Antibiotics in the Real World

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Antibiotics - Considerations:

- What is the likely organism?
- Parenteral vs Oral vs Other
  - Systemic perfusion
  - Bloodflow at site?
  - Abscess Capsule
  - Elimination Route
- What is the penetration to the area of interest?
  - It doesn't necessarily matter how much you give the patient…the issue is how much it gets delivered to the location of interest

Degree of Ionization

- Most antibiotics are weak acids OR weak bases
  - Non-ionized = Lipophilic
    - Crosses biological membranes well
  - Ionized = Hydrophilic
    - Ie Poorly Lipid Soluble
    - Classic example: Gentomicin
- Depends on the pH of surrounding fluid
  - e.g; weak base antibiotic (un-ionized in plasma)
  - Crosses membranes well
  - Arrives in acidic infection site (becomes more ionized)
  - Abx remain “Ion-trapped” in the acidic environment

Culture Results: In Vivo vs In Vitro

- Minimize resistance:
  - Culture and Sensitivity whenever possible
- Consider degree of penetration
- Activity in infected environment

- Examples of problems:
  - Aminoglycosides and Rhodococcus
  - Pseudomonas in TTW
  - Kirby-Bauer Discs of Ceftiofur

Snyergy vs Competition

- Beta-Lactam/Cephalosporin w Aminoglycosides:
  - Beta-Lactam disrupt cell wall
  - Increases uptake of aminoglycosides

- Macrolide with Rifampin
  - Different Mechanisms – Combo Minimizes Resistance
  - Newer research suggests Rifampin may decrease oral absorption (and thus plasma concentrations of oral macrolides

- Beta-Lactams with Tetracycline?
  - Beta-Lactams require ACTIVELY dividing bacteria to disrupt cell wall
  - Tetracyclines inhibit replication so…
  - DECREASED EFFICACY

- Fluoroquinolone with Rifampin
  - -Floxacins require active protein synthesis for effect
  - Rifampin inhibits protein synthesis

Anti-microbial Associated Colitis

- High Concentrations
- Highly Lipid Soluble
- Long courses of treatment

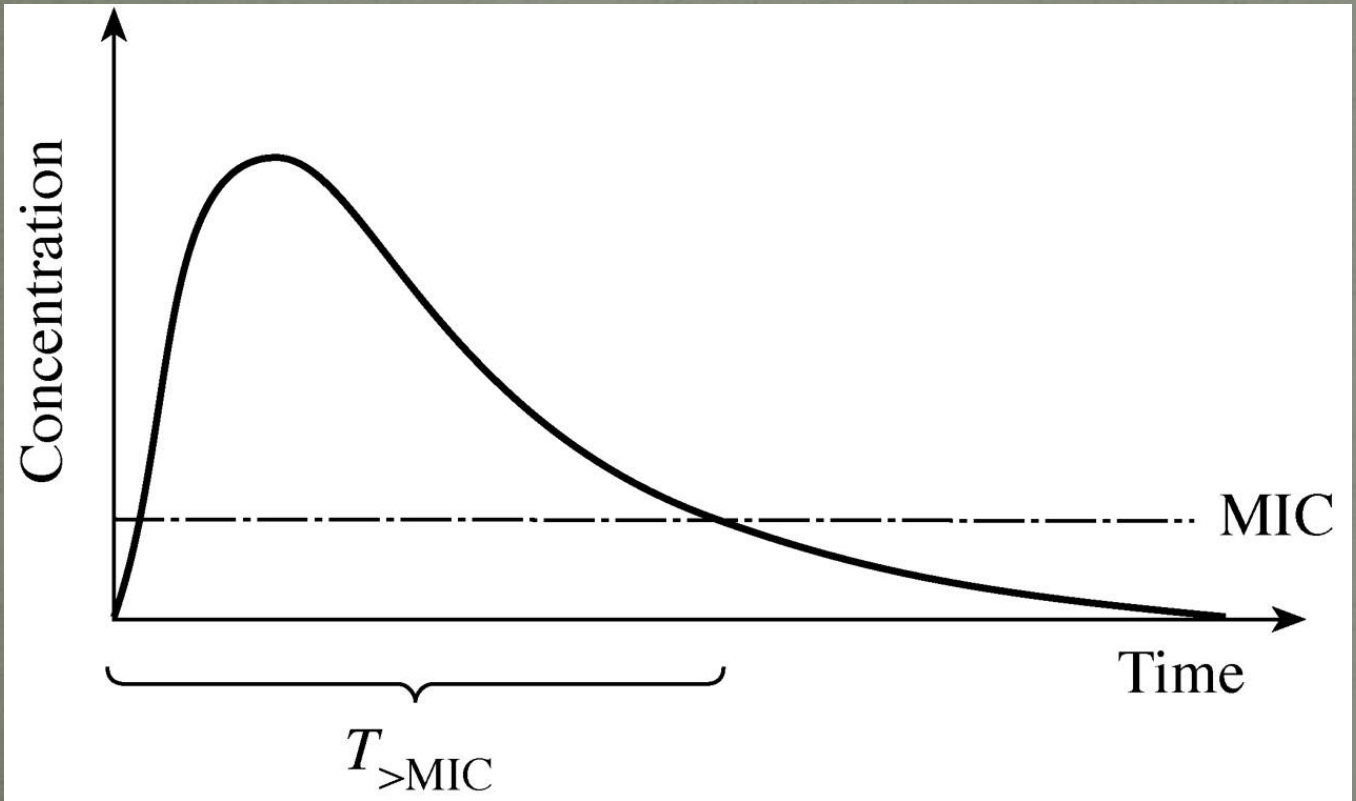
- Regional Variations
  - Nearly all classes of drug have been implicated

