Good choice for cellulitis, osteomyelitis, endocarditis, and bacteremia from MSSA.

- No MRSA coverage and **Coag negative Staph is usually resistant (>80%).**
- Dicloxacillin is a reasonable oral choice for non-severe cellulitis; otherwise, **for all serious MSSA infections (e.g. bacteremia, osteomyelitis, endocarditis), in general the entire course of therapy must be given intravenously.**
- Nafcillin tends to be better tolerated than Oxacillin (less hepatitis and rash)

4. Anti-pseudomonal PCNs - Piperacillin, Ticarcillin
Usually combined with beta lactamase inhibitors (see below) which confers broader activity; however, beta-lactamase component does not add activity vs Pseudomonas (so if Pseudomonas is sensitive, could use Piperacillin alone).

B. COMBINED PENICILLIN/BETA-LACTAMASE INHIBITORS: addition of beta lactamase inhibitor confers broader spectrum against common beta-lactamase producing organisms (such as **MSSA**, some gram negatives including H.influenza, Moraxella, **and virtually all anaerobes).**

- **Amoxicillin/Clavulanate (Augmentin)** – PO

Spectrum: Relatively broad spectrum with some gram positive (MSSA, Strep), some gram negatives, and anaerobes. Notable holes include **NO Pseudomonal activity** and other SPICE A organisms.
Used for: Sinusitis, respiratory infections, otitis media, some skin/soft tissue infections (including bite wounds), and more.

- **Ampicillin/Sulbactam (Unasyn)** – IV

Spectrum: Similar to Amoxicillin/Clavulanate, **except has activity vs most Acinetobacter** (sulbactam component has activity). Still no activity against other SPICE organisms.
Used for: similar situations as for Amoxicillin/Clavulanate but where IV form is desirable; also, some intraabdominal and GYN infections, aspiration pneumonia and lung abscesses, and more.

- **Caution with Unasyn for polymicrobial intraabdominal infections due to high rate of resistance of E.coli (>50% at some institutions)**
- **Piperacillin/Tazobactam (Zosyn)** – IV

Spectrum: similar to Unasyn in having gram positive, gram negative, anaerobic coverage, but better overall gram negative coverage, **including Pseudomonas and most SPICE A organisms.**
Used for: many purposes, including hospital-acquired/healthcare-associated PNA, severe skin/soft tissue infections including diabetic ulcers, intraabdominal infections.

- ***Very broad antibiotics so easier to remember common bugs that it does NOT cover: MRSA, most strains of VRE, many Coag negative staph strains, Atypicals (Chlamydia, Mycoplasma, Legionella), ESBLs.***

- Note Zosyn's higher dosing for PNA/Pseudomonas coverage: 4.5 g q6 hrs (vs. 3.375 g q6 for other indications)
- "Extended Infusion" strategy – 3.375 g over 4 hours, q8 hrs – some data suggesting better outcomes for treatment of Pseudomonas infections compared to standard dosing (goal to maximize time above MIC).
- **Ticarcillin/Clavulanate (Timentin)** – IV

Similar to Zosyn, but Timentin has activity vs Stenotrophomonas, and is less effective vs Pseudomonas and Enterococci.

C. CEPHALOSPORINS - higher resistance to beta-lactamases à better anti-staph activity

Spectrum (General Rules):

- **No cephalosporin covers Enterococcus** (except Ceftaroline).
- **Only Ceftazidime and Cefepime cover Pseudomonas.**
- **Only Cefoxitin and Cefotetan have good anaerobic coverage.**

1st Generation - **Cefazolin (Ancef, Kefzol)** - IV, **Cephalexin (Keflex)** - PO

Spectrum: Excellent Gram positive (MSSA and strep), minor Gram negative = Proteus, E.coli, Klebsiella.
Used for: Mild-moderate nonpurulent cellulitis (if do not suspect MRSA). Cefazolin ofted used for prophlaxis during surgery. Sometimes used for UTIs as well (especially during pregnancy).

