Antibiothicotherapy

Objectives

- Review the classification of antimicrobials
- Define pharmacokinetic and pharmacodynamic principles and their relationship to effective antimicrobial therapy
- Review relevant microbiologic information as it relates to choosing an antimicrobial
- Discuss patient and drug related factors that influence the selection of the appropriate antimicrobial agent
- Identify monitoring parameters to evaluate antimicrobial therapy

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
  - Macrolides
  - Clindamycin
  - Streptogramins (quinupristin/dalfopristin)
  - Oxazolidinones (linezolid)
  - Aminoglycosides
- Alter nucleic acid metabolism
  - Rifamycins
  - Quinolones
- Inhibit folate metabolism
  - Trimethoprim
  - Sulfamethoxazole
- Miscellaneous
  - Metronidazole
  - Daptomycin

Selecting an Antimicrobial

- Confirm the presence of infection
  - History and physical
  - Signs and symptoms
  - Predisposing factors
- Identification of pathogen
  - Collection of infected material
  - Stains
  - Serologies
  - Culture and sensitivity
- Selection of presumptive therapy
  - Drug factors
  - Host factors
- Monitor therapeutic response
  - Clinical assessment
  - Lab tests
  - Assessment of therapeutic failure

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

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Is the Patient Infected???

- CAREFUL history and physical exam including relevant laboratory data and signs and symptoms
  - Temperature
  - White blood cell count (WBC)
    - WBC in normally sterile fluids (e.g. CSF)
  - Any swelling or erythema at a particular site
  - Purulent drainage from a visible site
  - Patient complaints

- Predisposing factors
  - Surgery, procedures, physical limitations, etc.

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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

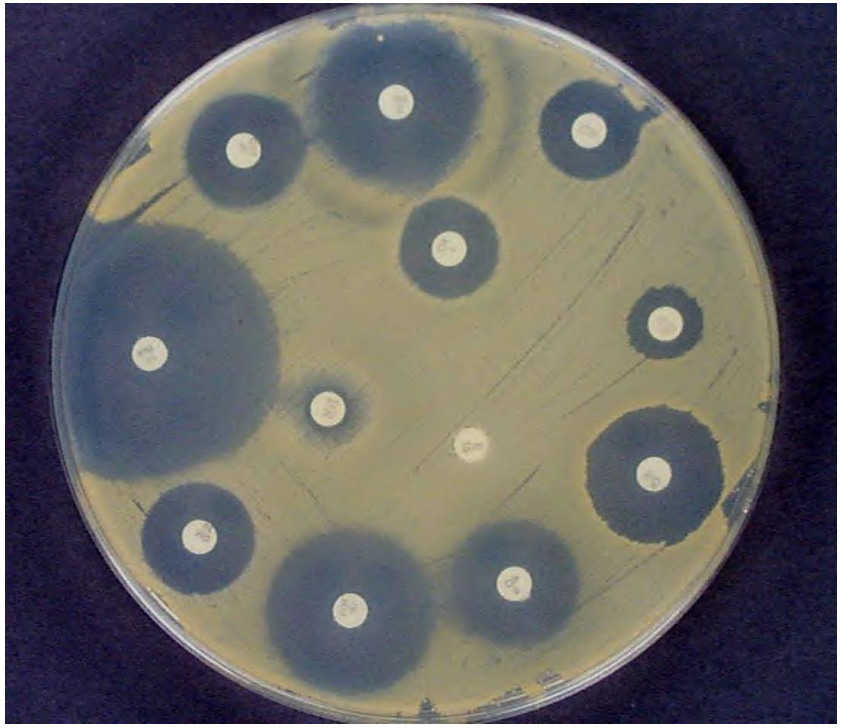
Example

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

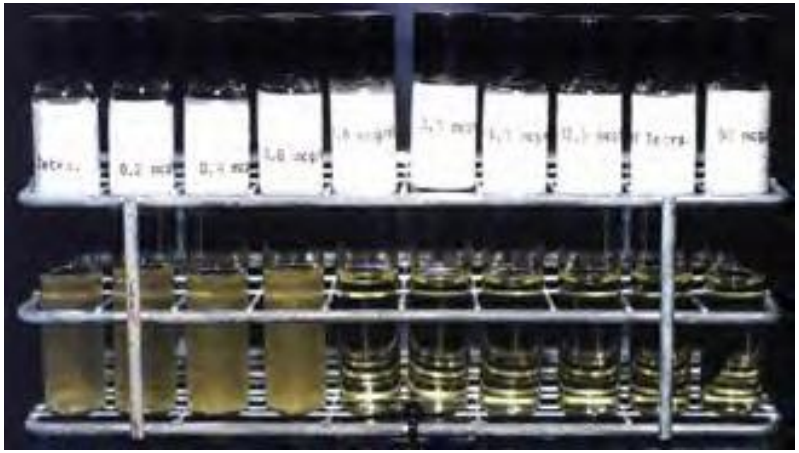
Susceptibility Testing Methods

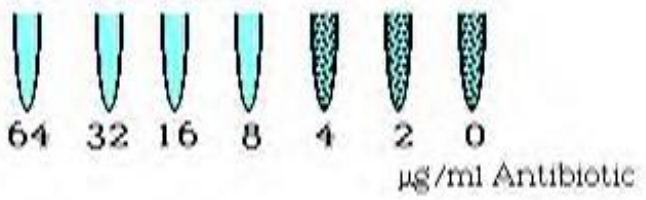
- Disk Diffusion (Kirby-Bauer disks)