- Highly correlated to Clostridium difficile overgrowth
  - Toxins A/B commonly associated with disease

- Take Home: Have Clients Closely Monitor Appetite, Feces
  - A pause in antimicrobial therapy is preferable to colitis
  - Consider CBCs, fecal testing

Time vs Concentration Dependent

- Time dependent: Maintain MIC “all the time”



Concentration Dependent:

- Classic – Aminoglycosides
- (Many consider fluoroquinolones as well)

- *Prolonged Post Antibiotic Effect*

- Achieve 10x MIC

- Trough doesn't just minimize patient toxicity, but actually re-sensitizes organisms to drug at next peak

Beta-lactams: Penicillin and Cefalosporins

- Inhibit Cell wall Synthesis -
- Gram Neg frequently have Beta-Lactamase enzymes – conferring resistance
- Bacteriostatic drugs (Chloro, Tetracyclines) inhibit activity
- Moderate Anaerobic Activity
  - Bacteroides frequently resistant
  - Clostridium frequently Sensitive
    - EXCEPT C. difficile!

Penicillin: Risks

- Na+ and K+ Salts
  - Rapid Administration can cause cardiac arrythmias
- Procaine Reaction
  - Occurs when accidentally arrive IV
  - Ataxia, Hyper-excitability ("seizure"), Muscle Tremors, Apnea, Cardiac Arrest
- Immune-Mediated:
  - Anaphylaxis (Type I Hypersensitivity)
  - Immune-Mediated Anemia and/or Thrombocytopenia (Type II Hypersensitiity)

Penicillins: Take-Home

- Gram Positives, Anaerobes

- K+ or Na+ Peniillin:
  - 22,000 mg/kg IV QID
- Procaine Penicillin:
  - 22,000 mg/kg IM BID

- Beware:
  - Procaine reactions
  - Fatal Arrythmias
  - Anaphylaxis

Cefalosporins: 1st and 2nd Generation

- Work via same mechanism as Penicillins, but with increased resistance
  - First Generation
    - Kills Staph and Strep
    - Improved Gram Neg Spectrum (> Penicillins)
    - Most Anaerobes are susceptible
  - Second Generation
    - Decreased Staph Efficacy
    - Improved Gram Neg Spectrum (> 1st Generation)
    - Still get most Anaerobes
    - 2x Cost vs 1st Generation

Cefalosporins: 3rd Generation

- Gram Neg Activity Further Increased
- Use Sparingly!
  - Only with documented multiple drug resistance
- Gram Positive Spectrum generally Good
  - Pseudomonas
  - Listeria and Enterococcus are Resistant

