Introduction to Antimicrobial Therapy

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Case #1

- L.G. is a 78 yo woman admitted for cardiac cath. 3-vessel disease was identified and she was taken to the OR for CABG.
- Post-op in CTICU - patient did well. Extubated on POD#2.
- Transferred to the floor POD#4
- POD#6: spiked a temp to 101.7 with respiratory distress. Re-intubated and transferred back to the ICU. Blood, urine, sputum cultures were obtained.

Case #1 *(cont.)*

- The decision is made to start the patient on broad-spectrum antibiotics for presumed pneumonia
- The Surgery Resident, being his first week, is unsure which antibiotic to start, but remembers that piperacillin/tazobactam is “a broad-spectrum antibiotic”
- What questions should the resident ask himself in deciding which antibiotic to choose?

Case #2

- 68 y.o. female with HTN, anxiety with chest pain symptoms
- 7/27/05: Cath - 3 vessel CAD with normal LV function
- 9/12/05: admitted for CABG x 4 with LIMA without complications
- 9/13/05: extubated, diffuse ECG changes c/w pericarditis, a-fib, worsening hypotension, increased pressor requirements, re-explored in OR (RV failure)
- 9/14/05: hypotension with low filling pressures, severe cardiogenic shock with ARDS, VF arrest, emergent sternotomy, IABP placed
- 9/18/05: IABP d/c’d, duotube placed
- 9/19/05: extubated
- 9/21/05: re-intubated

Case #2 *(cont.)*

- 9/23/05: febrile, increase in pressor requirements, blood cultures drawn, started empiric antibiotics: vancomycin 1g IV q24h + piperacillin/tazobactam 4.5 g IV q8h

Question: Are these empiric antibiotics appropriate?

- Spectrum?
  - Consider existing culture and susceptibility results
- Doses?
  - Consider existing or potential microbiology
  - Consider site of infection
  - Consider end-organ function

- 9/25/05: blood cultures +*P. aeruginosa*, tobramycin 160 mg IV q24h added, central lines changed (cordis, PA catheter)
- 9/27/05: cath tip +*P. aeruginosa*, *C. albicans;* additional blood cultures drawn

Question: Is the addition of tobramycin appropriate?

- Synergy?
- Dose?

What You Need to Know to Treat with Antibiotics…

- Know the drugs
- Know the microbiology
- Know the patient

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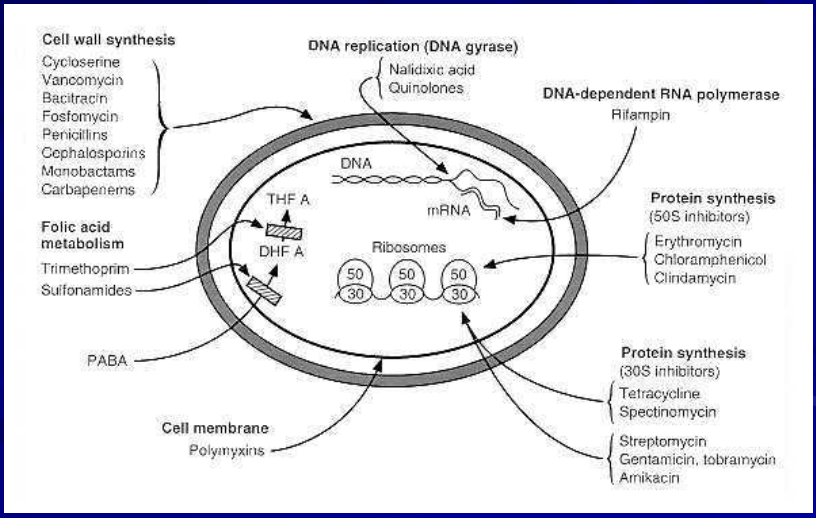
What are Antimicrobials???

