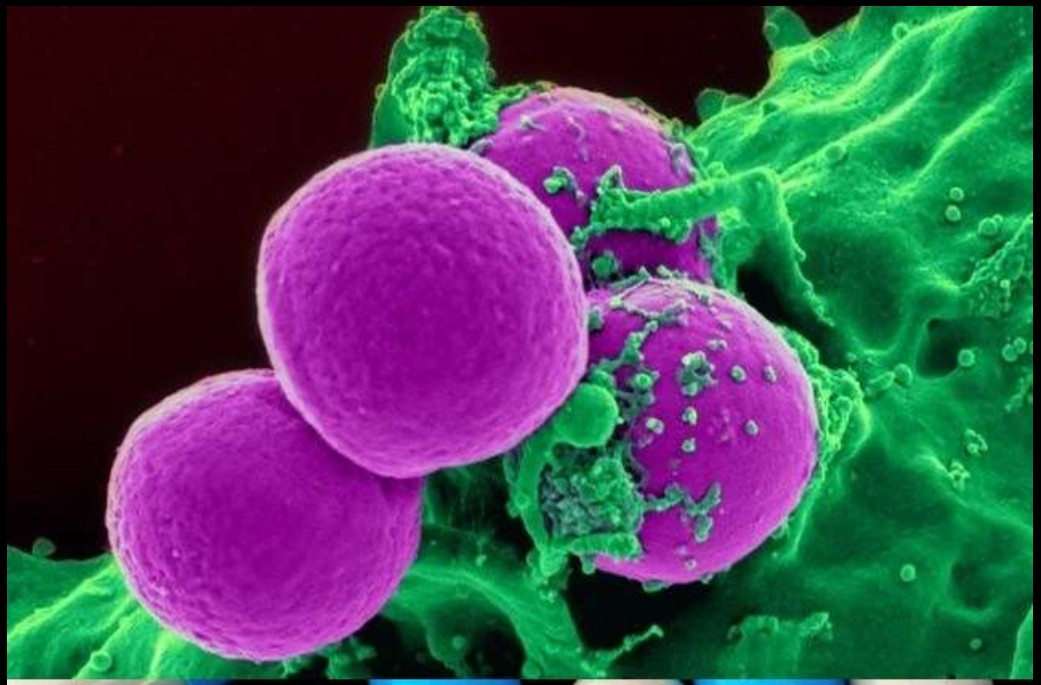
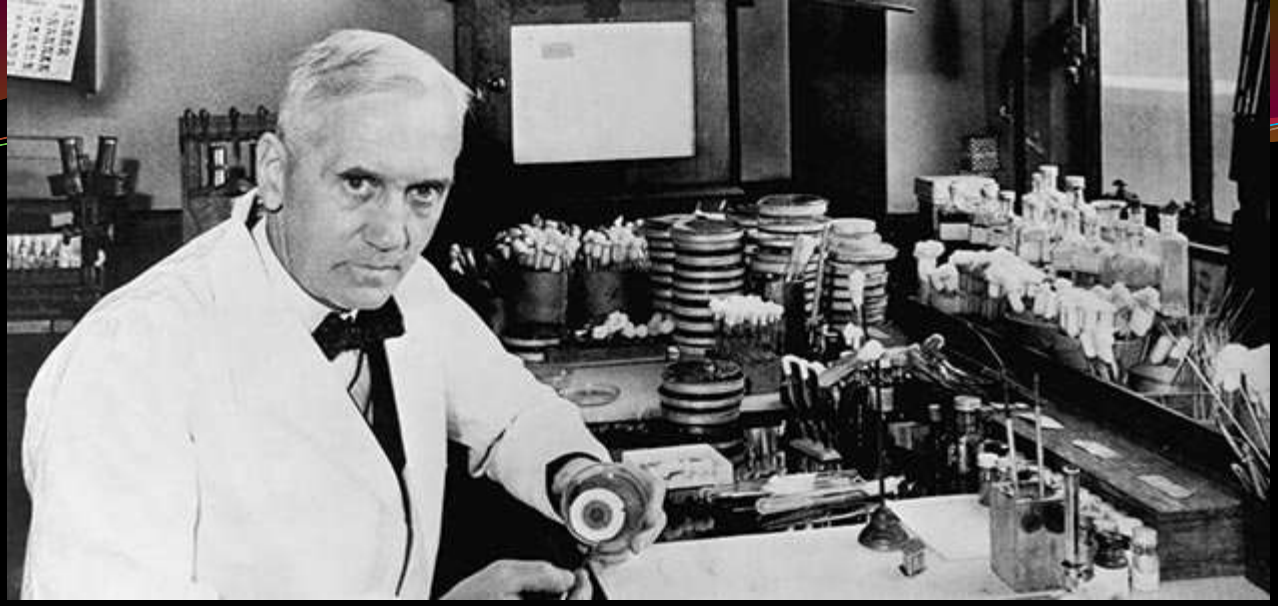
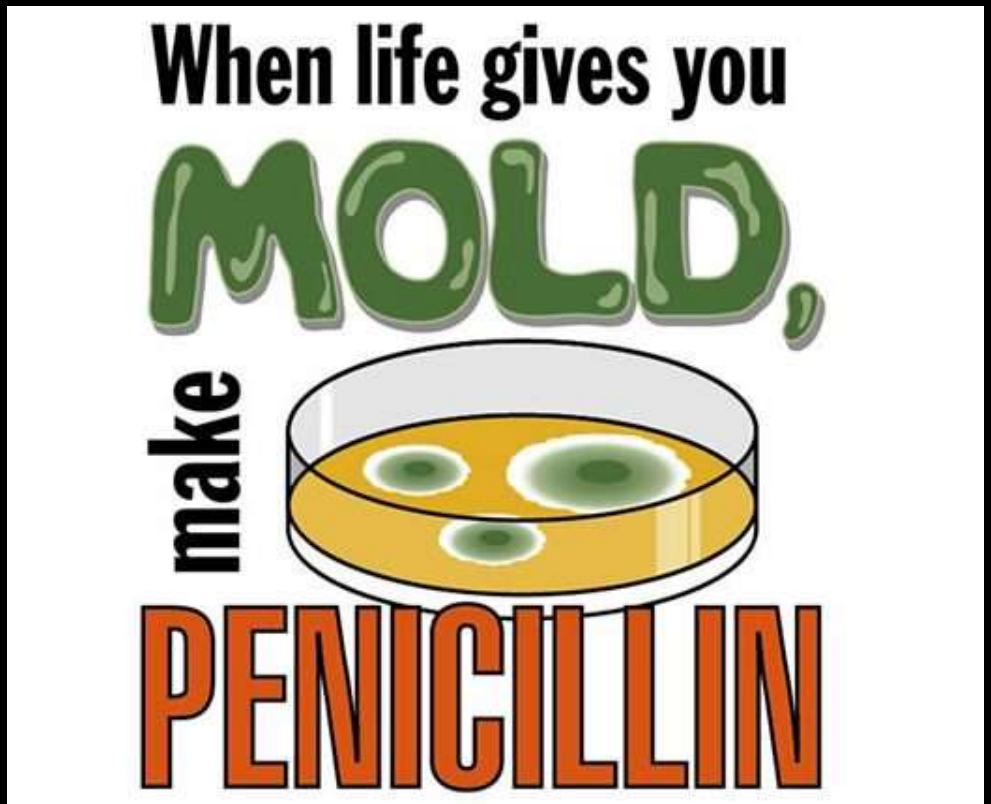
Introduction to Chemotherapy