Ceftiofur: 3rd Generation…

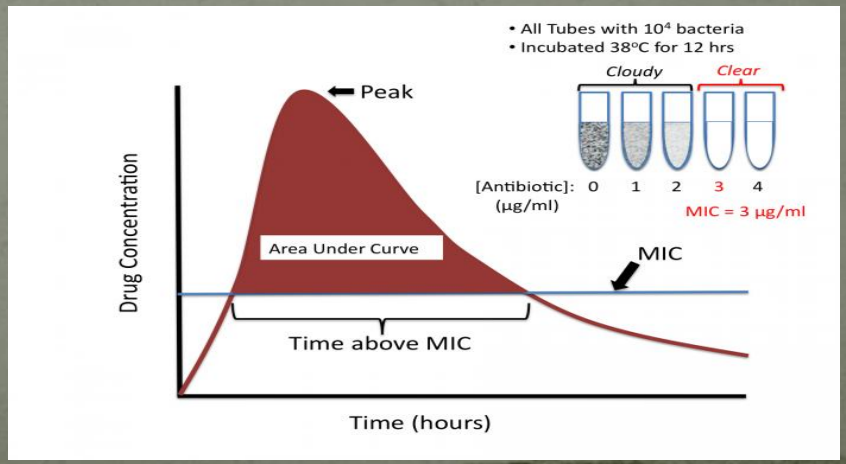
- Rapidly converted to desfuroyl-C in the liver
  - Hepatic disease may increase drug accumulation
- Enhanced gram negative spectrum
- Not effective against many Staph spp
  - Desfuroyl- is not active against most staph, even if ceftiofur is!
    - Staph aureus 4-8x LESS sensitive to defuroyl-C than ceftiofur
    - In vitro C sensitivity may be inaccurate
- Heavily Protein Bound
  - Especially bound to acute-phase proteins
    - Act as reservoir of the active drug
    - Carries bound drug to sites of inflammation
      - α_1_antitrypsin

Sulfa Drugs

- Inhibit folic acid pathway of nucleic acid synthesis
  - Substitute for PABA – static
  - -cidal in combination with pyrimethamine
- Broad Spectrum – many Gram pos and neg susceptible
- Minimal effect on Anaerobes
- Pyrimethamine gets protozoa
- Absorption as low at 56% if administered w food
- Ineffective in pus and necrotic tissue
  - Additional souces of PABA are present there

Sulfas w Trimethoprim: – once daily dosing?

- Efficacy varies with type of sulfa
- Efficacy depends most on maintaining adequate trimethoprim constituent
  - This requires twice daily dosing
- Sulfadiazine ("tucoprim" powder): 3-4 hr half-life
- Sulfamethoxazole ("Bactrim" tabs): 3.5-5 hr half-life



Sulfas: Complications

- Rifampin shortens the half-life
- Procaine penicillin may inactivate
  - Procaine is a PABA analogue

- Pregnant mares – folate synthase may be inhibited
  - Provide adequate fresh grass if long-term administration
  - OR provide folate

Sulfas: Take Home

- Trimethoprim Sulfamethoxizole (Tabs, Paste)
  - Hepatic Clearance
  - Broad Spectrum
- Trimethoprom Sulfadiazine (Powder)
  - Increased renal clearance
  - Good for UTIs
- 30mg/kg PO BID

Tetracyclines

- Inhibit bacterial protein synthesis
  - Enter cell via diffusion and tetracycline transporter
  - Mammalian cells lack transporter
- Lipophilc and most active at acidic pH
  - Excellent against abscesses
  - Doxycycline has the highest oral availability
- Broad-speectrum
  - Not good against staph, enterococcus and other gram negative enterics
- Nephritis Risk:
  - Oxytet – risk with high doses, concurrent dehydration or renal dz
- Dysbiosis Risk:
  - Clostridium difficile? Salmonella?

Tetracyclines: Take Home

- Doxycycline: 10mg/kg PO BID
- Broad-spectrum, inexpensive oral med
- Unlikely to effectively treat many anaerobes
- Watch GI signs

Fluoroquinolones

- DNA gyrase inhibitors
- Extremely lipid soluble
  - Kidneys, Urine, Liver, Bile
  - Endometrial tissue, synovial structures
- Concetrated in phagocytic cells
  - Enhanced killing at site of action
- Good Spectrum:
  - Gram Negative Enterics
  - Many Staphylococci
    - Resistant Staph may actively pump drug out of cell
    - Other mechanisms in Pseudomonas, Pasteurella
- Concentration Dependent
  - Except: Optimal concentration may not be PEAK concentration

Fluoroquinolones: Take-Home

- Enrofloxacin: IV, IM, or ORAL
  - 5 mg/kg IV SID
  - 7.5 mg/kg PO SID
  - Avoid IM use
- Good Spectrum
- Post Antibiotic Effect:
  - Prolonged periods between doses acceptable
  - Client compliance!!
- Risk Factors:
  - Cartilage damage
    - Avoid use in horses <6 yrs old