- Antimicrobials are drugs that destroy microbes, prevent their multiplication or growth, or prevent their pathogenic action
  - Differ in their physical, chemical, and pharmacological properties
  - Differ in antibacterial spectrum of activity
  - Differ in their mechanism of action

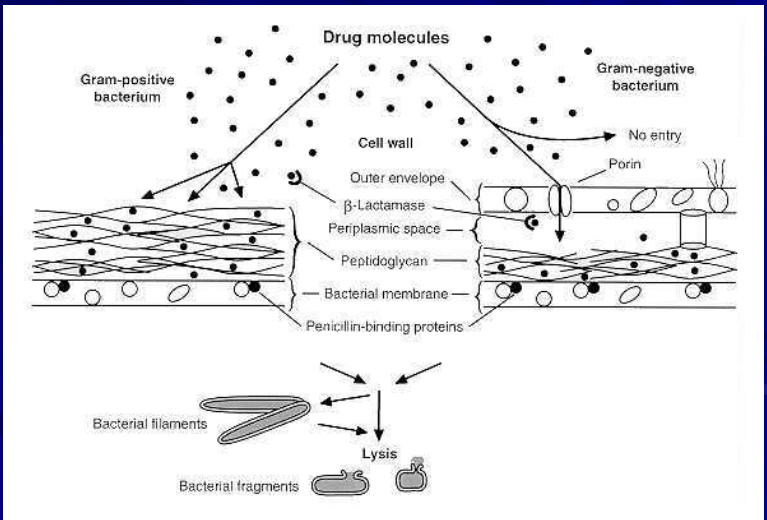
Classification of Antimicrobials

- Inhibit cell wall synthesis
  - Penicillins
  - Cephalosporins
  - Carbapenems
  - Monobactams (aztreonam)
  - Vancomycin
- Inhibit protein synthesis
  - Chloramphenicol
  - Tetracyclines
  - Glycylcycline (tigecycline)
  - Macrolides
  - Clindamycin
  - Streptogramins (quinupristin/dalfopristin)
  - Oxazolidinones (linezolid)
  - Aminoglycosides
- Alter nucleic acid metabolism
  - Rifamycins
  - Quinolones
- Inhibit folate metabolism
  - Trimethoprim
  - Sulfonamides
- Miscellaneous
  - Metronidazole
  - Daptomycin
  - Polymyxins