WHY IS THIS IMPORTANT?

- Antibiotics have drastically reduced the number of deaths due to infection.
- They have changed the face of health care.




When life gives you
MOLD,
make
PENICILLIN

HISTORICAL PERSPECTIVES

- The discovery of the first antibiotic was an accident.
  - Alexander Fleming accidentally contaminated a plate with a fungus.
  - He observed a clearly defined region of no bacterial growth where the fungi had contaminated the plate.
  - The area around the fungus was eventually referred to as a zone of inhibition.

…HISTORICAL PERSPECTIVES

- 12,500 tons of antibiotics are produced annually.
  - 25-50 % is fed to livestock to increase the rate of weight gain.
- From 1900 to 1980, mortality from infectious diseases dropped from 797 per 100,000 persons to 36 per 100,000 persons.

…HISTORICAL PERSPECTIVES

- No major discoveries of natural antibiotic substances have occurred for several years.
  - Efforts have now shifted to modifying existing antibiotics.
  - Searching in new places for potential antibiotics has also gained in prominence.
- Many antibiotics are produced by microorganisms as part of their survival mechanism.
  - They keep other organisms away.
  - They protect the supply of nutrients and oxygen.

General Terms

- Chemotherapy
- Antibiotic – substance produced by a microbe that may harm another microbes
- Antimicrobial – any agent that harms a Microbe
- Anti-infective – any agent that reduces or eliminates infection

Antimicrobial Drugs

- Chemicals used to treat microbial infections
- Before antimicrobials, large number of people died from common illnesses
- Now many illnesses easily treated with antimicrobials
- However, many antimicrobial drugs are becoming less useful

- 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

ANTIBIOTICS ARE PART OF BACTERIAL SELF PROTECTION

- Microorganisms that produce these substances have molecular mechanisms to control production and prevent self-destruction.
- Naturally produced antibiotics are products of secondary metabolic pathways.
  - These pathways are not turned on all the time.
  - Continuous production could adversely affect the organism.
  - Some bacteria restrict antibiotic production to the stationary phase.
  - Others keep the intracellular concentrations at low levels.