- **In PCN-allergic patients, Cefazolin is drug of choice for severe MSSA infections** (bacteremia, endocarditis, etc). Some use it preferentially in prolonged treatment courses over Nafcillin/Oxacillin due to overall better tolerance (less rash, diarrhea, interstitial nephritis, hepatitis)

2nd Generation

- **Cefuroxime** (PO and IV)

Spectrum: Gram positive and more gram negative's than 1st generation - gains activity vs H.influenza, Enterobacter, Neisseria.
Used for: respiratory infections (upper and lower tract), gonorrhea, UTIs, Lyme disease (alternative to Doxycycline), and more.

b."Cephamycins" - Cefoxitin, Cefotetan (IV)

Spectrum: get **anaerobes** and gram negatives, but no Pseudomonas and weak/unreliable gram positive coverage.
Used for: UTI's, non-severe intraabdominal infections, pelvic/GYN infections.

- **Bacteroides fragilis has high rates of resistance to Cefotetan (Cefoxitin is a bit better)** – for serious intrabdominal infections, should use other agents.
- Cefotetan can cause elevated INR.

3rd Generation

a. **Ceftriaxone (Rocephin)** – IV, **Cefotaxime** - IV, **Cefpodoxime** - PO

Spectrum: Good gram positive (although possibly worse than 1st generation) and excellent gram negative coverage (E.coli, Proteus, Klebsiella, Neisseria, H.influenza, and most SPACE organisms, but ***not Pseudomonas), no anaerobes*** .
Used for: Ceftriaxone used in many situations including community acquired PNA (with Azithromycin), meningitis (CTX has excellent CSF penetration), spontaneous bacterial peritonitis, some skin/soft tissue infections, bacteremia/endocarditis from susceptible strep, urinary tract infections/pyelonephritis, bone and joint infections, late Lyme disease, gonorrhea, pelvic infections, and more.

- Note small but important rate of resistance in Strep pneumo.
- Ceftriaxone usually once daily dosing (1-2 g) except for meningitis (2 g IV q12 hours). Cefotaxime is more frequent dosing (often used preferentially for spontaneous bacterial peritonitis due to good track record and high levels achieved in ascitic fluid, but Ceftriaxone probably equivalent).
- Cefpodoxime useful as a step-down to oral after IV Ceftriaxone, but like all beta lactams note poor serum bioavailability (so not suitable for bacteremia, deep-seated or serious infections).
- Ceftriaxone can cause biliary sludging and cholecystitis.
- **Ceftazidime** (IV) (3rd/4th Generation Cephalosporin)

Spectrum: ***only has Gram negative coverage (including Pseudomonas).*** Virtually no Gram positive or anaerobic coverage.
Used for: Pseudomonal infections, also can be used for neutropenic fever **(but beware lack of staph/strep coverage, so Cefepime often preferred).**

- **Most experts will avoid using Ceftriaxone or Ceftazidime (and any lower generation cephalosporin) for serious infections due to SPICE organisms, due to concern for inducible resistance from chromosomal beta-lactamase (AmpC).** Preferable to use Cefepime, Piperacillin/Tazobactam, or Carbapenem (best) in those situations as they are more stable, or non-beta lactams if susceptible.

4th Generation - Cefepime (IV)
Spectrum: broad gram positive (MSSA, strep) and gram negative including Pseudomonas, but **weak anaerobic coverage.**
Used for: empiric neutropenic fever (better than Ceftazidime due to strep coverage), hospital acquired PNA, meningitis if suspect gram negatives, complicated urinary tract infections, nosocomial meningitis, and more.

- For cefepime and ceftriaxone, beware CNS toxicity of encephalopathy, altered mental status, and seizures in the elderly and those with renal failure.
- **Ceftazidime and Cefepime sometimes have activity against certain ESBL producing organisms, but reports of failure in this setting so use with caution.**
- Ceftazidime and Cefepime have <1% cross-reactivity for non-anaphylactic allergies/intolerance

5th Generation - Ceftaroline (IV)
Spectrum: **Gram positive including MRSA, VISA, VRSA,** Strep, and Enterococcus faecalis including VRE (less activity vs E.faecium). Similar gram negative coverage as Ceftriaxone – no Pseudomonas and other nonlactose fermenting GNRs, no ESBL.
Used for: complicated SSTI and community-acquired PNA (FDA indications)

- Newest cephalosporin (FDA approved in 2010) and only one with activity vs MRSA and Enterococcus. However, not much data for treatment of enterococcal infections.
- Only 2 FDA approved indications, but being used more and more for off-label purposes (bone/joint infections, refractory MRSA/VISA bacteremia, etc.).