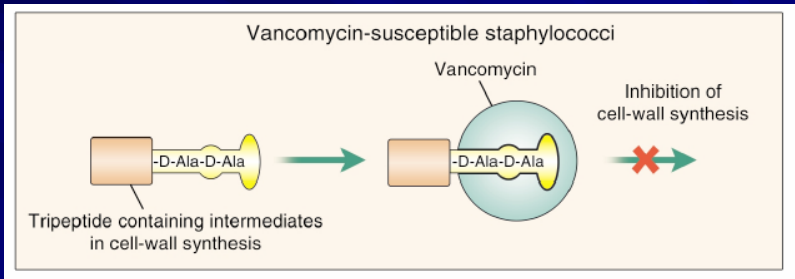
Classification of Antimicrobials



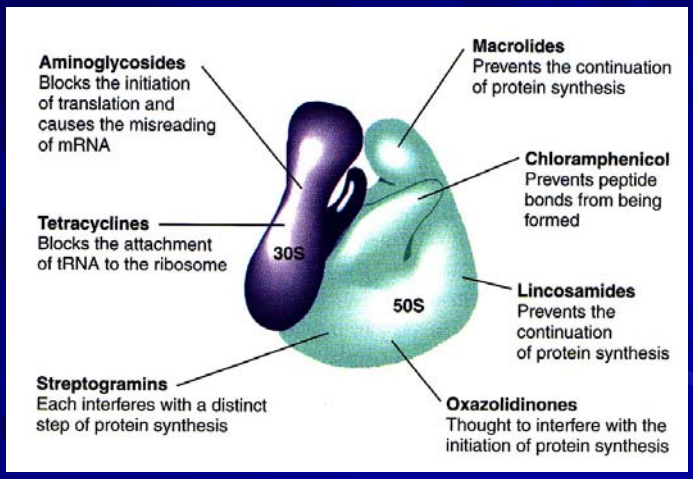
Beta-lactams



Vancomycin

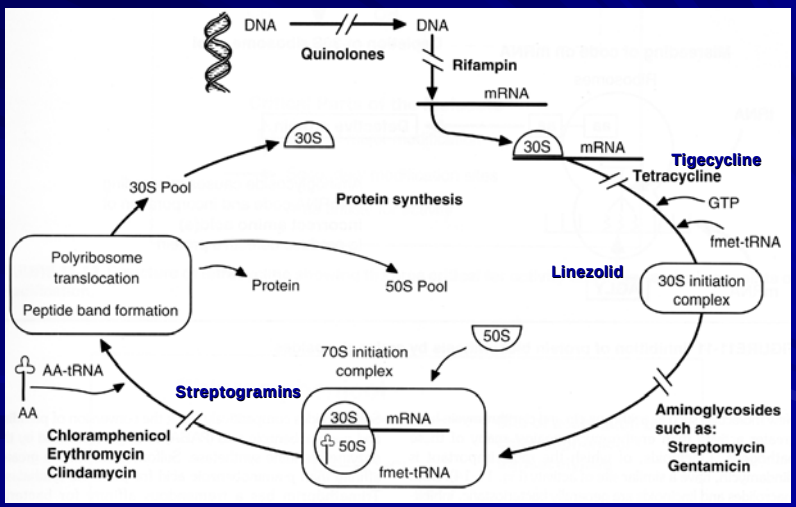


Protein Synthesis Inhibitors



Slide courtesy of Frank Lowy

Mechanisms of Action – Protein Synthesis Inhibitors



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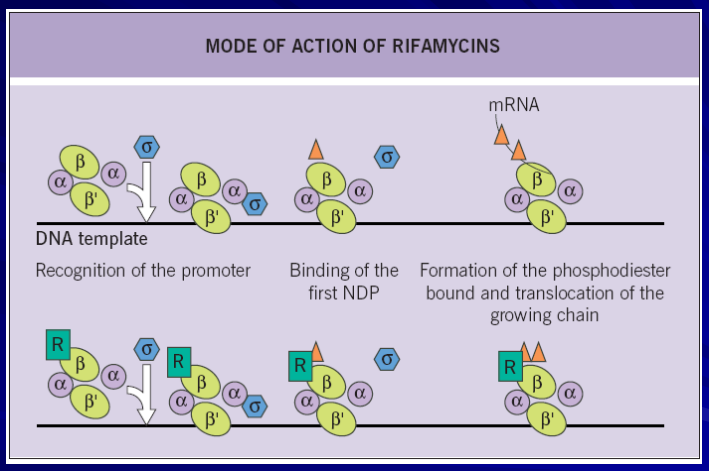
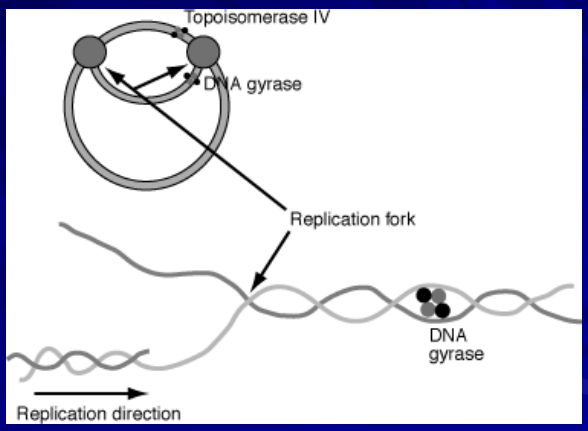
Rifamycins



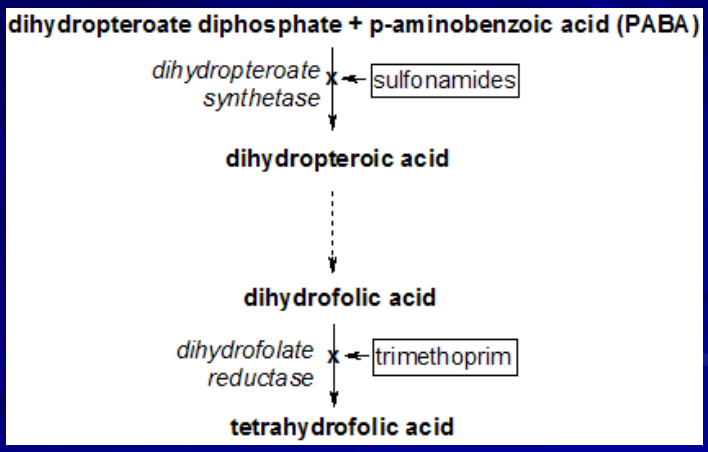
Rifamycins inhibit the β subunit of DNA-dependent RNA polymerase. Binding does not allow initiation of chain formation in RNA synthesis.