Features of Antimicrobial Drugs

- Most modern antibiotics come from species of microorganisms that live in the soil
- To commercially produce antibiotic:

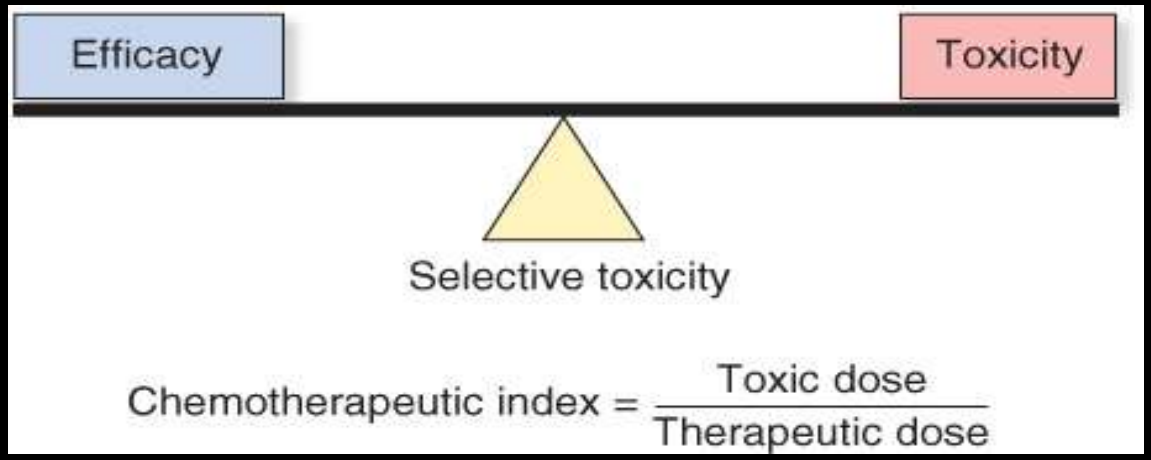
1. Select strain and grow in broth
2. When maximum antibiotic concentration reached, extract from medium
3. Purify
4. Chemical alter to make it more stable

Selective Toxicity

- Ability of an antibiotic to destroy target cells without damaging host cells
- Differences between microbes and host
  - Prokaryotic vs Eukaryotic
  - Cell wall
  - Inhibition of microbial enzymes
  - Disruption of bacterial protein synthesis

Features of Antimicrobial Drugs:
Selective Toxicity

- Cause greater harm to microorganisms than to host
- Chemotherapeutic index: lowest dose toxic to patient divided by dose typically used for therapy



Antimicrobials classifications

- Narrow vs. Broad Spectrum
- Susceptible organisms
  - Antibacterials
  - Antifungal
  - Antiviral
- Classification by mechanism
- Distinction: Bacteriocidal vs. Bacteriostatic

