ANTIBIOTIC REVIEW

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GENERAL THINGS TO KNOW

- General stuff (Disease States, Bugs, Drugs)
- Practice - Specific
  - Local epidemiology (organisms & resistance trends)
  - Formularies, cost
- Patient – specific
  - Exposure history, risk factors for specific drugs
  - Allergies, organ dysfunction, interacting medications, weight, height

THREE WAYS ANTIBIOTIC USED

Prophylaxis, Empiric, Definitive

- **PROPHYLAXIS**
  - **Medical:**
    - ~ Exposure to virulent pathogen
      - HIV, N. meningitis
    - ~ Immunocompromised
      - HIV with CD4<200, Asplenic, Neutropenic
  - **Procedural (Surgery)**

    Short course recommended / preferred

    ~ Endocarditis

THREE WAYS ANTIBIOTICS USED

Prophylaxis, Empiric, Definitive (2)

- **Empiric (usually up to 72 hours**)
  - Diagnosis of infection made based on S/S, lab, etc. Likely pathogens suspected but specific pathogen not yet known.
  - **Pick antibiotics based on:**
    = Likely pathogens, local susceptibility trends, and patient-specific factors (allergies, organ dysfunction)
  - **Pearls:**
    = Get cultures on the front end (including special tests)
    = Start appropriate antibiotics ASAP.

THREE WAYS ANTIBIOTICS USED

Prophylaxis, Empiric, Definitive (3)

- Definitive

  - Microbiologic or serologic diagnosis with susceptibilities known

  - Some results to broad-spectrum agents maybe suppressed by lab (cascaded reporting)
    - Call the microbiology lab

  - Additional testing may be needed (KB or E-test)

THREE WAYS ANTIBIOTICS USED

Prophylaxis, Empiric, Definitive (4)

- Definitive

  - Use the most effective, least toxic, narrowest spectrum, and most cost effective agent – the "Drug of Choice" (DOC)

    ~ May actually be a combination of drugs

      - Ampicillin and Gentamicin for *enterococcus* endocarditis

      - Know the alternatives especially for patients with allergy to drug of choice.

- Drug, dose, route, interval, and duration is disease state and patient specific.

How Long to Treat?

- **Not well defined!**
  - Usually less than 14 days
    ~ Longer for endocarditis, Osteomyelitis, Prostatitis (& varies by bug & drugs)
  - Track number of days of therapy in progress note & set endpoint
    ~ Coag Neg *Staph* Bacteremia: 5 – 7 days
    ~ *Staph aureus* Bacteremia: ≥ 28 days (all IV)

Prolonged unnecessary therapy increases risk of resistance, adverse effects, and cost

Know Your Bugs

Gram - Positive

- ***S. aureus:***
  - 25 – 50% Methicillin Resistant (MRSA)

  - MSSA DOC: cloxacillin; Cefazolin
  - CA-MRSA DOC: Vancomycin, Linezolid, Daptomycin
    - ~ If uncomplicated: Trimeth/Sulfa (99%), Clindamycin (70%)
- ***Enterococcus:***
  - DOC: (Ampicillin or Vancomycin)
    PLUS (Gentamicin or Streptomycin)
    Nitrofurantoin, Amp or Vanc alone for UTI
  - VRE: linezolid, daptomycin

Know Your Bugs

Gram – Positive

- ***S. pneumoniae:***

  -- 20 – 45% have decreased susceptibility to penicillin.