Susceptibility Testing Methods

- Broth Dilution





Susceptibility Testing Methods

- E-test (epsilometer test)

Selecting an Antimicrobial

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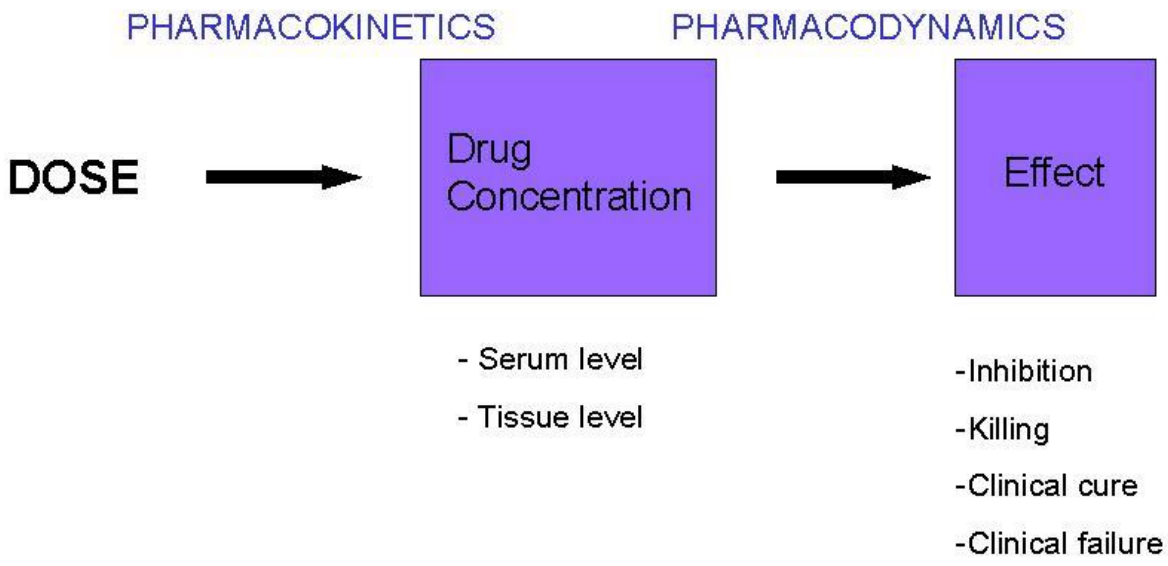
Drug Factors



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

Pharmacodynamics

- Attempts to relate drug concentrations to their effect in the body
  - Desirable = bacterial killing
  - Undesirable = drug side effects

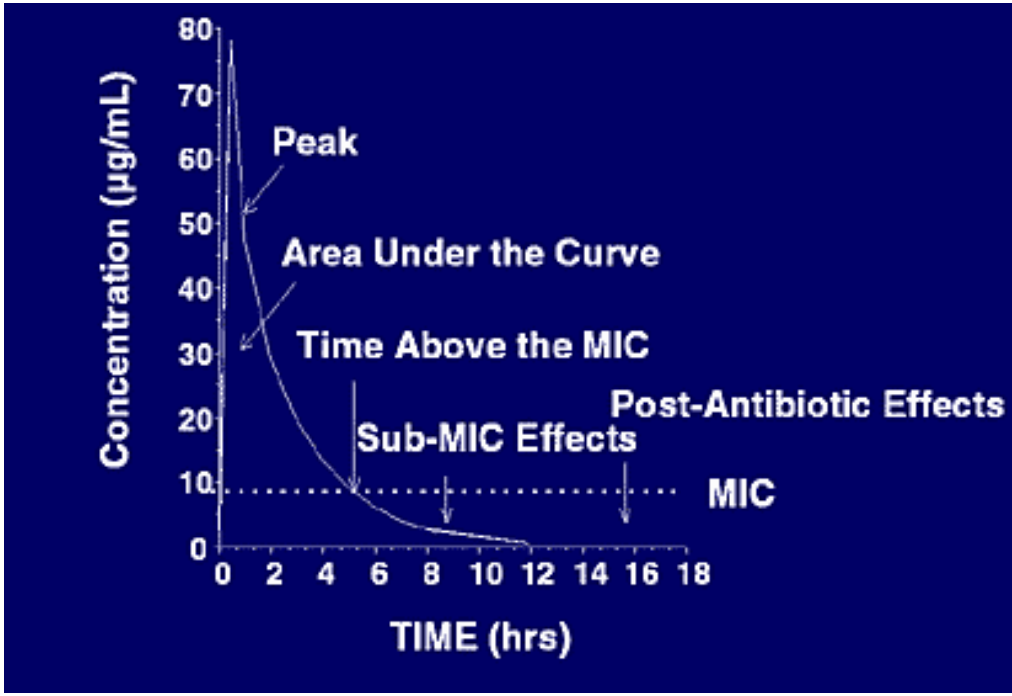
- Bacteriostatic
  - Inhibit growth or replication