Features of Antimicrobial Drugs: Spectrum of Activity

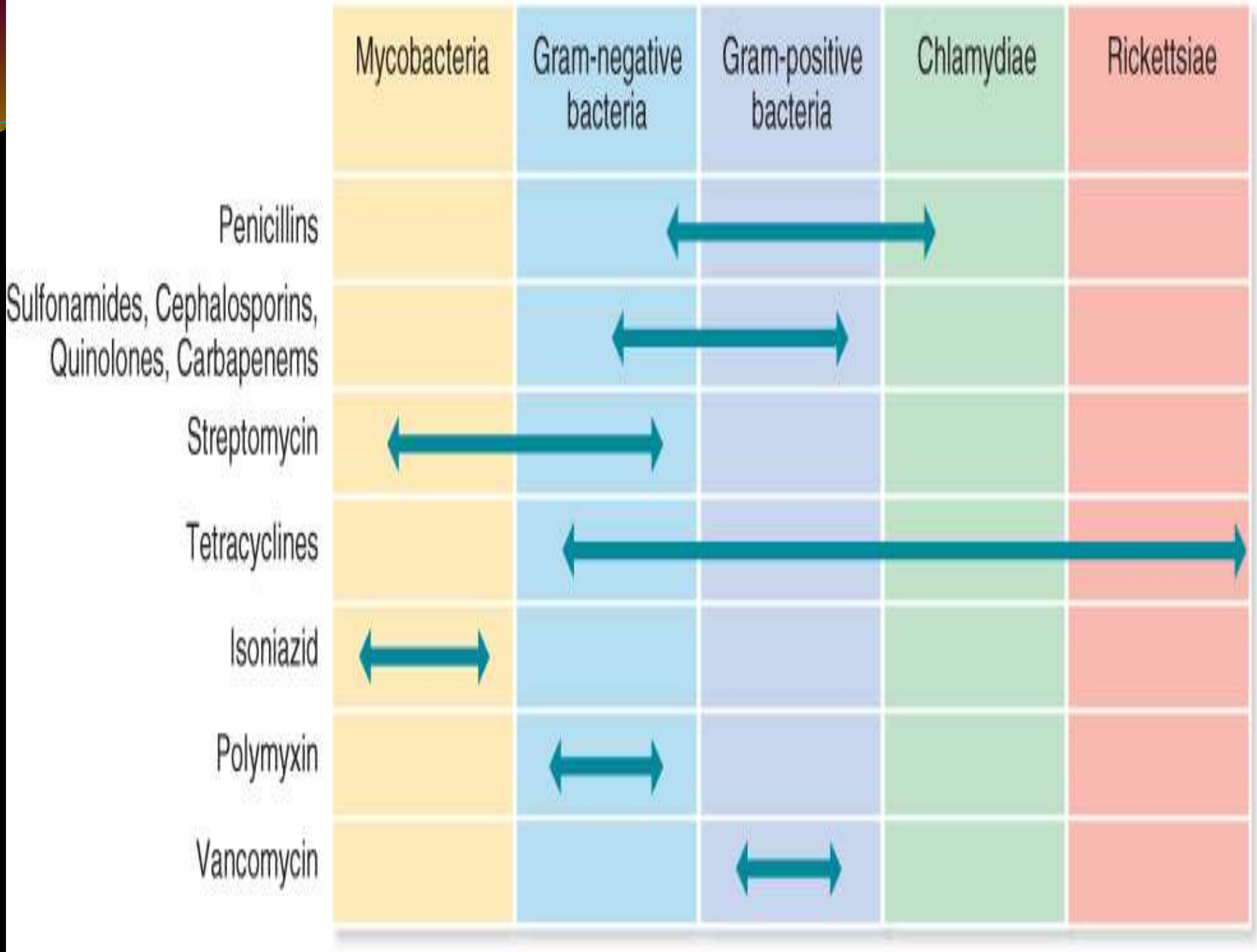
- Antimicrobial medications vary with respect to the range of microorganisms they kill or inhibit
- Some kill only limited range : Narrow-spectrum antimicrobial
- While others kill wide range of microorganisms: Broad-spectrum antimicrobial

…ANTIBIOTIC SPECTRA

- The first molecules that inhibited bacterial growth were natural products.
- Over time, these natural molecules have been modified.
- Several types of semi-synthetic antibiotics have been derived from these molecules.

. . .ANTIBIOTIC SPECTRA

- The original natural molecules used by humans as antibiotics have a very narrow spectrum.
  - Penicillin activity is restricted to Gram-positive bacteria.
- Natural molecules can be chemically modified making it possible to broaden their spectrum.
- Antibiotics are classified as either broad-spectrum or narrow-spectrum.


Mycobacteria
Gram-negative bacteria
Gram-positive bacteria
Chlamydiae
Rickettsiae
Penicillins
Sulfonamides, Cephalosporins, Quinolones, Carbapenems
Streptomycin
Tetracyclines
Isoniazid
Polymyxin
Vancomycin

Features of Antimicrobial Drugs: Antimicrobial Action

- Bacteriostatic: inhibit growth of microorganisms
- Bactericidal: Kill microorganisms

Features of Antimicrobial Drugs:
Effects of Combining Drugs

- Combinations are sometimes used to fight infections
- Synergistic: action of one drug enhances the activity of another or *vice versa*.
- Antagonistic: activity of one drug interferes with the action of another.

Features of Antimicrobial Drugs:
Adverse Effects

1. Allergic Reactions: some people develop hypersensitivities to antimicrobials
2. Toxic Effects: some antimicrobials toxic at high concentrations or cause adverse effects
3. **Suppression of normal flora (Suprainfection):** when normal flora killed, other pathogens may be able to grow to high numbers

Features of Antimicrobial Drugs:
Resistance to Antimicrobials

- Some microorganisms inherently resistant to effects of a particular drug
- Other previously sensitive microorganisms can develop resistance through spontaneous mutations or acquisition of new genes (more later).

