Objectives

- Introduction to basic antimicrobial principals
  - Pharmacokinetics
  - Pharmacodynamics
- Provide an overview of some of the most common antimicrobial drug classes
  - ß-lactam antibiotics
  - Aminoglycosides
  - Fluoroquinolones
  - A few others…

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Background

- Basic mechanism of action:
  - Time-dependant killing
  - Concentration-dependant killing
- Pharmacokinetics (PK)
  - Peak & Trough serum concentrations
  - Half-life (T ½)
  - Source of metabolism
  - Source of excretion (kidney, GI, etc)
- Pharmcodynamics (PD) – relationship between PK & minimum inhibitory concentration (MIC)

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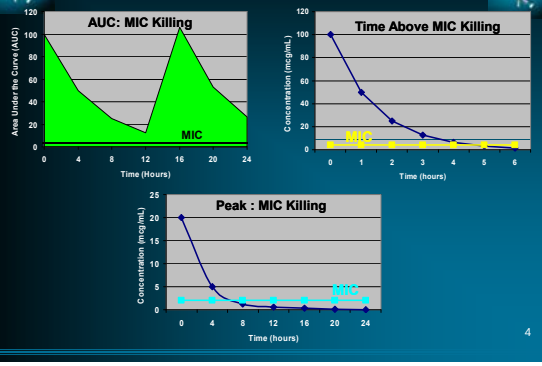
PD Principals



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PD Goals

Parameter	Goal	Antimicrobial Drug Classes
Time above MIC	>50-60% of the dosing interval	• All ß-lactams • Macrolides • Linezolid
Peak Conc : MIC ratio	≥ 10:1	Aminoglycosides vs. Gram(-) organisms
Area under the Curve (AUC) : MIC ratio	• ≥ 30-50:1 • ≥ 125:1	• Fluoroquinolones vs. Gram(+) orgs • Fluoroquinolones vs. Gram(-) orgs

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Patient Case: JR

- 73yom s/p AAA repair & then L-carotid endarterectomy
- *Pseudomonas* pneumonia:
  - S: Zosyn (MIC=64), Tobramycin (MIC≤1)
  - I: Cefepime (MIC=16)
- Current Antibiotics:
  - Cefepime 1g IV q6h
  - Tobramycin 540mg IV q48 (7mg/kg)
- *Is this adequate therapy?*

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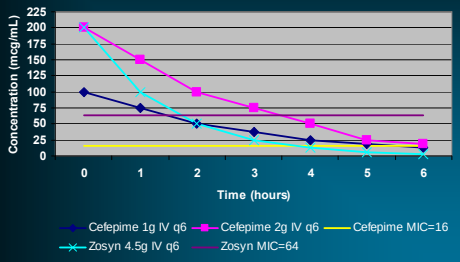
JR

Pharmacodynamic Modeling



PLAN: Increase Cefepime to 2g IV q6

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Mechanisms of Action

Mechanism of Action	Antibacterial Family
Inhibition of Cell Wall Synthesis	• ß-lactams • Vancomyicn
Inhibition of protein synthesis	• Aminoglycosides • Linezolid • Tetracyclines
Inhibition of DNA synthesis	• Fluroquinolones
Inhibition of folic acid synthesis	• Trimethoprim/ Sulfamethoxazole (Bactrim)
Inhibition of RNA synthesis	• Rifampin
Disruption of cell membrane integrity	• Daptomycin • Polymyxin B, E (Colistin)
Other	• Metronidazole • Nitrofurantoin

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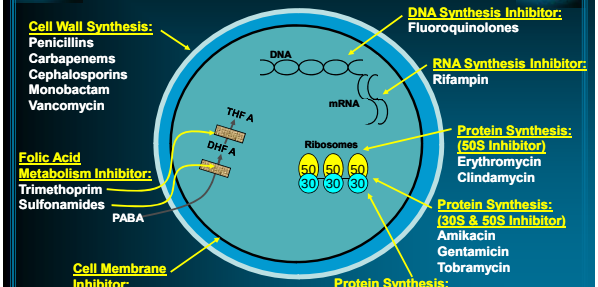
Mechanisms of Action