~ CNS Infections:

High dose (HD) Ceftriaxone (2g IV Q 12h) + HD Vanco

~ Outside CNS:

= Ceftriaxone; Respiratory FQ if at risk for resistance

= High dose amoxicillin

= +/- Doxycycline, TMP / SMX, Erythromycin

Know Your Bugs

Gram – Negative

- ***E. coli, Kleb. pneumoniae***

  ~ 50% resistant to Ampicillin

  ~ 25% resistant to Trimeth / Sulfa

  ~ 33% resistant to Ciprofloxacin

  increase in ESBL DOC carbapenems, less serious Cipro, TMP-SMX, nitro, fosfomycin

- ***P. aeruginosa***

  ~ "Best" Drugs (> 90% susceptible)

  = Ceftazidime, Cefepime, Piperacillin (with or w/o Tazo)

  = PLUS an Amikacin for synergy in serious infections

  ~ Less effective (80% susceptible)

  = Tobramycin, Gentamicin

  ~ If C & S verifies susceptibility (65 – 80% susceptible)

  = Imipenem, Meropenem, Aztreonam, Ciprofloxacin

Know Your Bugs

Gram – Negative

- Bad nosocomial Gram – Negative
  - ~ *Acinetobacter baumanii*
    - = Doc Colistin with meropenem (bleaching effect)
      - +/- Amikacin
      - -Alternative is tigecycline
  - ~ *Stenotrophomonas maltophilia* (resistant to Imipenem)
    - = DOC Trimethoprin/Sulfamethoxazole (Bactrim)
    - = 10 mg/kg/day of TMP components (2Ds tablets Q12h)

- Most ICUs have their own flora & susceptibility patterns. Patients become colonized within 48-72 hrs with these bugs

Know Your Bugs
Other Bacteria

- **Anaerobes**

  Peptostreptococcus, Clostridium, & *Bacteroides*

  - Overall:

    Amox/Clav, Pip/Tazo, Meropenem, Imipenem, and Tigecycline

  - Mouth & Lungs: Clindamycin
  - Abdomen: Metronidazole

- **Atypical**

  Legionella, *Mycoplasma, Chlamydia*

  - Macrolides, Tetracycline, Respiratory fluoroquinolones

Know Your Bugs
By Mechanism of Action

- **Cell –Wall**
  - ~ Penicillin – Binding Proteins (PBP): Beta-Lactams
    - = Penicillins +/- beta-lactamase inhibitors
    - = Cephalosporins
    - = Others (imipenem, aztreonam)
  - ~ Percursor molecules: Vancomycin
- **Intracellular**
  - ~ Ribosomes: Macrolides (5OS), Tetracycline (30S), Aminoglycosides (30S & 50S)
  - ~ DNA gyrase: Quinolones
  - ~ Folate metabolism: Trimethoprim-Sulfa

Know Your Bugs

Mechanism of Resistance

- **Altered target – PBP's.**
  - ~ Absolute Change = no binding
    = MRSA is resistant to all beta-lactams
  - ~ Relative Change = ⇩ binding, ⇧ MIC
    = Drug resistant *S. pneumoniae*
- **Enzymes destroy – Beta-lactamases**
  - ~ Penicillinase: MSSA, *H. influenzae*, anaerobes
    = Add beta – lactamase inhibitor or change structure
  - ~ Cephalosporinase: *Enterobacter* et al
  - ~ Extended Spectrum Beta Lactamase (ESBL): *Kleb Pneumo, E. coli*

Penicillins

- Penicillin PO, IV & IM
  = GP (*Strep*)
- Amoxicillin PO, Ampicillin IV
  = GP (*Strep*), some GNR (70% *H. influenzae*)
- Cloxacillin PO, IV
  = GP (MSSA)
- Amoxicillin / clavulanate (AUGMENTIN) PO, IV
  = GP (*strep*, GNB, Anaerobes)
- Piperacillin / Tazobactam (Tazocin) IV
  = GP, GNR (> 90% PA), Anaerobes

	GP	GN	Ana	DOC
Penicillin	Strep	None	Some	Syphilis, Strep
Ampicillin Amoxicillin	Strep	Some	Some	Enterococcus. Listeria
cloxacillin	MSSA	None	None	MS – SA
Amox / clav	Strep	Some; H. Influenzae	Great	Mixed Community
Pip / Tazo	Strep MSSA	H. influ. Pa et al	Great	Mixed Nosocomial