So, The Criteria of the Ideal Antibiotic:

- Selectively toxic to microbe but nontoxic to host.
- Soluble in body- tissue distribution – BBB.
- Remains in body long enough to be effective - resists excretion and breakdown.
- Shelf life.
- Does not lead to resistance.
- Cost not excessive.
- Hypoallergenic.
- Microbiocidal rather than microbiostatic.
- Concerns suppression of normal flora - antibiotic associated colitis with *Clostridium difficule* and it's toxins or *Candida albicans.*

Mechanisms of action of Antibacterial Drugs

1. Inhibit cell wall synthesis
2. Inhibit protein synthesis
3. Inhibit nucleic acid synthesis
4. Injury to plasma membrane
5. Inhibit synthesis of essential metabolites

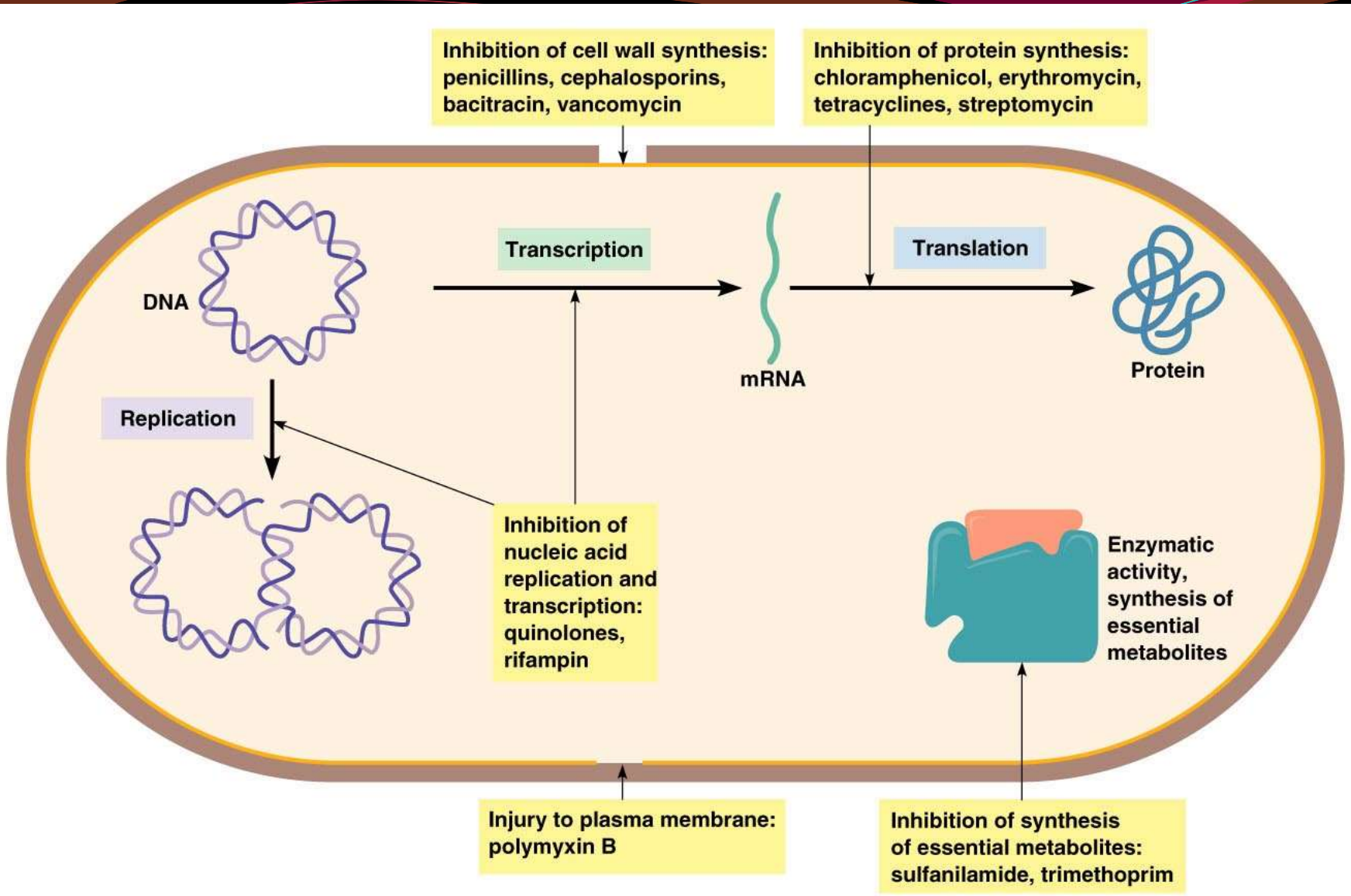


Figure 20.2

Classification of Antibacterial agents

- 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

Therapy with combined AMA's

Rationale

- **Broaden the spectrum**
  - **For emperical therapy**
  - **Treatment of polymicrobial (mixed) infections**
- **To enhance antimicrobial activity i.e. synergism for a specific infection**
- **To reduce severity or incidence of adverse effects.**
- **To prevent emergence of resistance**