Quinolones



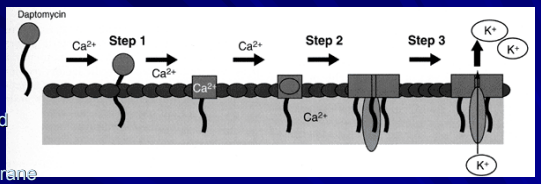
Inhibit the activity of topoisomerases, which are enzymes responsible for the supercoiling of the DNA (DNA gyrase) and relaxation of the supercoiled DNA (topoisomerase IV)

Inhibitors of Folate Metabolism



Miscellaneous

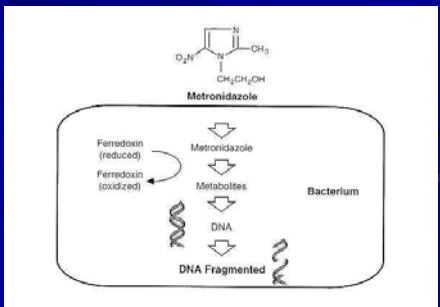
- Daptomycin



  - Calcium-dependent binding and insertion of the lipophilic tail into gram-positive cytoplasmic membrane
  - Oligomerization and channel formation occurs
  - Ion leakage and collapse of organism leads to cell death

- Metronidazole

  - Metronidazole enters a bacterium where, via the electron transport protein ferrodoxin, it is reduced. The drug then binds to DNA and DNA breakage occurs.



Antimicrobial therapy

- **Empiric**
  - Infecting organism(s) not yet identified
  - More “broad spectrum”
- **Definitive**
  - Organism(s) identified and specific therapy chosen
  - More “narrow” spectrum
- **Prophylactic or preventative**
  - Prevent an initial infection or its recurrence after infection

What You Need to Know to Treat with Antibiotics…

- Know the drugs
- **Know the microbiology**
- Know the patient

Culture Results

- Minimum inhibitory concentration (MIC)
  - The lowest concentration of drug that prevents visible bacterial growth after 24 hours of incubation in a specified growth medium
  - Organism and antimicrobial specific
  - Interpretation
    - Pharmacokinetics of the drug in humans
    - Drug's activity versus the organism
    - Site of infection
    - Drug resistance mechanisms
- Report organism(s) and susceptibilities to antimicrobials
  - Susceptible (S)
  - Intermediate (I)
  - Resistant (R)

Culture Results
Example

BLOOD CULTURE 2004-07-30 10:56	
SPECIMEN DESCRIPTION:	BLOOD
CULTURE:	POSITIVE FOR ESCHERICHIA COLI (*sens*)
CULTURE:	GRAM STAIN OF POSITIVE BOTTLE: GRAM NEGATIVE RODS REPORTED TO DR ----- AT 1119 ON 07/31/04
Collection time: 2004-07-30 10:56 Received time: 2004-07-30 10:56	
Status: final, Accno: F50319BCBLUD047U	

POSITIVE FOR ESCHERICHIA COLI																
METHOD:MICROSCAN MIC																
AMI	AMP	CFZ	CPM	CFT	CEZ	CTX	CRM	CIP	GEN	IMP	LVX	MER	P/T	TIM	TOB	T/S	PIP
<=4 S	<=8 S	<=4 S	<=2 S	<=4 S	<=2 S	<=8 S	<=4 S	<=1 S	<=1 S	<=4 S	<=2 S	<=4 S	<=8 S	<=16 S	2 S	<=2/38S	<=16 S

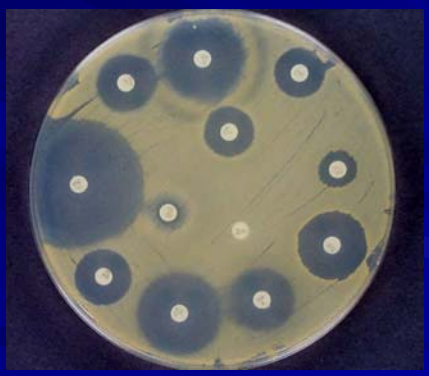
Culture Results
Example

BLOOD CULTURE 2004-06-02 10:42	
SPECIMEN DESCRIPTION:	BLOOD
CULTURE:	POSITIVE FOR ESCHERICHIA COLI (*sens*)
CULTURE:	GRAM STAIN OF POSITIVE BOTTLE: GRAM NEGATIVE RODS
Collection time: 2004-06-02 10:42 Received time: 2004-06-02 10:42	
Status: final, Accno: W30194BCBLUD0462	