Metronidazole

- Very Lipophilic
- Complications:
  - Moderate doses may decrease appetite
  - Long term or high dose: ataxia, lethargy, anorexia, seizures
- Spectrum
  - Anaerobic Infections
    - Effective against most Clostridia spp
  - Protozoa
    - Giardia
  - (Not in food animals)

Metronidazole: Take Home

- Wide dose range: 10-25 mg/kg PO, TID to QID
- Excellent for anaerobes
  - Oral, sinus infections
  - Anaerobic abscesses
- Treats Anti-microbial associated colitis:
  - Clostridium difficile
  - Salmonella
- Decreased appetite frequently occurs
  - Consider administration per rectum
  - 70% absorption

Chloramphenicol and Florfenicol

- Chloro isolated from a soil actinomycete from Venezuala in 1947
- Very Lipophilic
  - Penetrates synovial fluid
  - High hepatic and renal concentrations
- Very Broad Spectrum

- Antagonizes beta-lactams, aminoglycosides
- Bone Marrow Suppression has not been seen with florfenicol
- Anti-microbial associated colitis: florfenicol

Chloramphenicol: Take Home

- 30-50 mg/kg PO TID-QID
- Broad spectrum
- Minimal Resistance

- Relatively expensive
- Compliance Issues
- Human health risks?
    - Consider compounding

Macrolides

- Active within leukocytes
  - Highly lipid-soluble
  - Ion Trapping
- Inhibits protein synthesis
  - Similar mechanism to chloramphenicol, florfenicol
- Diverging Reports on tulathromycin
  - Some evidence of good safety and efficacy
- Narrow Spectrum:
  - Pasteurella, Haemophilus
  - Mycoplasma
  - Rhodococcus equi

Macrolides: Take Home

- Azithromycin: 10mg/kg PO SID
- Clarithromycin: 10mg/kg PO SID
- Complications:
  - Hyperthermia
  - Diarrhea

Rifampin

- Suppresses RNA Synthesis
- Resistance occurs rapidly
  - Mycobacterial history
- Rhodococcus and Mycobacteria

- Highly Lipophilic
  - Penetrates CNS, Abscess Capsules
- 5 mg/kg PO BID

- Take Home: Internal Abscesses of ANY sort
  - Including refractory Osteomyelitis
- Use in combination with other meds to minimize resistance

Aminoglycosides: Spectrum

- Initially developed to treat TB
  - Effective against Gram Neg Enterics
  - Newer Ags: Gentamicin, Tobramicin
    - Also Typ. effective against Pseudomonas

  - Inhibits normal protein synthesis: ribosomes are mis-read
  - Tx: Gram Negative, Staph
- Must be pumped into bacterial cell
    - Anaerobes not affected – Bacterial uptake is O_2-dependent
- Decreased effect in acidic abscess

- Proper Dosing is Critical
  - Both frequency AND dosage
  - Resistance occurs quickly – but reverses when blood levels wane

Aminoglycoside Toxicity

- Highly ionized at blood pH = hydrophilic
- Renal filtration
  - Concentrated in renal tubules = toxicity
  - Similar to bacterial metabolism: Renal tubular cells "heal" when drug concentrations wane
  - Initial doses are safer than repeated doses
  - Dehydration, shock, endotoxemia and diuretics = Risk!
  - Clinical signs and chemistry changes may be delayed
    - Monitor Urinary output
    - Monitor for casts

Gentomicin & Amikacin

- Amikacin:
  - Lowest resistance:
    - Reserved for gentomicin-resistant bacteria
    - Regional perfusion = effective treatment of most pathogens in joint fluid, bone and serum of treated limb

- Gentomicin:
  - Proteus, Klebsiella, Pseudomonas
  - 6.6 mg/kg IV SID
  - 24 hours usually enough to allow the bacterial cells to resume sensitivity

Aminoglycosides: Take Home

- Concentration dependent
  - Ie peak concentration confers bacterial killing
  - Long post-administration effect
    - Continued bacterial susceptibility
- Gentomicin: 6.6 mg/kg IV SID
- Amikacin: 21 mg/kg IV SID
  - Increase concentrations in foals due to high ECF
  - >80% vs 60% in adults
- Synergy with Beta-Lactams
- Regional Limb Perfusions