Therapy with combined AMA's

- **For emperical therapy**
  - **Bacterial diagnosis not known**
  - **Gram +ve, Gram –ve, Anaerobic**
  - **Till culture senstivity report**
- **Treatment of polymicrobial (mixed) infections**
  - **Bronchiectasis, UTI, Peritonitis, Abcesses, bed sores.**
  - **Aerobic + anaerobic organisms both**

Therapy with combined AMA's

- 2/more AMA have to be used to cover the pathogens.
- Drugs chosen : C/S, Bacteriological diagnosis, Senstivity pattern,
- Clindamycin /metronidazole for anaerobes
- Single agent.

Therapy with combined AMA's

To achieve synergism:

When two antimicrobials of different classes are used together

Their can be synergism (supra-additive)

additive

antagonism

- **Two bacteriostatic agents: Additive**

  eg. combination of tetracyclines, chloramphenicol, erythromycin

Exception, Sulphonamide + Trimethoprim **Supraadditive / synergism**

- **Two bactericidal agents:**

Additive if organism is sensitive to both

eg. Penicillin + streptomycin

Carbenicillin + gentamycin

Rifampin + isoniazid

- Combination of bacteriostatic with bactericidal agents: Synergistic / Antagonistic
- If organism sensitive to cidal drug- response to the combination is equal to the static drug given alone
  - Apparent antagonism
  - Cidal drugs act on rapidly multiplying bacteria.
  - Static drug retards multiplication

- If the organism has low senstivity to the cidal drug – **synergism** may be seen. (RARE – Not to be quoted)

Therapy with combined AMA's

To reduce severity or incidence of adverse effects.

- Possible **if combination is synergistic** so that doses can be reduced
- Needed with AMA's with **low safety margin**, which when used alone in effective doses produce unacceptable toxicity e.g.
  - Amphotericin B + Rifampin / minocycline
  - Amphotericin B + flucytosine

- **To prevent emergence of resistance**
  - **If the incidence of resistant mutants of a bacillus infecting an individual for drug P is 10^{-5} and for drug Q is 10^{-7}, then only one out of 10^{12} bacilli will be resistant to both.**
  - **Chances of relapse will be less**
  - **Chronic infections needing prolonged therapy eg: Tb, Leprosy, H.pylori, HIV etc.**

Therapy with combined AMA's

Disadvantages

- Risk of toxicity
- Multiple drug resistance
- Increased cost
- Antagonism of antibacterial effect if bacteriostatic & bactericidal agents are given concurrently.

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

Selection of antimicrobial agent

Judicious selection requires

- Clinical judgement &
- Detailed knowledge of Pharmacological properties of the antibiotic
- As well as microbiological factors i.e. potential infecting microorganisms

- Emperical therapy
- Definitive therapy
- Prophylactic or preventive therapy

Emperical therapy

- Infecting microorganism is unidentified
- Antibiotic must cover all the likely pathogens. Combination therapy/Single broad spectrum agent is employed
- Requires knowledge of infecting microorganisms
- Clinical picture suggests the likely microorganism

Definitive therapy

- Culture sensitivity is done
- Once the infecting microorganism is identified Definitive antimicrobial therapy is instituted
- Narrow spectrum

Prophylactic therapy (Chemoprophylaxis)

- Preventing the setting of an infection
- Suppressing contacted infection before it becomes clinically manifest
  - Prophylaxis against specific infections

    Tuberculosis INH (susceptible contacts of open cases)
  - Prevention of infection in high risk situations

  Eg: immunocompromised host, surgical prophylaxis, catheterization, dental extraction,