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Penicillins

- Bactericidal cell-wall synthesis inhibitors
- Gram(+) activity maintained across spectrum
- Gram(-) activity dependent on ability to cross porin channels
- ß-lactamase inhibitor combinations:
  - Methicillin-Sensitive *S. aureus* (MSSA) coverage
  - Enhanced anaerobic activity

http://www.pastorschwarz.cz/www/web/knihovna/internet/Penicillium%20notatum.gif

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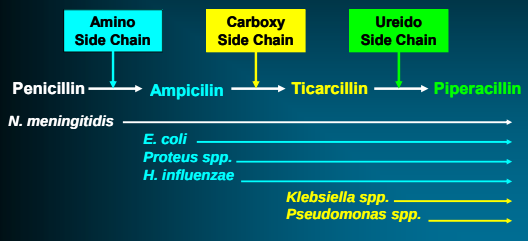
PCN Gram(-) Spectrum of Activity



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Penicillins

- Major Adverse Events:
  - Anaphylaxis
  - Rash and/or hives
  - Seizures
- Anti-*Staphylococcus aureus* Penicillins
  - Resistant to ß-lactamase
  - NO Gram(-) activity
  - ORMC Formulary: Nafcillin 2g IV q4 (no renal adjustment)

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Extended-Spectrum Penicillins

- Piperacillin/Tazobactam (Zosyn®)
  - Sodium content → 1.85 mEq per gram
  - Dosing:
    - Serious Infection/Pneumonia: 4.5g IV q6
    - Other Infections: 3.375g IV q6
- Ticarcillin/Clavulanic Acid (Timentin®)
  - Sodium content → 5.2 mEq per gram
  - 2nd Line agent for *Stentrophomonas maltophilia*

Cephalosporins

- Bactericidal cell-wall synthesis inhibitors
- DO NOT treat *Enterococcus spp.*
- Gram(+) activity generally decreases with each generation
- Gram(-) activity increases with generation
- Weak anaerobic activity with 2nd generation

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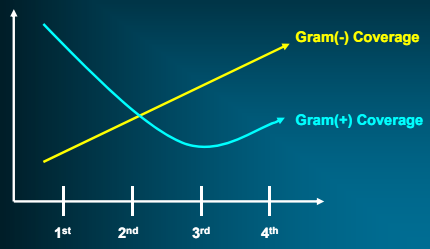
Cephalosporin Spectrum of Activity



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Cephalosporins

- 1st Generation (EX: Cefazolin)
  - Excellent *MSSA* activity
  - Some Gram(-) activity – *E. coli, Klebsiella*
  - Major role in surgical prophylaxis
- 2nd Generation (EX: Cefotetan, Cefoxitin)
  - Good Gram(-), moderate Gram(+) & anaerobic coverage
  - Primarily used for abdominal surgery prophylaxis

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Cephalosporins

- 3rd Generation (EX: Ceftriaxone, Ceftazidime)
  - 1st ß-lactams with *Pseudomonas* coverage (Ceftazidime)
  - Ceftazidime selects out multi-drug resistant organisms (MDR Gram(-), VRE, *C. difficile*, MRSA)
  - Ceftriaxone –
    - Excellent CSF penetration
    - Excellent *Streptococcus pneumoniae* drug
- 4th Generation (EX: Cefepime)
  - Excellent *MSSA* and *Pseudomonas spp* coverage



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Cephalosporins

- Major Adverse Events
  - Rash
  - Anaphylaxis
  - Seizures
- Cross-Sensitivity with Penicillins
  - 1-10%
  - Concern if patient has history of anaphylaxis

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Carbapenems

- Bactericidal cell-wall synthesis inhibitors
- Broadest-spectrum antimicrobials available
- Stable against most ß-lactamases
- Some *intrinsic* Resistance:
  - *Enterococcus faecium*
  - *MRSA*
  - *Stenotrophomonas maltophilia*
  - *Burkholderia spp.*
  - PCN-resistant *S. pneumoniae*

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Carbapenems

- 4 Drugs:
  - Imipenem/Cilastatin (Primaxin®)
  - Meropenem (Merrem®)
  - Ertapenem (Invanz®)
  - Doripenem (Doribax®)

- Incomplete class cross-resistance
- Major Adverse Events:
  - Seizures (Imi >> Mero >> Dori)
  - Rash
  - Anaphylaxis
- Cross-Sensitivity with Penicillins < 1%

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Monobactam

- A.K.A.: Aztreonam (Azactam®)
- Bactericidal cell wall synthesis inhibitor
- Pure Gram(-) coverage –
  - including *Pseudomonas*
- No cross-sensitivity with penicillins / cephalosporins
- Major Adverse Events:
  - Rash
  - GI upset
  - Injection-site thrombophlebitis

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Fluoroquinolones

- DNA synthesis inhibitors:
  - DNA-gyrase inhibitor in Gram(-) bacteria
  - Topoisomerase IV inhibitor in Gram(+) bacteria
- Concentration dependant killers
  - Gram(-) AUC:MIC Goal ≥ 125:1
  - Gram(+) AUC:MIC Goal ≥ 10:1