- Bactericidal
  - Cause cell death

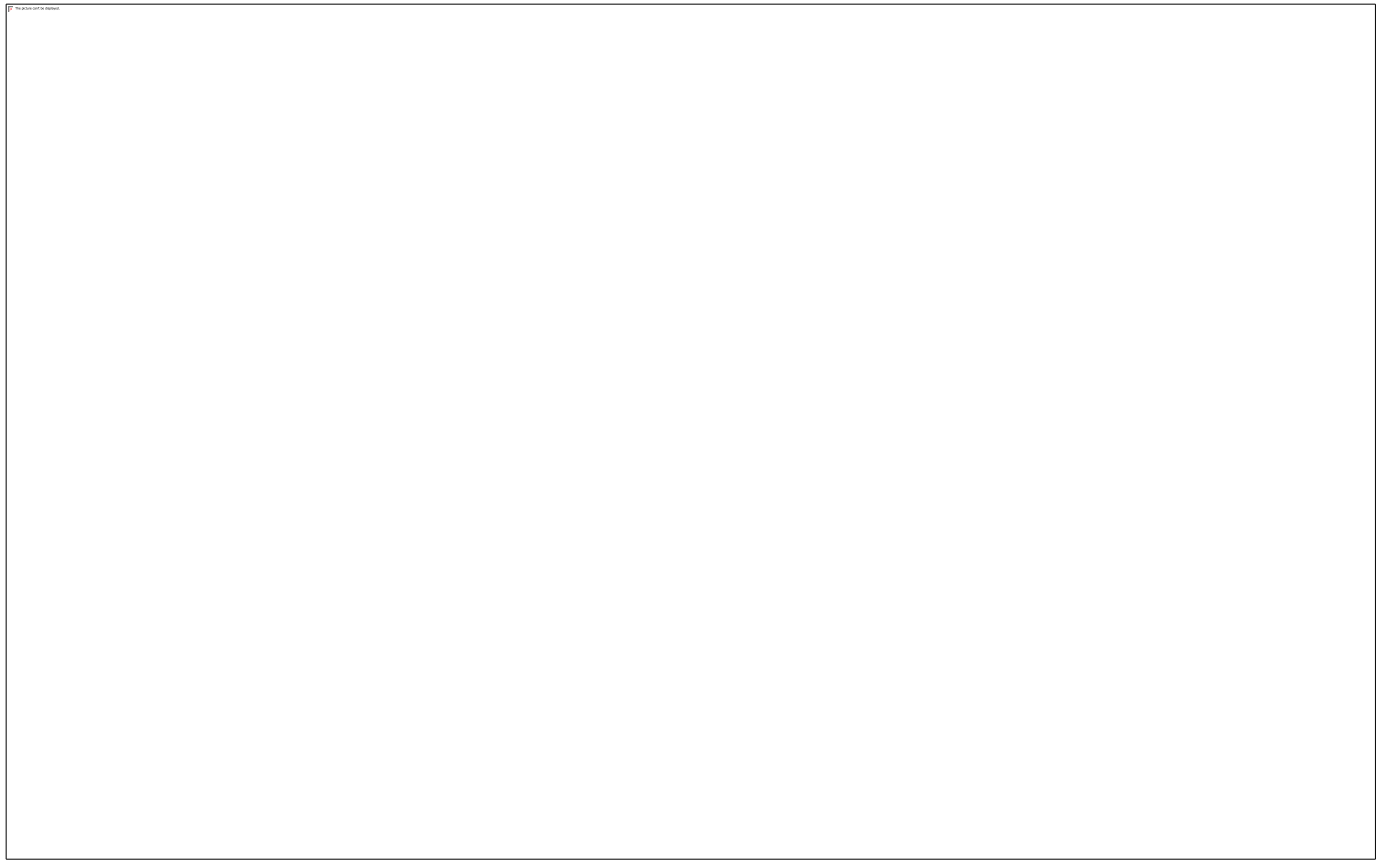
Pharmacokinetics, Pharmacodynamics, and the MIC

