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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- **Know the drugs**
- Know the microbiology
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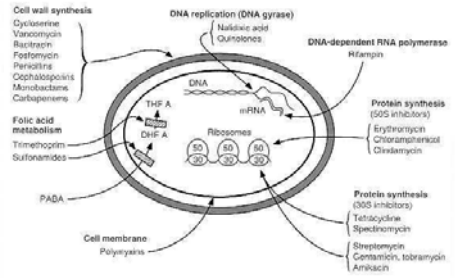
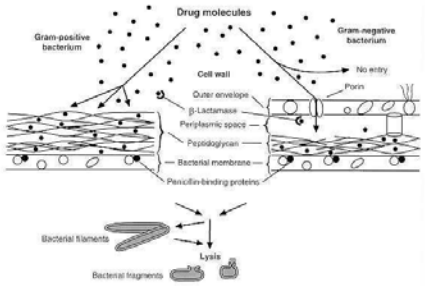
Classification of Antimicrobials



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

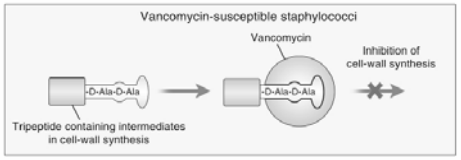
Beta-lactams



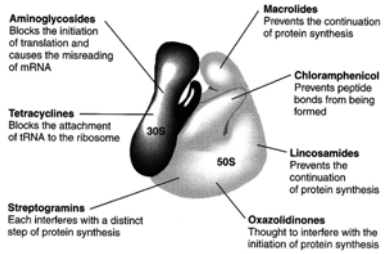
Classification of Antimicrobials

- 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

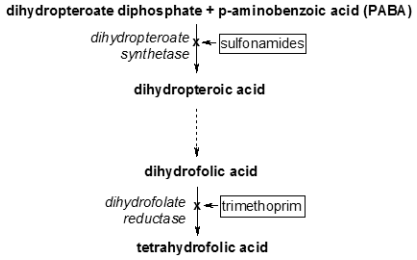
Vancomycin



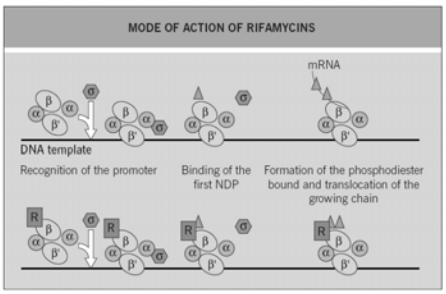
Protein Synthesis Inhibitors



Inhibitors of Folate Metabolism

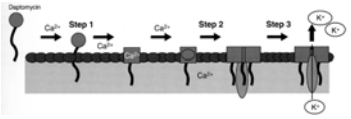


Rifamycins

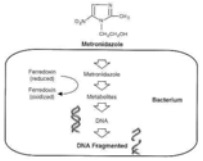


Miscellaneous

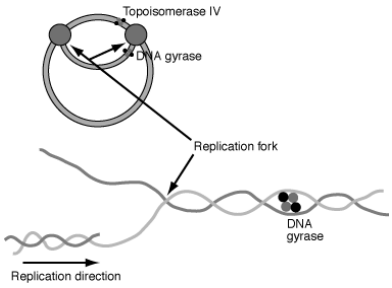
- Daptomycin



- Metronidazole



Quinolones



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
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: W3019HBCBLUD0462	

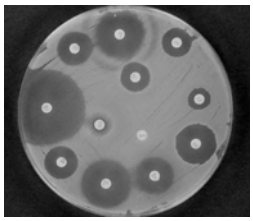
POSITIVE FOR ESCHERICHIA COLI																		
METHOD MICROSCAN MIC																		
AMI	AMP	CEZ	CPM	CFT	CE/C	CTX	CRM	CIP	GEN	IMP	LVX	MER	PT.	TIM	TOB	ES		PIP
<=4 S	>16 R	>16 R	<=2 S	8 S	16 I	<=8 S	>16 R	>2 R	2 S	<=4 S	>4 R	<=4 S	<=8 S	64 I	2 S	<=2/38S		64 I

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)