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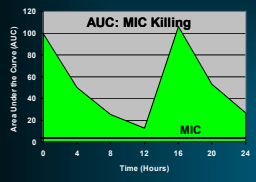
Fluoroquinolones



Cipro 400mg IV – AUC~25

Pseudomonas MIC ≤0.25

Urine AUC:MIC = 100:1

Sputum AUC:MIC = 10:1 (only ~10% penetration)

- Anti-*Pseudomonal* Agents:
  - Ciprofloxacin
  - Levofloxacin (non-formulary)

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Fluoroquinolones

- Gram(+) Coverage:
  - Class has POOR *Staphylococcus aureus* drugs
  - Select out MRSA
  - Newer agents excellent *Strep. pneumoniae* coverage
- Major Adverse Events:
  - QT Prolongation
    Moxifloxacin >>> levofloxacin >>> ciprofloxacin
  - *C. difficile* colitis
- Drug Interactions: phenytoin, warfarin

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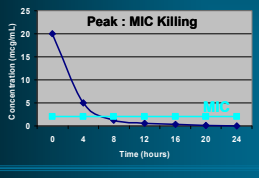
Aminoglycosides

- Inhibit bacterial protein synthesis at 30S & 50S ribosomal subunits
- Concentration-dependant killers
  - Goal Peak : MIC = 10 : 1
  - Post-antibiotic effect



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Aminoglycosides

- Place in Therapy:
  - Treatment of Gram(-) Infections
  - Gentamicin for Gram(+) synergy in combination with a ß-lactam or vancomycin
- Major Adverse Events:
  - Nephrotoxicity (high trough)
  - Ototoxicity (prolonged duration of therapy)
- Drug Interactions:
  - Neuromuscular blockers

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Aminoglycosides

- Gentamicin/Tobramycin
  - Gram(-) non-Burn: 7mg/kg IV q24
  - Gram(-) Burn: 2.5-3mg/kg IV q8-12h
  - Gentamicin Gram(+) Synergy: 1mg/kg IV q8
- Amikacin
  - Gram(-) non-Burn: 15-20mg IV Q24
  - Gram(-) Burn: 7.5 mg/kg IV Q8

Dose Calculator: www.surgicalcriticalcare.net

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Aminoglycosides

- Colistin (Polymyxin E)
  - Reserved for multi-drug resistant Gram(-) orgs
  - Nebulized: 150mg inhaled q12h
  - IV (VERY nephrotoxic): 2.5 mg/kg IV q8-12
- Polymyxin B
  - Also reserved for multi-drug resistant orgs
  - IV: 15,000-25,000 units/kg/day divided q12
- No way to monitor levels for IV polymyxins

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Aminoglycosides

Polymyxin B & Colistin

- Major Adverse Events:
  - Nephrotoxicity
  - Neurotoxicity
- Drug Interactions:
  - Neuromuscular blockers

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Vancomycin

- Inhibits bacterial cell wall synthesis
- Time-dependant killer (time above MIC)
  - Some concentration-dependant characteristics
- Uses:
  - IV: treatment of Gram(+) infections
  - PO: treatment of *C. difficile* colitis

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Vancomycin

- Dosing:
  - IV: 20mg/kg IV x1, then 15mg/kg IV q8-12h
  - PO: 125-250mg PO q6h
- Major Adverse Events:
  - Red Man Syndrome – *slow down infusion*
  - Not nephrotoxic – but accumulates

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Linezolid (Zyvox®)

- Oxazolidindione – inhibits bacterial protein synthesis
  - Bacteriostatic: *Enterococcus, Staphylococcus*
  - Bacteriacidal: *Streptococcus*
- DOC: VRE
- Large volume of distribution
- Dosing: 600mg IV/PO q12

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Linezolid (Zyvox®)

- Major Adverse Events
  - Thrombocytopenia/Pancytopenia
  - Blurred vision
  - Serotonin Syndrome
- Drug Interactions
  - Selective Serotonin Reuptake Inhibitors (SSRIs)

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Synercid®

- Quinupristin/Dalfopristin – inhibits bacterial protein synthesis
- Major organisms:
  - *VRE*
  - *MSSA & MRSA*
  - *Streptococcus pyogenes*
- Dose:
  - 7.5mg/kg IV q8-12 (no renal adjustment)

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Synercid®

- Major Adverse Events
  - Hyperbilirubinemia
  - Infusion site reaction
  - Infusion-related arthralgias/myalgias
- Drug Interactions
  - No significant