- 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

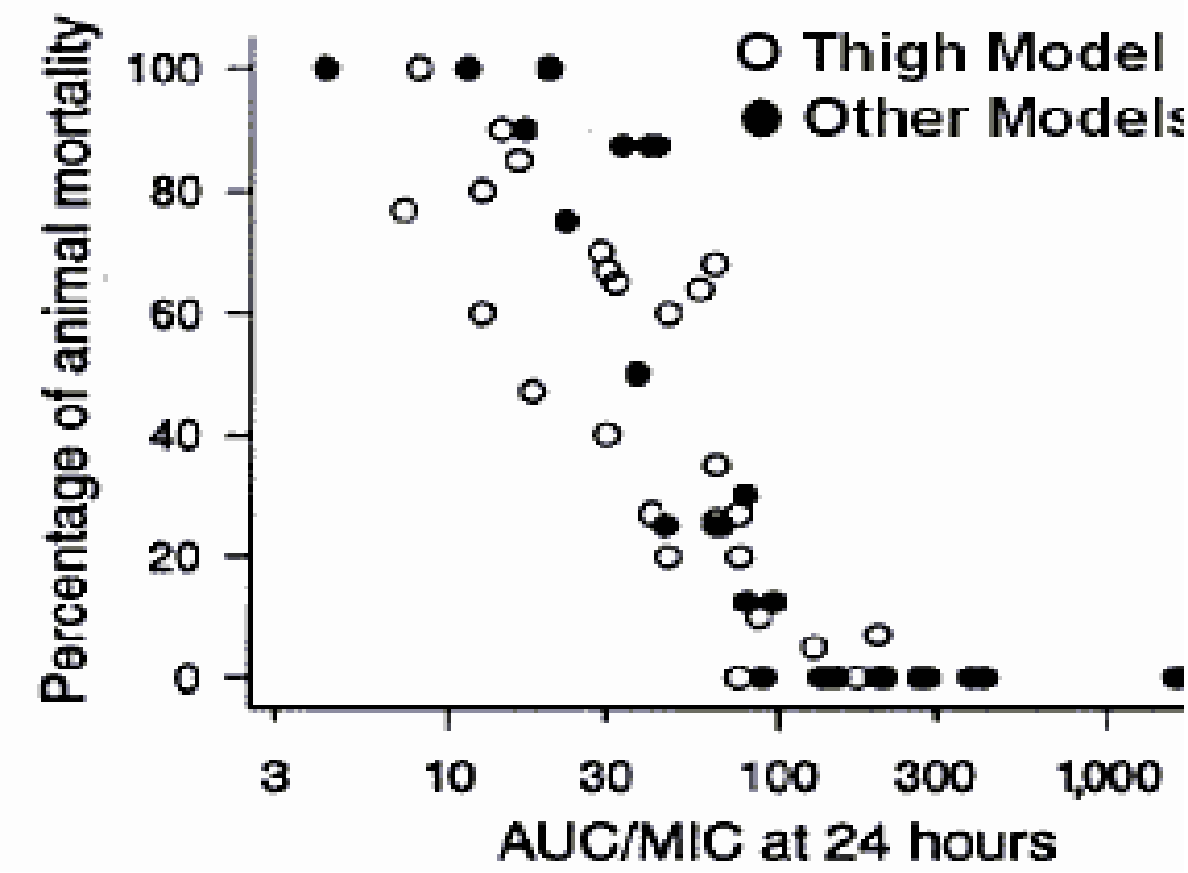
- Post antibiotic effect (PAE)
  - Delayed regrowth of bacteria following exposure to the antimicrobial
    - Varies according to drug-bug combination