Cephalosporins & Other Beta-Lactams

- Cephalexin PO
  Cefazolin IV
  - GP (MSSA), GNR
- Cefuroxime
  - GNR (80% PA)

- Ceftriaxone IV, IM
  - GP (*S. pneumo*),
  -GNR
- Ceftazidime IV
  - GNR (> 85% PA)
- Cefepime IV
  - GP (*S. pneumo*)
  - GNR (>90% PA)
- Ceftaroline, IV
  - GP (MRSA)
  - GNR (NOT PA, ESBL)
- Ceftobibrole: IV
  - GP : MRSA
  - GN: PA

- Aztreonam
  - Beta-Lactam allergy

- Imipenem, ertapenem
  Meropenem
  - GP (including MSSA)
  - 95% GNR
  - Anaerobes

	GP	GN	Ana	DOC
Cefazolin	Strep MSSA	*E.Coli*	None	SPPLX SSTI
Ceftriaxone	Strep S. Pneiumo	*E.coli, Kleb*	None	CAP Meningitis
Ceftazidime	Poor	*E coli, Kleb,* PA	None	HAP et al
Cefepime	Strep MSSA	*Ecoli, Kleb*, PA	None	HAP et al Nosocomial
Imipenem Meropenem	Strep MSSA	Most including ESBL	Great	Mixed Nosocomial
Colsitin	None	Most GNB **(<u>No activity against:</u> *serratia, proteus, burkholderia, moraxella, providencia, morganella)***	None	KPC, PDR PA, acinetobacter

Beta-Lactam Adverse Effects

- Allergic / Hypersensitivity in 3 – 10% of pts.
  = Rash (4-8%) to anaphylaxis (0.01-0.05%, 10-20 minutes)
    ~ Carbapenems: 5% cross reactive, Cephs 10%
    ~ Vasculitis, Cytopenias, Fever, Interstitial Nephritis
- N/V with PO
- Seizures w/ high dose in renal insufficiency
- Ceftriaxone: Biliary sludging and bilirubin displacement (don't use in neonates)

VANCOMYCIN

- Exclusively Gram-Positive Spectrum

  - Methicillin Resistant *Staph*
  - Ampicillin Resistant *Enterococcus*
  - Multi-drug Resistant *S. pneumonia*
  - 2nd line for *C. difficile* Colitis (only indication for PO Vanco)
- IV only, Check levels & adjust frequency for renal impairment
- Troughs = 10 – 20 (15-20 for pneumonia)
- Peaks = 20-40 (higher in pneumonia)
- 15 – 20 mg/kg/dose (1g) IV Q8 – 12h (Q24h+ for CICr < 60)
  - Call pharmacy for help with dosing.

QUINOLONES

- Ciprofloxacin
  - GNR (75% PA)
- Levofloxacin, Moxifloxacin
  - GP (*S. pneumo*), GNR (respiratory; PA 70% w/ Levo)
- Cl in pregnancy & children
  - Rash/photosensitivity, Chelates (PO), CNS side effects, Tendon Rupture QTc prologation, Hypo/Hyperglycemia

AMINOGLYCOSIDES (all IV or IM)

- Gentamicin, Tobramycin
  - GNR (Tobra > Gent vs. *P. aeruginosa*)
- Amikacin, Streptomycin
  - TB, Multi-drug Resistant GNR
- Renal elimination, variable penetration in to tissue

  CNS < 5%, Lungs 50%, Urine 10 – 100 X
- Dosing:
  - Pick dose based on site/bug and interval per renal function (GFR < 60).
  - OD for GNR, MDD for GP
- Nephrotoxicity (non-oliguric) & Ototoxic
  - Prolonged exposure to elevated levels (troughs >2).