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

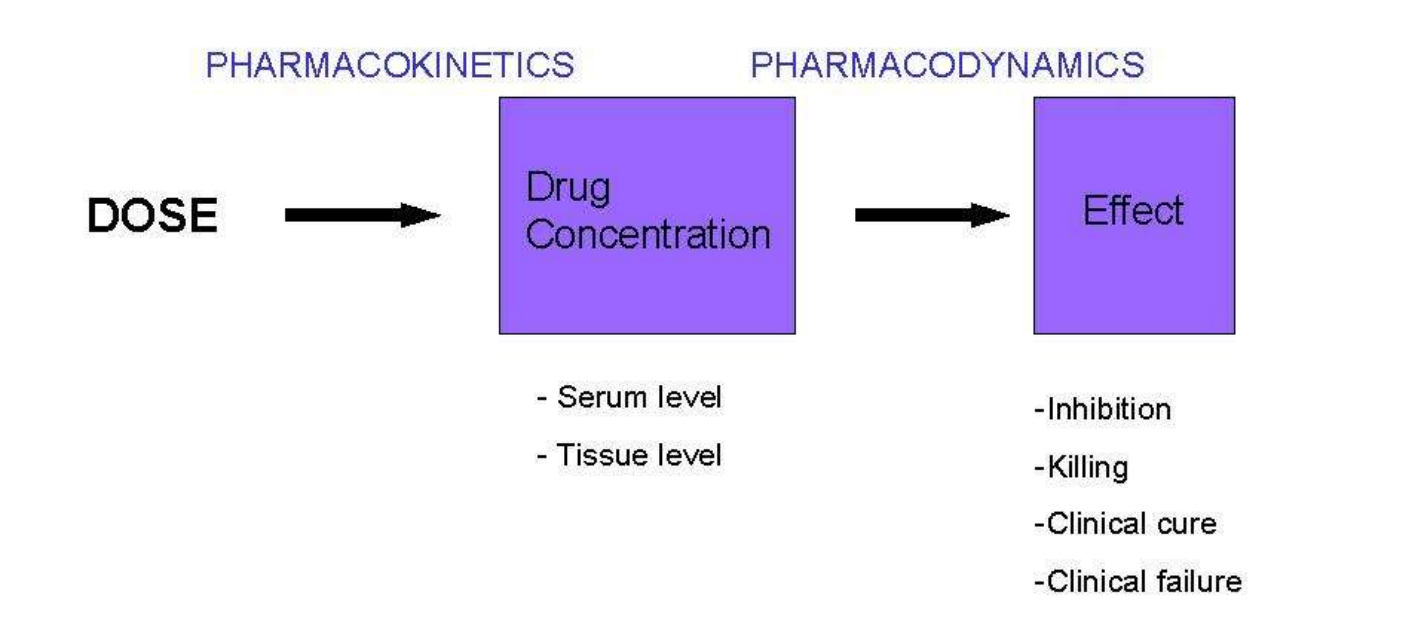
Culture Results

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

Drug Factors



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
  - 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
  - Altered drug disposition
- 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

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

Selecting an Antimicrobial

- Confirm the presence of infection
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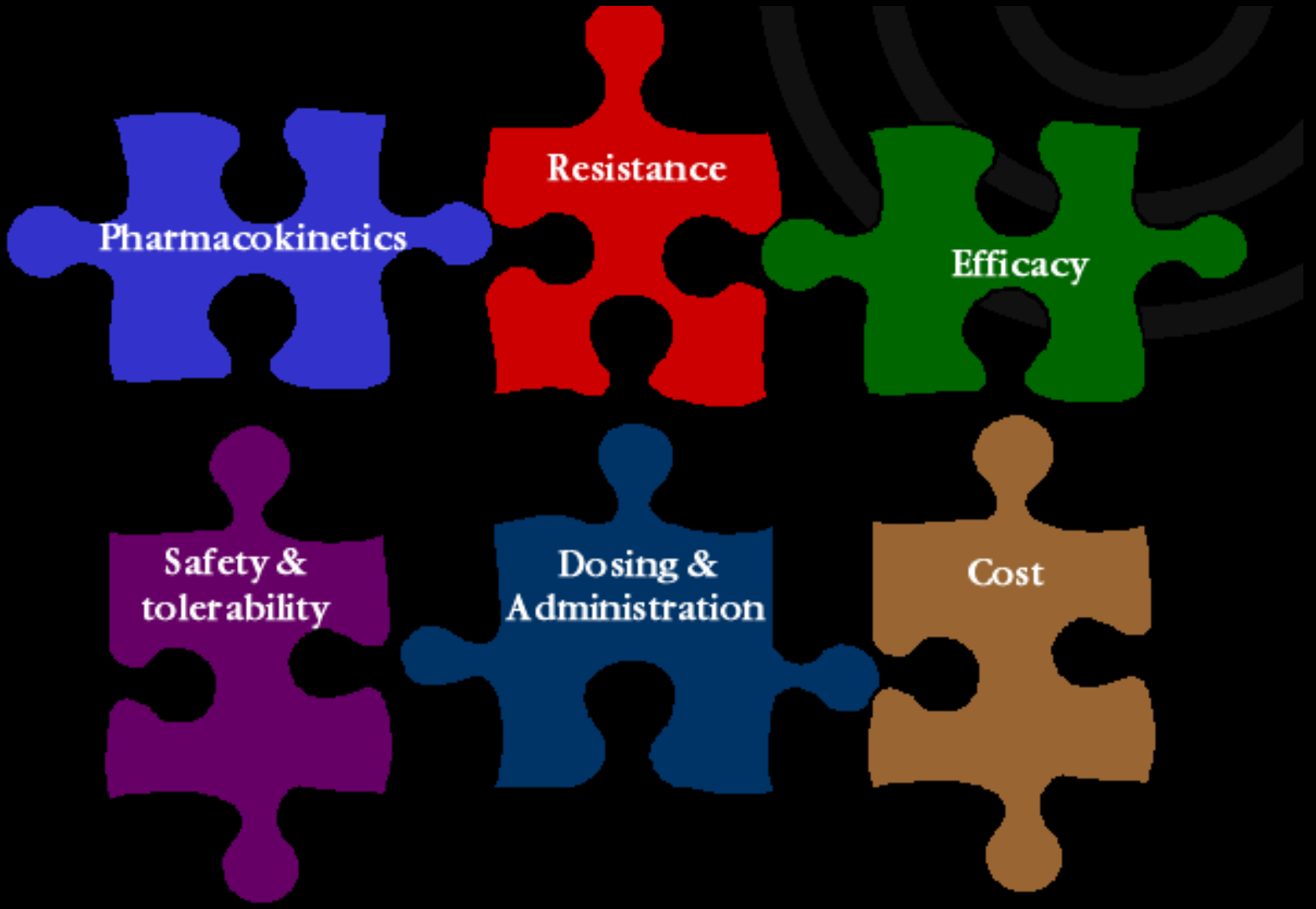
Antimicrobial Factors in Drug Selection