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

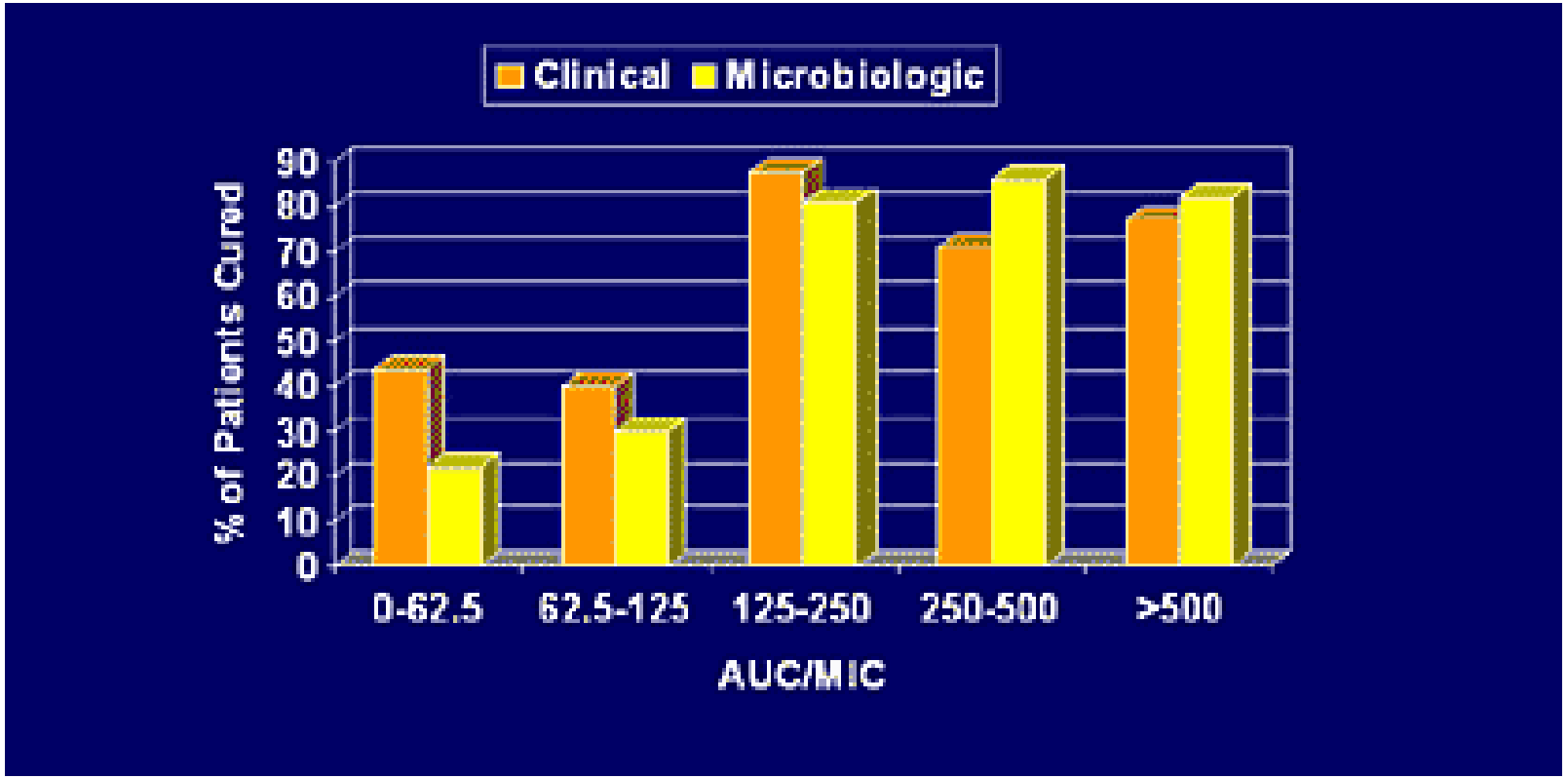


AUC/MIC and Survival Relationship for Quinolones



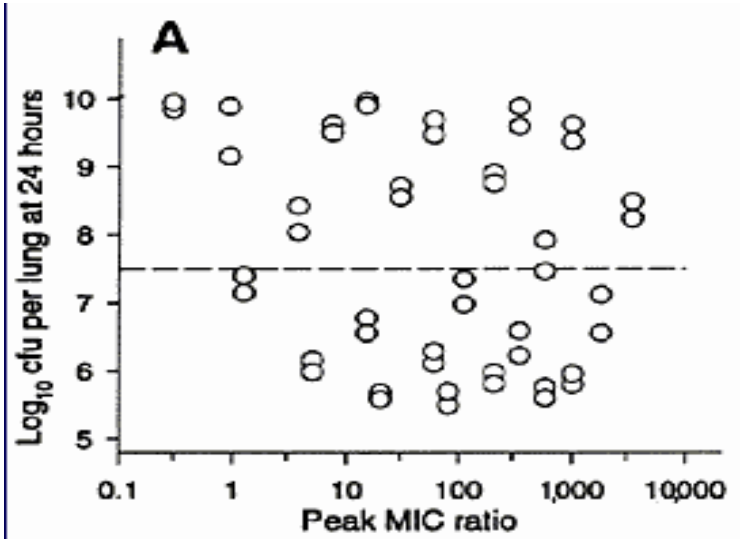
JID 1989:159:281-2.

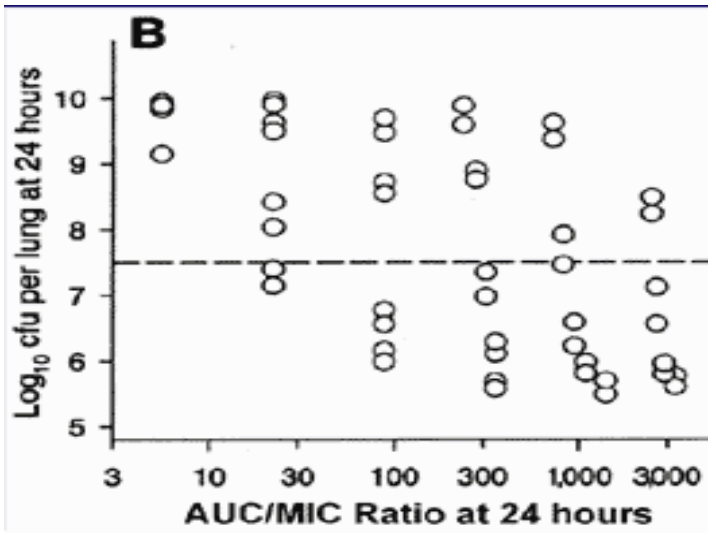
AUC/MIC and Outcomes Relationship for Ciprofloxacin