Macrolides & Lincosamides

- **Erythromycin**
  - GP (Strep) & Atypicals
  - GI side effects and inhibits CYP450 = drug interactions
- **Azithromycin IV, PO**

  Clarithromycin PO
  - GP (Strep), Atypicals & Respiratory GNR; non tuberculous *Mycobacterium*
- **Clindamycin (all PO, IV)**
  - GP (GP 75% MRSA), Anaerobes
  - AE: *C. difficile* colitis

Other Antibacterials

- **Tetracycline PO, Doycyclne PO & IV**
  - GP, GN, Atypicals; Brucella
  - Binds orally with calcium deposits on teeth, photosensitivity

- **Trimethoprim / Sulfamethoxazole**
  - GP (MSSA & MRSA), GNR
  - Rash and other ADE's, Drug interactions with warfarin
- **Metronidazole**
  - Anaerobes & Protozoa
  - Reactions with EthOH, Metallic taste, drug interactions with warfarin
- **Nitrofurantoin**
  - UTI (including VRE)
  - Contraindicated at GFR < 60

Know your Drugs

Pharmacodynamics

- Pharmacodynamics (PD)
  - **Bacteriostatic: Inhibit**
    ~ Generally avoid for endocarditis, meningitis, osteomyelitis, and febrile neutropenia
    ~ Tetracyclines, Macrolides, TMP / SMX, Linezolid
  - **Bacteriocidal: Kill**
    ~ Dose dependent (Peak:MIC > 10)
      - Aminoglycosides, Quinolones
    ~ Exposure dependent (T >MIC)
      - Beta – lactams, vancomycin

Know your Drugs

- **Absorption: IV vs PO**

  - Great PO absorption with
    fluoroquinolones (watch drug interactions),
    Metronidazole, TMP/SMX, doxycycline.
  - IV only:

  ~ Vancomycin (except *for C. difficile*)

  ~ All antipseudomonal agents except ciprofloxacin

  ~ some cephalosporins (advanced generation)
  ceftriaxone IM for GC

  ~ Meropenem, Imipenem, ertapenem (IM available) and Aztreonam

  ~ Aminoglycosides (gentamicin)
    - may give small dose IM

Know Your Drugs

- **DISTRIBUTION**
  - **CNS Penetration:**
    - Excellent: Metronidazole, chloramphenicol, fluconazole, TB drugs
    - Adequate with high doses: Ceftriaxone, ceftazidime, ampicillin
    - Problematic: Vanconmycin, aminoglycosides
  - **Lungs:**
    - Good: quinolones, Macrolides, beta-lactams
    - Modest: aminoglycosides

Know Your Drugs

- **Metabolism / Elimination**
  - **Kidneys**
    - Adjust for renal dysfunction (Cl Cr)
    - May use lower doses for UTI
  - **Liver**
    - Rare adjust for liver dysfunction
    - Potential for drug interactions

Drug Interactions

- **Drugs cleared by CYP 450**

  Statins, Cyclosporine, Benzodiazepines, Theophylline, Anticonvulsants, oral hypoglycemic

  - Levels increase by (Metabolism inhibited by)
    - Macrolides (Erythromycin)
    - Azoles (Fluconazole, Itraconazole)
    - Protease inhibitors
    - Ciprofloxacin
  - Levels decreased by (Metabolism induced by)
    - Rifampin

- **Oral Contraceptives**
  - Decreased with rifampin & cloxacillin

Drug Interactions

- **Warfarin:**
  - Effect & INR profoundly increased by
    - trimethoprim/sulfamethoxazole
    - metronidazole
  - Significant increase with
    - fluconazole, Ciprofloxacin
  - Decreased by
    - Rifampin
- **Multivalent Cations (Ca, Mg, Iron)**
  - Decreases absorption of:
    - Fluroquinolones
    - Tetracyclines