Case Presentation #1

- S.I. is a 72 y.o. male with history of SAH s/p aneurysm clipping about 2 months ago. His post-op course was complicated by ventilator-associated pneumonia, hydrocephalus requiring a VP shunt, and renal failure. Now admitted with acute mental status changes and fever.

- PMH: SAH, DM, HTN, hypercholesterolemia
- FH: non-contributory
- SH: +tobacco (4 cigarettes/day)
- Allergies: NKDA
- Occupation: attorney

Case Presentation #1

- PE:
  - T 102.7°F,
  - Tachycardic
- Labs:
  - WBC 14.7, Hct 34.3, plts 295
  - Na 138, K 4.1, Cl 102, HCO_3 25, BUN 26, SCr 1.4
  - LFTs wnl
  - Cultures pending
  - CSF: WBC 725 (96% neutrophils); protein 148; glucose 39
- Diagnosis: VP shunt infection
- Treatment: Antibiotics and shunt removal
  - Antibiotics?
  - Route?
  - Dose?

Case Presentation #2

- 43 y.o. male with congenital bladder extrophy (s/p multiple surgeries now with ureterocolostomy and colostomy), residual short bowel syndrome, multiple hospital admisisons for UTIs, sepsis, recently admitted for 1 month with polymicrobial line sepsis, line removed, PICC placed. Returns 10 days later complaining of abdominal pain, N/V.

- PMH: HTN
- FH: non-contributory
- SH: no tobacco, occasional alcohol use
- Allergies: PCN

Case Presentation #2

- PE:
  - T 99.7°F
  - Lungs clear
  - Abdomen soft, but indurated area below urostomy bag

- Labs:
  - WBC 12.4 (↑ from 7.1), Hct 34.8, Plts 290
  - Na 139, K 3.7, Cl 105, HCO_3 20, BUN 40, SCr 1.8
  - LFTs wnl
  - U/A: 20 WBCs

- CT scan:
  - Abdominal: cystic mass in pelvis with new hydronephrosis

- 4 days into hospital admission, the cystic collection spontaneously drains. Patient febrile to 101.7°F, tachycardic, increased WBC to 26.4. Cultures drawn. Started on broad spectrum antibiotics.

Case Presentation #1

- Factors to consider:
  - Site of infection (likely organisms gram positive and gram negative)
    - Recently hospitalized
    - Neurosurgery
  - Antibiotic penetration into CSF
    - Route of administration
  - Age
  - Renal function

- Patient empirically started on vancomycin 1 gram IV Q24h and cefepime 2 grams IV Q12h.

Cultu

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

Case Presentation #2

- Factors to consider:
  - Most likely abdominal source (gram negative and anaerobic organisms)
  - PCN allergy
  - Renal/hepatic function
  - Multiple admissions and multiple infections
    - ?resistant organisms
  - IV vs. PO antibiotics
    - Short bowel syndrome

- Patient received empiric levofloxacin 500 mg IV Q24h, metronidazole 500 mg IV Q12h, and vancomycin 1g IV Q24h.

C

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

QUESTIONS?