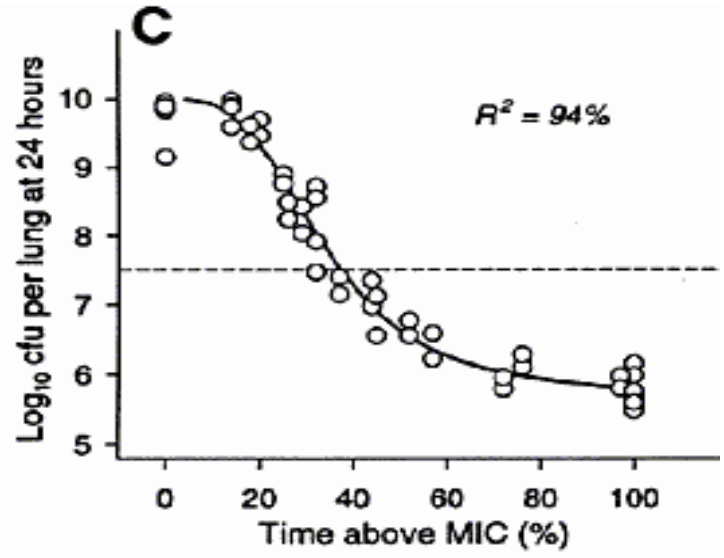


AAC 1993; 37: 1073-81.

Pharmacodynamic Parameters and Colony Count after 24 hours for Cefotaxime in *K. pneumoniae*







Diagn Microbiol Infect Dis
1995; 22: 89-96

Antimicrobial Pharmacodynamic Parameters

Antimicrobials	Pharmacodynamic Characteristics	Goal of Regimen	Parameter Correlating with In Vivo Efficacy
Aminoglycosides **Quinolones** **Metronidazole** **Daptomycin**	Concentration-dependent Killing and Prolonged Persistent Effects	Maximization of Concentrations	Peak/MIC AUC_{0-24}/MIC
Penicillins **Cephalosporins** **Aztreonam**	Time-dependent Killing and NO Persistent Effects	Maximization of Exposure Time	Time Serum Levels Exceed MIC/MBC
Carbapenems **Vancomycin** **Clindamycin** **Macrolides**	Time-dependent Killing and Prolonged Persistent Effects	Maximization of Exposure Time (serum levels can fall below the MIC)	Time Serum Levels Exceed MIC/MBC

Post Antibiotic Effect (PAE)

- Delayed regrowth of bacteria following exposure to an antibiotic
  - Varies according to drug-bug combination
- Gram-positive organisms
  - Most antibiotics (beta-lactams) exhibit PAE ~1-2 hours
  - Aminoglycosides exhibit PAE < 1 hour
- Gram-negative organisms
  - Most beta-lactams (except imipenem) have a negligible PAE
  - Aminoglycosides and quinolones have PAE $\geq$ 2 hours
- Clinical significance unknown
  - Helps choose appropriate dosing interval

Aminoglycoside Concentrations

1.7 mg/kg q8h dosing

Aminoglycoside Concentrations

5 mg/kg q24h dosing

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

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

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

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

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

Site of Infection
Will the antibiotic get there?

- Choice of agent, dose, and route important
  - Oral vs. IV administration
    - Bioavailability, severity of infection, site of infection, function of GI tract
  - Blood and tissue concentrations
    - Ampicillin/piperacillin $\rightarrow \uparrow$ concentrations in bile
    - Fluoroquinolones $\rightarrow \uparrow$ concentrations in bone
    - Quinolones, TMP/SMX, cephalosporins, amoxicillin $\rightarrow \uparrow$ concentrations in prostate
  - Ability to cross blood-brain barrier
    - Dependent on inflammation, lipophilicity, low mw, low protein binding, low degree of ionization
    - 3rd or 4th generation cephalosporins, chloramphenicol, ampicillin, PCN, oxacillin
  - Local infection problems
    - Aminoglycosides inactivated by low pH and low oxygen tension
    - Beta-lactams $\rightarrow$ inoculum effect

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
  - Pharmacokinetic interactions
    - Alter drug absorption, distribution, metabolism, or excretion
  - Pharmacodynamic interactions
    - Alter pharmacologic response of a drug
    - Selection of combination antimicrobial therapy (≥ 2 agents) requires understanding of the interaction potential

Drug Interactions

- Pharmacokinetic
  - An alteration in one or more of the object drug's basic parameters