D. CARBAPENEMS - Imipenem/Cilastin, Meropenem, Ertapenem, Doripenem (all IV)

Spectrum: ***Broadest spectrum antibiotics***, cover Gram positive, Gram negative including Pseudomonas (**except Ertapenem**) ***and ESBL*** *(extended spectrum beta lactamase producers)*, also anaerobes.
Used for: many serious infections due to resistant gram negatives, including hospital/health-care associated PNA, meningitis, intraabdominal infections, complicated skin and soft tissue infections

- **The most reliable class of antibiotics against ESBL organisms** and the SPICE A organisms.
- Very broad - easier to remember common bugs that it doesn't cover. MRSA, most VRE, Atypicals, Stenotrophomonas (carbapenem use is a risk factor for Stenotrophomonas infection).
- Great penetration virtually everywhere, including CSF .
- **Ertapenem does NOT cover Pseudomonas**, but does still cover ESBL (main advantage is convenient once/day dosing - great outpatient IV drug). **Other differences of Ertapenem (vs other carbapenems) is lack of activity vs Acinetobacter and Enterococci.**
- Doripenem – newest carbapenem, main theoretical advantage = increased in vitro potency against Pseudomonas, and lower likelihood of development of resistance in vitro (clinical benefit not yet demonstrated)
- Main additional side effect = Lower seizure threshold - greatest risk w/ Imipenem (esp with renal failure), less w/ Meropenem.

E. MONOBACTAM - Aztreonam

Spectrum: only has activity vs. **aerobic gram negatives**, no gram positive or anaerobes (similar activity as Ceftazidime).
Used for: hospital acquired/healthcare associated PNA, UTIs, intraabdominal infections, sepsis, skin and soft tissue infections. Generally used in combination with other antibiotics due to gram-negative limited spectrum.

- Main advantages:1) **No cross-reactivity with PCN allergy (except with Ceftazidime – cross-reactivity due to identical side chain)** and 2) Does not cause renal failure (almost no significant toxicity)
- ***Beware significant rate of resistance of Pseudomonas in most institutions, so empiric double coverage often required.***

Comparison of the 3 broadest spectrum beta-lactams: Cefepime, Zosyn, and Carbapenems (non-Ertapenem) have activity against both Gram positive (MSSA, Strep) and Gram negative including Pseudomonas. They do NOT cover: MRSA, VRE, Atypicals, among others.

- **Cefepime** – main weakness is **weak anaerobe coverage and no Enterococcus**
- **Zosyn** (Piperacillin/Tazobactam) – broader due to excellent anaerobe coverage, activity vs Amp-susceptible Enterococcus. No ESBL coverage.
- **Carbapenems** (except Ertapenem) – broadest yet due to anaerobic coverage, Amp-susceptible Enterococcus, and ***ESBL***

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II. PROTEIN SYNTHESIS INHIBITORS

Mechanism: bind to either 30 S or 50 S ribosomal unit. Most are bacteriostatic, except for Aminoglycosides (generally considered cidal due to irreversible binding and disruption of outer cell membrane)

1. <u>Macrolides</u> - <u>Erythromycin, Clarithromycin, Azithromycin</u> -50S Ribosomal Inhibitor (PO and IV)
Spectrum: Atypical organisms (Chlamydia, Mycoplasma, Legionella), also some activity vs. Gram positive cocci and some gram negatives.
Used for: Azithromycin - low-risk bronchitis, COPD exacerbations, community-acquired pneumonia, sinusitis, Strep throat in PCN allergic patients, and more. Used in conjunction with Ceftriaxone for CAP that requires hospitalization. Used for MAC treatment (combination therapy) and for prophylaxis in HIV/AIDS patients with CD4 <50. Also used for STD Chlamydia.

- **Azithromycin is the drug of choice for most atypical infections.**
- Erythromycin now used mostly as GI motility agent – prior to endoscopy, or to advance feeding tubes.
- Clarithromycin also used for MAC treatment (in combination with other drugs).
- Azithromycin has better H.influenza activity than Clarithromycin/Erythromycin.
- **~25% of Strep pneumo is resistant to Azithromycin**, so combine with Ceftriaxone for patients sick enough to hospitalize with community-acquired PNA (or recent abx use).
- Side effects: **QT prolongation** (recent NEJM article suggested slight increased risk of cardiovascular death with Azithromycin), prominent GI side effects, rash.