POSITIVE FOR ESCHERICHIA COLI																	
METHOD:MICROSCAN MIC																	
AMI	AMP	CFZ	CPM	CFT	CEZ	CTX	CRM	CIP	GEN	IMP	LVX	MER	P/T	TIM	TOB	T/S	PIP
<=4 S	>16 R	>16 R	<=2 S	8 S	16 I	<=8 S	>16 R	>2 R	2 S	<=4 S	>4 R	<=4 S	<=8 S	64 I	2 S	<=2/38S	64 I

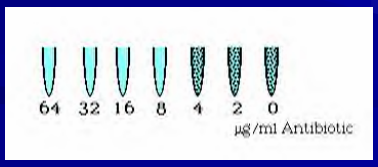
Susceptibility Testing Methods

- Disk Diffusion (Kirby-Bauer disks)



Susceptibility Testing Methods

- Broth Dilution



Susceptibility Testing Methods

- E-test (epsilometer test)

What You Need to Know to Treat with Antibiotics…

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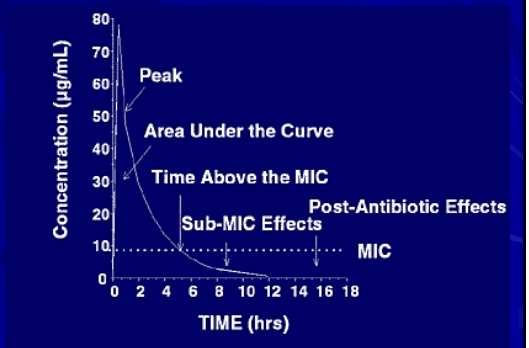
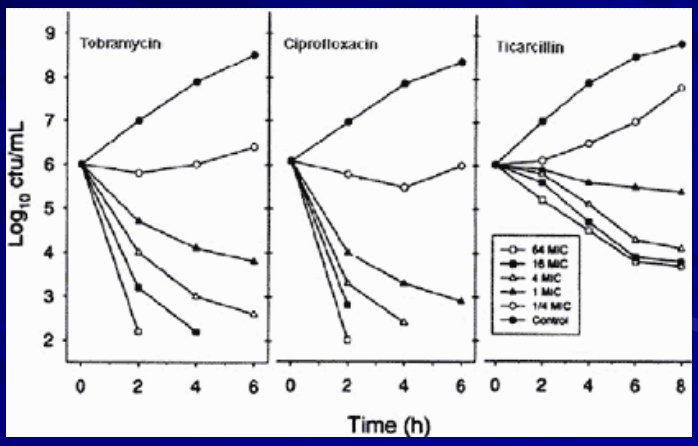
Pharmacokinetics, Pharmacodynamics, and the MIC

- Concentration vs. time-dependent killing agents
  - Concentration dependent agents ↑ bacterial killing as the drug concentrations exceed the MIC
    - Peak/MIC (AUC/MIC) ratio important
    - Quinolones, aminoglycosides
  - Time-dependent agents kill bacteria when the drug concentrations exceed the MIC
    - Time>MIC important
    - Penicillins, cephalosporins
- Post antibiotic effect (PAE)
  - Delayed regrowth of bacteria following exposure to the antimicrobial
    - Varies according to drug-bug combination