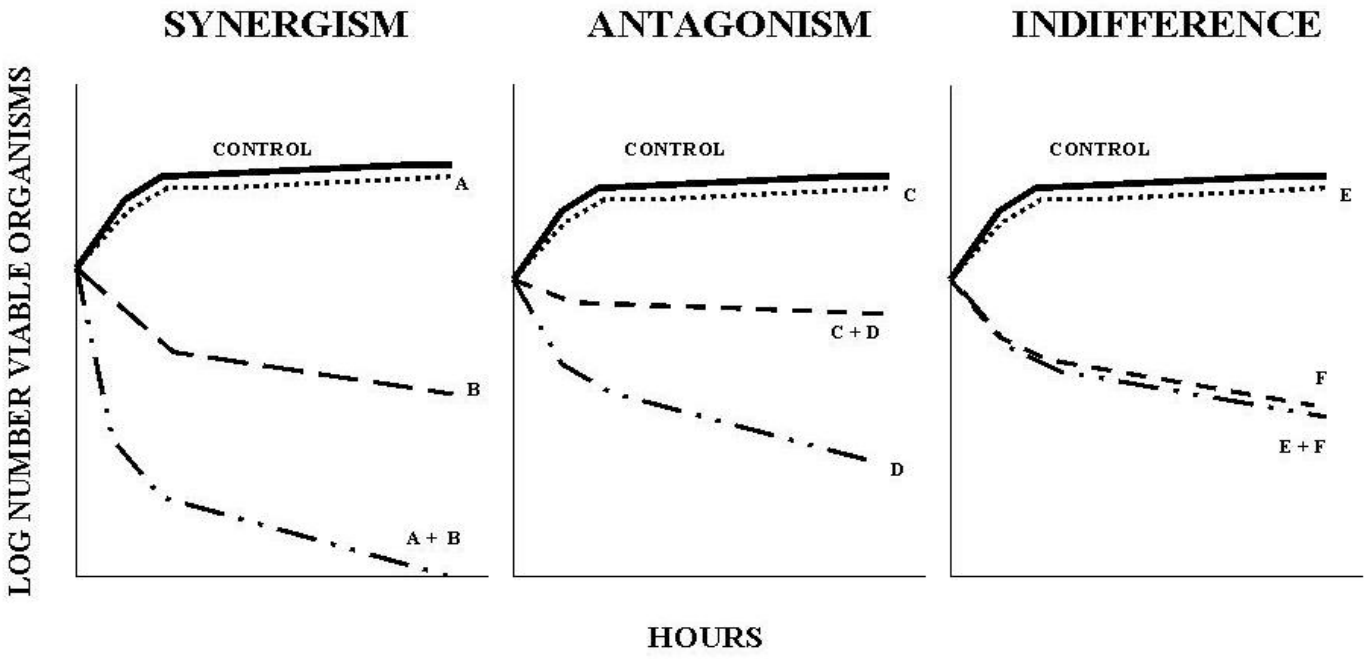
- Absorption
  - Bioavailability
- Distribution
  - Protein binding
- Metabolism
  - CYP450
- Elimination
  - renal