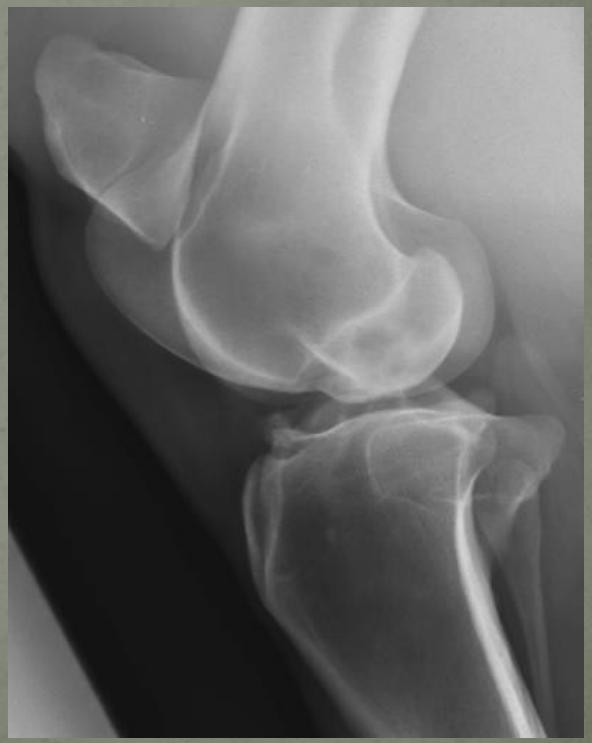
Therapeutic Drug Monitoring

Regional Limb Perfusions:

- Acheives 10-20x concentration in local tissue
- Beta-lactams have been used
  - Ceftiofur
  - Imipenem-Cilastin
- Resistance may increase with daily treatments
  - Consider q48 hr tx
- Best efficacy: concentration-dependent drugs
  - Long Post-administration effect:
    - Aminoglycosides
    - Fluoroquinolones

Regional Limb Perfusions: IV vs IO

- Synovial and subQ concentrations are higher IV
- IV is more convenient
- Limited IV repeatability



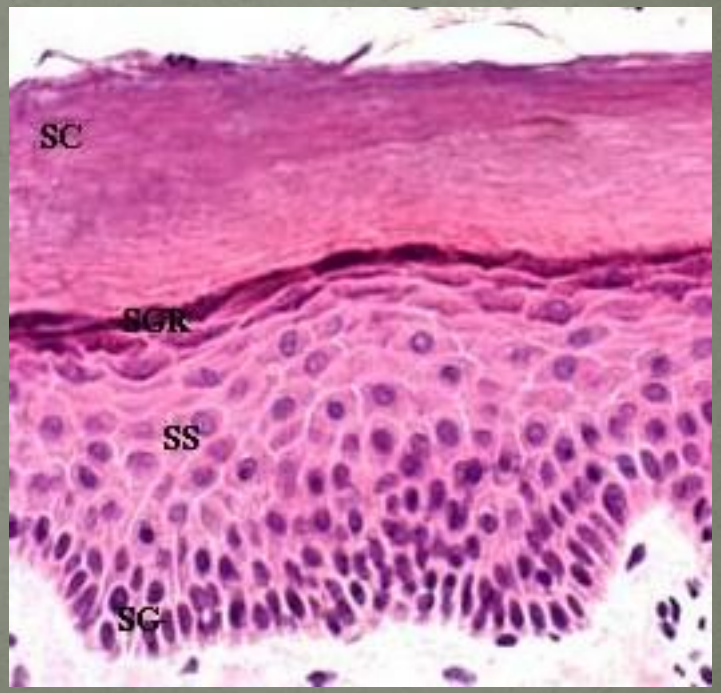
- Subchondral bone – consider IO

Intra-Synovial: Prophylactic vs Therapeutic

- Cefalosporins and other beta-lactamase-resistant meds
  - imipenem
- Typical preventative & tx:
  - Aminoglycosides
    - Concentration-dependent effect
    - Minimal irritation to synovium
    - Spectrum:
      - Enhanced by high local concentrations
        - 10x MIC
      - Staph
      - Gram Negative Enterics

Topical Meds

- Enhance absorption:
  - DMSO
  - Perfuse periph tissues
- Efficacy is based on:
  - Mechanism of action
  - Contact time
  - Penetration to site of infection
    - Biologic barriers!



- Thank you!!!
- Please feel free to call or email with follow-up questions!!!

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Pleuropneumonia

Synovial infection

Anaerobic Abscess

DIC Foal