ANTIBACTERIAL PHARMACODYNAMIC CHARACTERISTICS

Class	Mechanism of Action	Concentration vs Time Dependent Activity	Bactericidal vs Bacteriostatic Activity	Mechanisms of Resistance
Antibacterial Agents				
B-Lactams				
Penicillins	Inhibition of PBP activity resulting in ⇩peptidoglycan layer synthesis in cell wall	Time	Cidal	• Altered PBP (MRSA, PRSP) • B-Lactamase production (PPNG; TEM and SHV-producing organisms; ESBL-producing K. pneumonia and E. coli; AmpC gene induction in Enterobacter, Citrobacter, Morganella, Providentia, Serratia, and Pseudomonas species)
Cephalosporins (e.g., cefazolin)		Time	Cidal	
Carbapenems (e.g., imipenem)		Time	Cidal	• Loss of outer membrane porin channels for entry (Pseudomonas aeruginosa)
Aminoglycosides (e.g., gentamcin)	• Ionic interaction with cell wall • Disruption of protein synthesis of 30S ribosomal subunit via codon misreading	Conc	Cidal	• Production of aminoglycosides modifying enzymes (acetylases, adenylases, phosphorylases) resulting in drug inactivation • 30S ribosomal mutation • Decreased membrane permeability
Fluoroquinolones (e.g., ciprofloxacin)	Inhibition of DNA gyrase and topoisomerase IV activity	Conc	Cidal	• Altered binding site due to mutation in DNA gyrase and/or topoisomerase IV • Active efflux pump

ANTIBACTERIAL AND ANTIFUNGAL PHARMACODYNAMIC CHARACTERISTICS (CONT'D)

Class	Mechanism of Action	Concentration vs. Time Dependent Activity	Bactericidal vs Bacteriostatic Activity*	Mechanisms of Resistance
Glycopeptides (e.g., vancomycin)	Binding to D-ALA-D-ALA terminus complex in peptidoglycan layer of cell wall to inhibit PBP binding & activity	Time	Cidal	• Ligase conversion of D-ALA-D-ALA to D-ALA-D lactate which prevents vancomycin binding
Macrolides (e.g., erythromycin)	Binding to 50S ribosomal subunit and interruption of protein synthesis via transpeptidation or translocation inhibition	Time (Azithromycin – Conc)	Static	• 23S Ribosomal subunit methylation by erm gene products • Active efflux (e.g., efflux pump from msr gene inducton in S. aureus or from mef induction in S. pneumonia or S. pyogenes) • Macrolide modification or inactivation
Nitroimidazoles e.g., metronidazole	Toic free radical formation	Conc	Cidal	• Unclear / uncommon
Oxazolidinones (e.g., linezolid)	Disruption of protein synthesis at 30S/50S ribosomal subunits	Time	Static (cidal to streptococci)	• Ribosomal binding site alteration
Streptogramins (e.g., quinupristin/ Dalfopristin)	Binding to 50S subunit of ribosome resulting in inhibition of peptide chain elongation and peptidyl transferase activity; quinupristin and dalfopristin are synergistic	Time	Cidal (staphylococci, streptococci, Enterococcus faecium) Static (Enterococcus faecalis)	• 23S Ribosomal subunit methylation by erm gene products (MLSB resistance) • Active efflux • Enzyme inactivation

ANTIBACTERIAL AND ANTIFUNGAL PHARMACODYNAMIC CHARACTERISTICS (CONT'D)