Susceptibility Testing Methods

- Disk Diffusion (Kirby-Bauer disks)



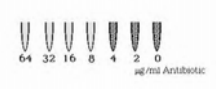
Culture Results
Example

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: F50319BCBLUD0947U	

POSITIVE FOR ESCHERICHIA COLI																		
METHOD MICROSCAN MIC																		
AMI	AMP	CEZ	CPM	CFT	CEZ	CTX	CRM	CIP	GEN	IMP	LVX	MER	PT.	TIM	TOB	ES		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

Susceptibility Testing Methods

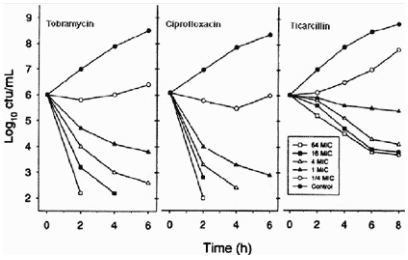
- Broth Dilution



Susceptibility Testing Methods

- E-test (epsilometer test)

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



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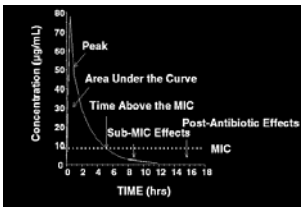
Antimicrobial Pharmacodynamic Parameters

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

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



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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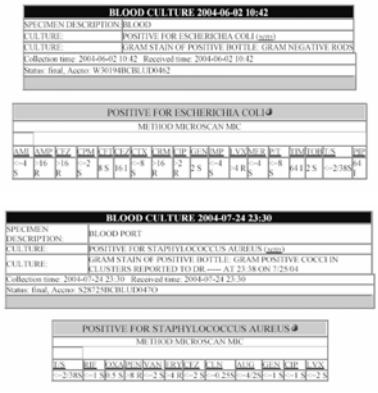
Site of Infection

- 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

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



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POSITIVE FOR ESCHERICHIA COLI

METHOD MICROSCAN MIC

AM	AMP	CEZ	CPM	CFT	CLZ	CTX	CRM	CIP	GEN	IMP	LVX	MOX	PT	TMP	TOB	U/S	SXT
<=4 S	>16 R	>16 R	<=2 S	>8 R	8 S	16 I	<=8 S	>16 R	>2 R	2 S	<=4 S	>4 R	<=4 S	<=8 S	>64 R	2 S	<=2/38 S	<=4 S

BLOOD CULTURE 2004-07-24 23:30

SPECIMEN DESCRIPTION:	BLOOD PORT
CULTURE:	POSITIVE FOR STAPHYLOCOCCUS AUREUS (gram)
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: S28725BL BLUD0470

POSITIVE FOR STAPHYLOCOCCUS AUREUS

METHOD MICROSCAN MIC

TCY	CIP	OXA	PEN	VAN	ERY	CLZ	CLN	QUI	GEN	CIP	LVX
<=2/38 S	<=1 S	0.5 S	<=8 R	<=2 S	>4 R	<=2 S	<=0.25 S	<=4 S	<=1 S	<=1 S	<=2 S

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…

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

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

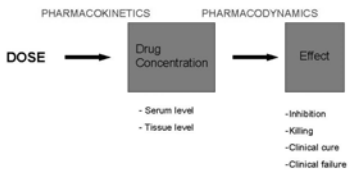
Site of Infection

- 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

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

Drug/PK/PD Factors



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

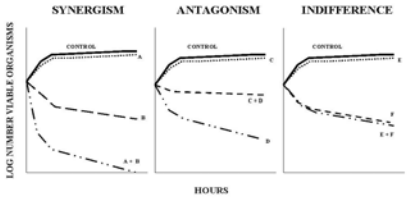
- Pharmacokinetic
  - An alteration in one or more of the object drug's basic parameters
- Absorption
  - Bioavailability
- Distribution
  - Protein binding
- Metabolism
  - CYP450
- Elimination
  - renal
- Pharmacodynamic
  - An alteration in the drug's desired effects
- Synergistic/additive
  - May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

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

Combination Antimicrobial Therapy

- Synergistic
- Antagonistic
- Indifferent



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

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

QUESTIONS?