- 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



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Monitoring

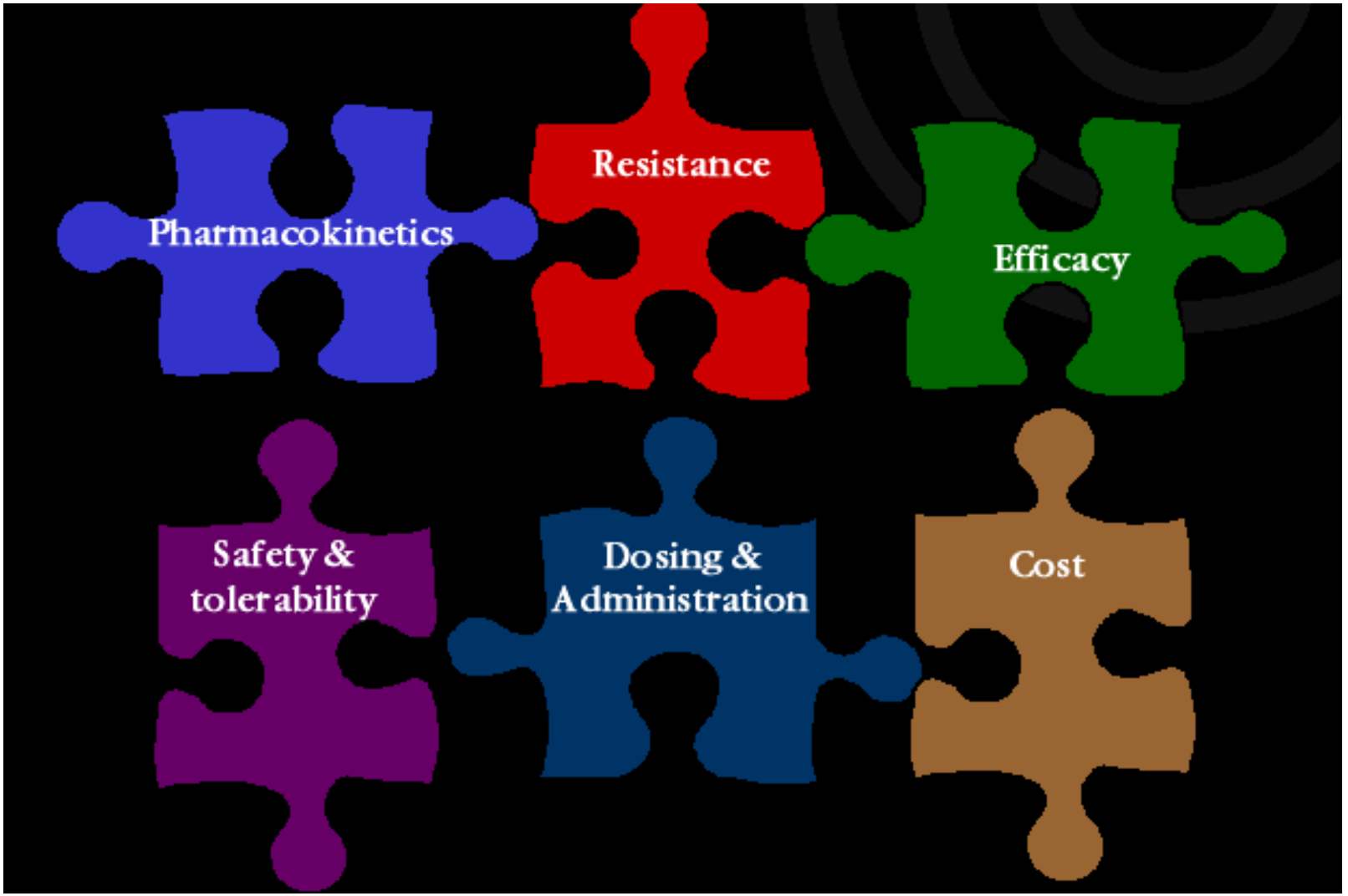
- Efficacy and toxicity of antimicrobials

- Clinical assessment
  - Improvement in signs and symptoms
    - Fever curve, ↓ WBC
    - ↓ erythema, pain, cough, drainage, etc.

- Antimicrobial regimen
  - Serum levels
  - Renal and/or hepatic function
  - Other lab tests as needed
  - Consider IV to PO switch

- Microbiology reports
  - Modify antimicrobial regimen to susceptibility results if necessary
    - Resistance?
  - “Narrow” spectrum of antimicrobial if appropriate

Antimicrobial Factors in Drug Selection



Cultures grew….

CULTURE & SMEAR CSF 2004-10-09 11:28	
SPECIMEN DESCRIPTION:	CEREBROSPINAL FLUID
GRAM SMEAR:	MANY WBCS SEEN
GRAM SMEAR:	NO ORGANISMS SEEN
CULTURE:	HEAVY STAPHYLOCOCCUS AUREUS (*sens*)
CULTURE:	REPORTED TO DR.--- AT 0930 ON 10/10/04
Collection time: 2004-10-09 11:28 Received time: 2004-10-09 11:28	
Status: final, Accno: S67172B400 04A9	

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

Cultures grew MSSA, patient's therapy changed to oxacillin + rifampin.
Shunt removed. WBC ↓. Patient completed course of IV antibiotics.

Monitor for resolution of infection

Monitor hepatic profile

Cultures grew….

BLOOD CULTURE 2004-07-27 14:25	
SPECIMEN DESCRIPTION:	BLOOD 2
CULTURE:	POSITIVE FOR KLEBSIELLA PNEUMONIAE (*sens*)
CULTURE:	GRAM STAIN OF POSITIVE BOTTLE: GRAM NEGATIVE RODS REPORTED TO DR.----- @11:35 ON 07/28/04.
Collection time: 2004-07-27 14:25 Received time: 2004-07-27 16:00	
Status: final, Accno: T15684BCBLUD047R	

POSITIVE FOR KLEBSIELLA PNEUMONIAE																	
METHOD:MICROSCAN MIC																	
AMI	A/S	CFZ	CPM	CFT	CEZ	CTX	CRM	CIP	GEN	IMP	LVX	MER	P/T	TIM	TOB	T/S	PIP
<=4 S	>16/8R	>16 R	<=2 S	8 S	16 I	>32 R	>16 R	<=1 S	<=1 S	<=4 S	<=2 S	<=4 S	>64 R	>64 R	<=1 S	>2/38R	>64 R

Levofloxacin and metronidazole continued to complete a course of therapy. Surgical intervention. Vancomycin discontinued.

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, 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
- Use antimicrobials only when needed for as short a time period as needed to treat the infection in order to limit the emergence of bacterial resistance