2. <u>Tetracyclines</u> – <u>Doxycycline, Tetracycline, Minocycline</u> - 30S Inhibitors (PO and IV)
Spectrum: Fairly broad spectrum with some Staph and MRSA coverage, some gram negative coverage, and atypicals. **Has activity for unusual pathogens including: Rickettsia, Lyme disease, Tularemia, Vibrio, Brucella, Q fever, Anthrax**
Used for: Doxycycline - Skin and soft tissue infections when suspect community-acquired MRSA, respiratory tract infections, and unusual infections as above. Drug of choice for early Lyme disease, and for Lyme prophylaxis after tick bite. Also used for malaria prophylaxis, acne and rosacea.

- Side Effects: photosensitivity, GI discomfort, teeth discoloration, inhibits bone growth in children, teratogenic, steatosis and hepatotoxicity.
- **Doxycycline is the preferred tetracycline in most cases** due to convenient BID dosing, and lack of food-drug interactions.
- Often part of empiric therapy in toxic-appearing patients with fever and rash (mainly for Rocky Mountain Spotted Fever).
- **Good choice for mild-moderate skin/soft tissue infections due to community-acquired MRSA infection, but has poor strep coverage** so often combined with beta lactam like Cephalexin.
- Doxycycline has excellent bioavailability .

3. <u>Clindamycin</u> -50 S inhibitor (PO and IV)
Spectrum: Excellent activity vs. **Anaerobes and Gram positive cocci** – Strep and Staph, including ~ ***50% of community-acquired MRSA***, **but NOT Enterococci.**
Used for: skin/soft tissue infections, pelvic infections, lung abscess, sinusitis. Also has activity vs PCP (combine with primaquine) and toxoplasmosis (combine with pyrimethamine)

- Beware increasing resistance among Bacteroides – not a good choice for severe intraabdominal infections.
- **Reasonable empiric drug for cellulitis due to Strep/Staph coverage, but beware of resistant MRSA. Also ~10% of MSSA is resistant.**
- If MRSA (or MSSA) appears susceptible – **always have lab check "D-test" à looks for inducible resistance to Clindamycin** in strains that are resistant to Erythromycin. If D-test positive, do not use Clindamycin.
- **Also used often for its *Antitoxin effect* in Toxic Shock Syndrome or Necrotizing Fasciitis** due to Group A Strep (less evidence for MRSA).
- **Does not penetrate CSF – cannot use for brain abscesses.**
- Traditionally causes highest rate of C.diff among all Abxs (~10%).

4. <u>Aminoglycosides</u> - <u>Gentamicin, Tobramycin, Amikacin, Streptomycin</u> -30S inhibitor (all IV)
Spectrum: Extremely efficacious vs. **aerobic Gram negatives including Pseudomonas. NO activity vs. Gram positives (except when used for synergy) or anaerobes.**
Used for: serious gram negative infections especially when Pseudomonas is suspected (pneumonia, bacteremia, urinary tract infections). Used with beta-lactams against gram positive organisms for ***synergistic effect*** (mainly in endocarditis).

- **For synergy, best evidence and utility for Enterococcal endocarditis** (if susceptible). **Also strong recommendation for Strep enterocarditis** (duration depends on Strep MIC). **Weakest evidence for Staph aureus native valve endocarditis** – optional for max 3-5 days (decreases bacteremia by ~1 day, increases renal failure, and no effect on mortality) à most ID physicians now tend to avoid it for Staph infections. **For Staph prosthetic valve endocarditis, aminoglycoside recommended for 2 weeks with Rifampin.**
- Poor urine and CSF penetration. Also less effective at low pH such as in lung/bronchial secretions – not great for PNA (avoid monotherapy).
- Ofted used as 2nd agent of "double coverage" when suspecting serious Pseudomonas infection (including for HAP/HCAP/VAP)
- Side effects = ATN/nephrotoxicity (manifests after 3-5 days, usually reversible) and