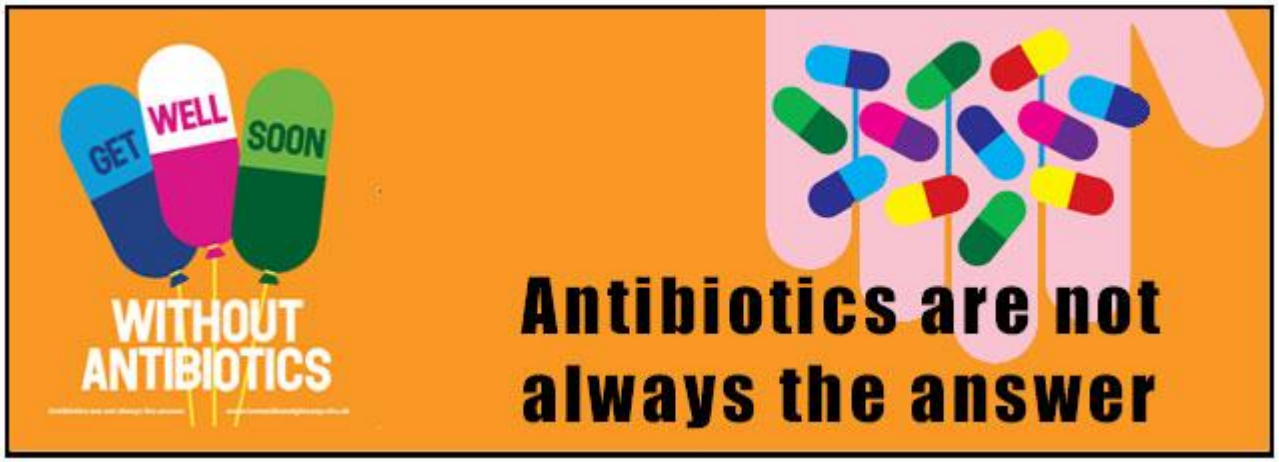
Class	Mechanism of Action	Concentration vs. Time Dependent Activity	Bactericidal vs Bacteriostatic Activity*	Mechanisms of Resistance
Lincomycins (e.g., clindamycin	Disruption of protein synthesis at 50S ribosomal subunit via inhibition of amino acid linking	Time	Static	• 23S ribosomal mutation/methylation (MLSB resistance)
Rifamycins (e.g., rifampin	Binding interference at 30S ribosomal subunit / mRNA complex binding interference	Time	Static	• Single step mutation in ß-subunit of DNA-dependent RNA polymerase (e.g., S. aureus)
Tetracyclines	Binding to 30S ribosomal subunit and disruption of protein synthesis at 50S subunit via inhibition of amino acid linking	Conc	Static	• Decreased uptake • Active efflux pump
Sulfa (e.g., sulfamethoxazole/trimethoprim	Disruption of folate synthesis; ⇩ DNA synthesis	Conc	Static	• Production of new dihydrofolate reductase and dihydropteroate synthetase • ⇧ PABA • Decreased membrane permeability
Antifungal Agents				
Polyenes (e.g., amphotericin B)	Disruption of cell membrane via intercalation with sterols, disrupting cell integrity		Cidal	• Uncommon • Decreased ergosterol cell membrane content (e.g., via previous azole use)

* Nature of activity at recommended doses against usual pathogens

ANTIBACTERIAL AND ANTIFUNGAL PHARMACODYNAMIC CHARACTERISTICS (CONT'D)

Class	Mechanism of Action	Concentration vs. Time Dependent Activity	Bactericidal vs Bacteriostatic Activity*	Mechanisms of Resistance
Azoles (e.g., fluconazole)	Disruption of fungal sterol synthesis via inhibition of cytochrome P450-dependent 14a-demethylase which is required for conversion of lanosterol to ergosterol		Static	• Modification of cytochrome P450-dependent 14a-demethylase • Active efflux pumps
5-Flucytosine	Cellular conversion to 5-fluorouracil, a false pyrimidine, and subsequent interference with DNA and protein synthesis		Cidal	• Common, especially if agent used alone
Echinocandins (e.g., caspofungin)	Inhibition of ß-1, 3-glucan synthetase resulting in disruption of cell membrane synthesis		Cidal (Candida species)	• Unknown

PBP = penicillin-binding proteins
MRSA = methicillin-resistant Staphylococcus aureus
PRSP = penicillin-resistant Streptococcus pneumonia
PPNG = penicillin-producing Neisseria gonorrhoeae
ESBL = extended-spectrum ß-lactamase
D-ALA = D-alanine
PABA = para-aminobenzoic acid


GET
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ANTIBIOTICS
Antibiotics are not
always the answer