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Daptomycin

- Cell membrane disruption leading to inhibition of DNA/RNA/protein synthesis
- Bacteremia, Endocarditis, Skin/Soft Tissue infections
- Does NOT treat pneumonia!
- Spectrum of Activity:
  - *MRSA*
  - *VRE*

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Daptomycin

- Dose:
  - 4-6mg/kg IV q24
  - Adjust for renal dysfunction
- Major Adverse Events:
  - Anemia
  - Constipation/N/V
  - Injection-site reactions

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Bactrim®

- Sulfamethoxazole/Trimethoprim
- Interferes with bacterial folic acid synthesis
- Drug of Choice:
  - *Stenotrophomonas maltophilia*
  - *Pneumocystis carinii* pneumonia (PCP)
  - Alternative for *MRSA*

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Bactrim®

- Dosing:
  - Based on Trimethoprim (TMP) component
  - UTI: Bactrim® DS (800/160) 1 po bid
  - Severe Infections (MRSA/PCP/*Stenotrophomonas*): 5 mg TMP/kg IV/PO/PT q6-8h
  - Adjust for renal dysfunction

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Bactrim®

- Major Adverse Events:
  - Stevens-Johnson Syndrome
  - Rash
  - Hyponatremia (IV)
  - Hyperkalemia
  - GI upset (large PO doses)

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Tetracyclines

- Inhibit bacterial protein synthesis
- Bacteriostatic
- Spectrum of Activity
  - Gram (+) including *MRSA*
  - Gram (-)
  - Atypicals (*Mycoplasma, Chlamydia, Rickettsia)*
  - Alternative for *H. pylori*

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Tetracyclines

- 3 Agents:
  - Tetracycline 250-500mg po q6
  - Doxycycline 100mg po/IV q12
  - Minocycline
- Major Adverse Events:
  - Photosensitivity
  - Teeth/enamal discoloration in children
  - Hepatotoxicity

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Tigecycline

- A glycylcline – protein synthesis inhibitor
- Spectrum of Activity:
  - Gram (+) including *MRSA* and *VRE*
  - Gram (-) including *E. coli & Klebsiella*
  - Anaerobes
- Does not cover:
  - *Pseudomonas spp.*
  - *Proteus spp.*

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Tigecycline

- Dose: 100mg IV x1, 50mg IV q12
- Major Adverse Events:
  - N/V
  - Abdominal pain
  - Super infections *(P. aeruginosa, Proteus)*

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Macrolides

- Inhibit RNA-dependant protein synthesis
- Spectrum of Activity
  - Gram (+) – including *MSSA*
  - Gram (-) *(Haemophilus spp)*
  - Atypicals *(Chlamydia spp, Mycoplasma, Legionella)*
- Several Agents:
  - Erythromycin
  - Clarithromycin
  - Azithromycin

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Macrolides

- Erythromycin
  - Used for ADE – GI motility
  - Used for surgical prophylaxis with neomycin
- Azithromycin – used for CAP
- Clarithromycin – used for CAP, *H. pylori*
- Major Adverse Events:
  - Abdominal pain/cramping (E >> C >> A)
  - N/V/Diarrhea
  - Headache

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Clindamycin

- Inhibits bacterial protein synthesis
- Spectrum of Activity
  - Gram (+) – *MSSA, Streptococcus,* some *MRSA*
  - Anaerobes
- Excellent alternative for Penicillin-allergic patients
- Major Adverse Events:
  - Diarrhea

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Metronidazole

- Interacts with DNA causing strand breakage and ultimately inhibits protein synthesis
- Spectrum of Activity: Anaerobes
  - *C. difficile* diarrhea
- Major Adverse Events:
  - N/V
  - Diarrhea
- Dosing:
  - *C. difficile:* 500mg PO/PT q6

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Antimicrobial Resistance

- Unsuppressed production of β-lactamase
  - AMP_C
  - ESBL
- Alteration in bacterial cell membrane
  - Vancomycin-resistant *Enterococcus*
- *Pseudomonas spp.*
  - Aminoglycoside-altering enzymes
  - Efflux pump – pump out drug
  - Alter porin channel – drug can't get in

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Take Home Points

- Penicillins – increase Gram(-) and maintain Gram(+)
- Addition of β-lactamase inhibitor = anaerobic coverage
- Cephalosporins – avoid 3rd generation
- Carbapenems – reserve for last resort
- Vancomycin – aim high trough
- Pharmacodynamic-based drug dosing

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