Concentration-dependent and Time-dependent agents vs. *Pseudomonas aeruginosa*

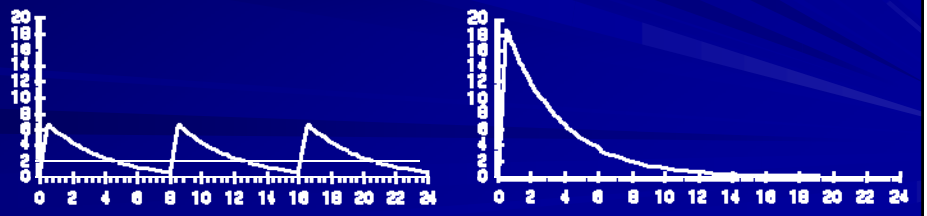


Antimicrobial Pharmacodynamic Parameters

Drug Class	Pattern of Activity	PK-PD parameter
Beta lactams **PCNs** **Cephs** **Carbapenems**	Time-dependent killing and minimal persistent effects	T > MIC
Vancomycin	Time-dependent killing and prolonged persistent effects	T > MIC
Aminoglycosides **Metronidazole**	Concentration-dependent killing and prolonged persistent effects	Peak / MIC
Fluoroquinolones **Daptomycin**	Concentration-dependent killing and prolonged persistent effects	24 h AUC / MIC
Macrolides **Clindamycin** **Tetracyclines** **Ketolides** **Linezolid**	Time-dependent killing and prolonged persistent effects	24 h AUC / MIC

Rationale for Extended-Interval Aminoglycoside Dosing

- Concentration-dependent killing
- Post-antibiotic effect
- Tissue penetration
- Negligible troughs potentially reduce toxicity
  - Renal accumulation is saturable



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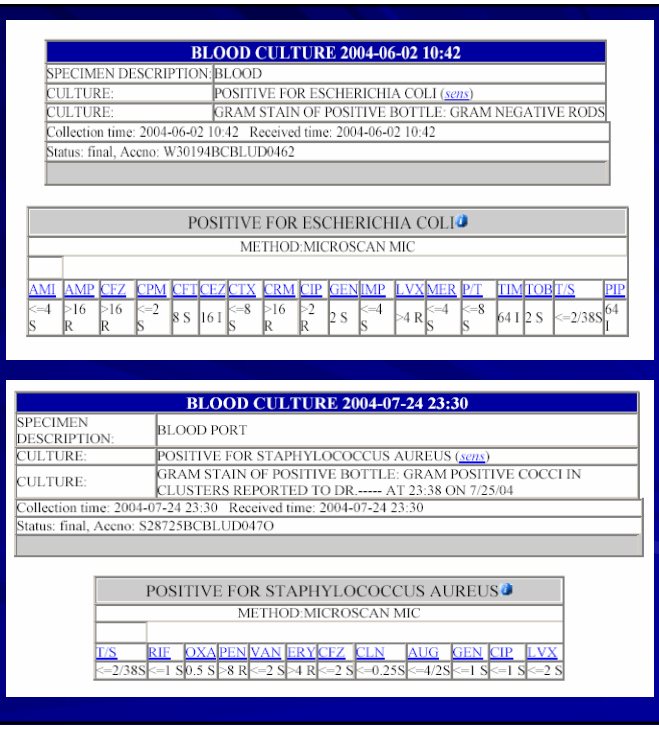
Site of Infection

- Most important factor to consider in antimicrobial selection
- Defines the most likely organisms
  - Especially helpful in empiric antimicrobial selection
- Determines the dose and route of administration of antimicrobial
  - Efficacy determined by adequate concentrations of antimicrobial at site of infection
  - Serum concentrations vs. tissue concentrations and relationship to MIC



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<=4 S	>16 R	>16 R	<=2 S	8 S	16 I	<=8 S	>16 R	>2 R	2 S	<=4 S	>4 R	<=4 S	<=8 S	64 I	2 S	<=2/38S	64 I

BLOOD CULTURE 2004-07-24 23:30	
SPECIMEN DESCRIPTION:	BLOOD PORT
CULTURE:	POSITIVE FOR STAPHYLOCOCCUS AUREUS (*sens*)
CULTURE:	GRAM STAIN OF POSITIVE BOTTLE: GRAM POSITIVE COCCI IN CLUSTERS REPORTED TO DR.----- AT 23:38 ON 7/25/04
Collection time: 2004-07-24 23:30 Received time: 2004-07-24 23:30	
Status: final, Accno: S28725BCBLUD047O	

POSITIVE FOR STAPHYLOCOCCUS AUREUS											
METHOD:MICROSCAN MIC											
T/S	RIF	OXA	PEN	VAN	ERY	CFZ	CLN	AUG	GEN	CIP	LVX
<=2/38S	<=1 S	0.5 S	>8 R	<=2 S	>4 R	<=2 S	<=0.25S	<=4/2S	<=1 S	<=1 S	<=2 S

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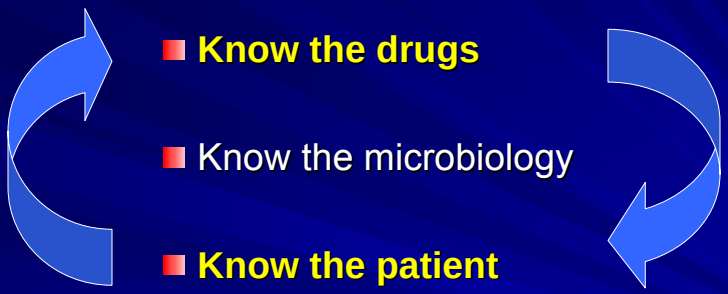
Host Factors

- Allergy
  - Can be severe and life threatening
  - Previous allergic reaction most reliable factor for development of a subsequent allergic reaction
  - Obtain thorough allergy history
  - Penicillin allergy
    - Avoid penicillins, cephalosporins, and carbapenems in patients with true anaphylaxis, bronchospasm
    - Potential to use cephalosporins in patients with a history of rash (~5-10% cross reactivity)
- Age
  - May assist in predicting likely pathogens and guide empiric therapy
  - Renal and hepatic function vary with age
    - Neonates and elderly

Host Factors

- Pregnancy
  - Fetus at risk of drug teratogenicity
    - All antimicrobials cross the placenta in varying degrees
    - Penicillins, cephalosporins, erythromycin appear safe
  - Altered drug disposition
    - Penicillins, cephalosporins, and aminoglycosides are cleared more rapidly during pregnancy
    - ↑ intravascular volume, ↑ glomerular filtration rate, ↑ hepatic and metabolic activities
- Genetic or metabolic abnormalities
  - Glucose-6-phosphate dehydrogenase (G6PD) deficiency
- Renal and hepatic function
  - Accumulation of drug metabolized and/or excreted by these routes with impaired function
  - ↑ risk of drug toxicity unless doses adjusted accordingly
  - Renal excretion is the most important route of elimination for the majority of antimicrobials
- Underlying disease states
  - Predispose to particular infectious diseases or alter most likely organisms

What You Need to Know to Treat with Antibiotics…



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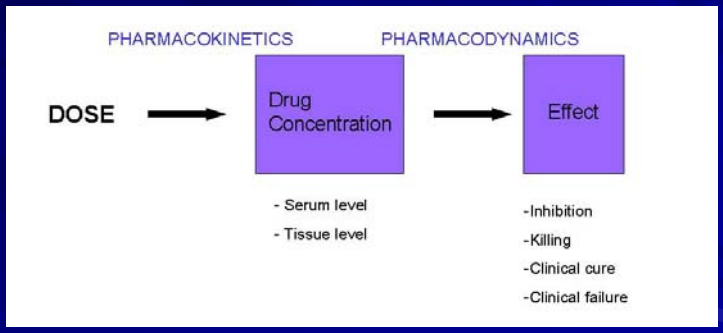
- **Know the patient**

Site of Infection

- Most important factor to consider in antimicrobial selection
- Defines the most likely organisms
  - Especially helpful in empiric antimicrobial selection
- Determines the dose and route of administration of antimicrobial
  - Efficacy determined by adequate concentrations of antimicrobial at site of infection
  - Serum concentrations vs. tissue concentrations and relationship to MIC

Drug/PK/PD Factors



Pharmacokinetics

- Absorption
  - IM, SC, topical
  - GI via oral, tube, or rectal administration
  - Bioavailability = amount of drug that reaches the systemic circulation
- Distribution
  - Affected by the drug's lipophilicity, partition coefficient, blood flow to tissues, pH, and protein binding
- Metabolism
  - Phase I
    - Generally inactivate the substrate into a more polar compound
    - Dealkylation, hydroxylation, oxidation, deamination
    - Cytochrome P-450 system (CYP3A4, CYP2D6, CYP2C9, CYP1A2, CYP2E1)
  - Phase II
    - Conjugation of the parent compound with larger molecules, increasing the polarity
    - Generally inactivate the parent compound
    - Glucuronidation, sulfation, acetylation

Pharmacokinetics

- Elimination
  - Total body clearance
    - Renal + non-renal clearance
    - Affects half-life ($t_{1/2}$)
  - Renal clearance
    - Glomerular filtration, tubular secretion, passive diffusion
    - Dialysis
  - Non-renal clearance
    - Sum of clearance pathways not involving the kidneys
    - Usually hepatic clearance, but also via biliary tree, intestines, skin
  - Half-life
    - Steady state concentrations reached after 4-5 half lives
    - Varies from patient to patient
    - Affected by changes in end-organ function and protein binding

Concomitant Drug Therapy

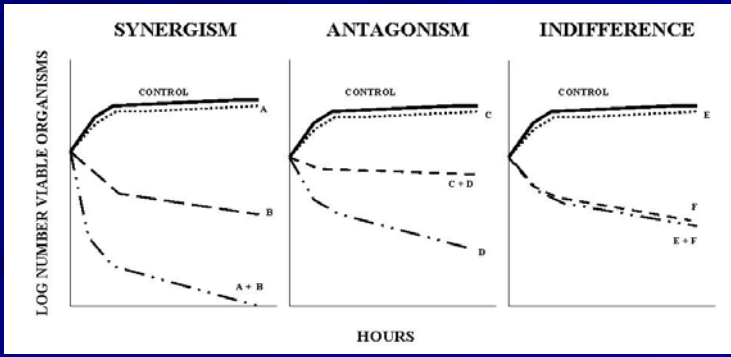
- Influences the selection of appropriate drug therapy, the dosage, and necessary monitoring
- Drug interactions
  - ↑ risk of toxicity or potential for ↓ efficacy of antimicrobial
  - May affect the patient and/or the organisms
  - Selection of combination antimicrobial therapy (≥ 2 agents) requires understanding of the interaction potential
  - Pharmacokinetic interactions
  - Pharmacodynamic interactions

Drug Interactions

- Pharmacokinetic
  - An alteration in one or more of the object drug's basic parameters
- Absorption
  - Bioavailability
- Distribution
  - Protein binding
- Metabolism
  - CYP450
- Elimination
  - renal
- Pharmacodynamic
  - An alteration in the drug's desired effects
- Synergistic/additive
  - May lead to desired or toxic effect
- Antagonistic
  - May lead to detrimental effects
- Indirect effects
  - Effect of one drug alters effect of another

Combination Antimicrobial Therapy

- Synergistic
- Antagonistic
- Indifferent



Other Drug Factors

- Adverse effect profile and potential toxicity
- Cost
  - Acquisition cost + storage + preparation + distribution + administration
  - Monitoring
  - Length of hospitalization + readmissions
  - Patient quality of life
- Resistance
  - Effects of the drug on the potential for the development of resistant bacteria in the patient, on the ward, and throughout the institution

Antimicrobial Therapy

- **Site of infection / Microbiology**
  - Where is it?
  - Which organisms need to be covered?
    - Gram positives, gram-negatives, anaerobes
    - *P. aeruginosa*, MRSA
  - What are the organisms in the unit?
- **Antibiotic**
  - Does the patient have any allergies?
  - Will the antibiotic reach sufficient concentrations at the site of infection?
    - Penetration
    - Blood-brain barrier
  - How is the antibiotic cleared?
  - What are the potential toxicities?
  - What is the impact on resistance?
  - Drug interactions?
    - Good vs. bad
- **Patient**
  - Comorbid illness
    - Alters most likely organisms and potential sites of infection
    - Toxicities
  - End-organ function
  - Age/weight

Summary

- Antimicrobials are essential components to treating infections
- Appropriate selection of antimicrobials is more complicated than matching a drug to a bug
- While a number of antimicrobials potentially can be considered, spectrum, clinical efficacy, adverse effect profile, pharmacokinetic disposition, and cost ultimately guide therapy
- Once an agent has been chosen, the dosage must be based upon the size of the patient, site of infection, route of elimination, and other factors
- Optimize therapy for each patient and try to avoid patient harm

QUESTIONS?