PHARMACOLOGY/THERAPEUTICS I BLOCK III HANDOUTS -2015-16

26. Introduction Antibiotics I – O'Keefe
27. Introduction to Antibiotics II – O'Keefe
28. Penicillins – Grim
29. Aminoglycosides – Grim
30. Cephalosporins, Carbapenems & Monobactams – Reid (Video)
31. Vancomycin, Linezolid & Daptomycin – Reid (Video)
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S. Erdman, Feb 2015

SPECTRUM OF ACTIVITY SUMMARY CHART

Antibiotic / Organism	Penicillins							Cephalosporins						Carb	Mon	FQ		Mac	AG	Vanc	Syner Linez Tediz Dapt Tela Dalb Orita	Tet	Tige	TMP-SMX	Col	Clin	Met
	Pen G	Naf	Amp	Una Aug	Tic	Pip	Tim Zos	1st	2nd	3rd	4th	Anti-MRSA ceftar	Cefto -Tazo	Imip Mero Erta Dori	Aztre	Cip	Levo[ƨ] Moxi	Eryth Clari Azith	Gent Tobra Amik			Tet Doxy Mino					
Group Strep	X	X	X	X		X	X	X	X	X[‡]	X	X	X	X		±X	X	X		X	X	X	X	±X		X	
Viridans Strep	X	X	X	X		X	X	X	X	X[‡]	X	X	X	X		±X	X	X	X	X	X	X	X			X	
PSSP	X		X	X		X	X	X	X	X[‡]	X	X	X	X		±X	X	X		X	X	X	X			X	
PRSP										X[‡]	X	X					X			X	X						
Enterococcus	X		X	X		X	X							X			±X		X	X	X	X	X				
VRE																					X[***]						
MSSA		X		X			X	X	X	X[‡]	X	X		X		±X	X	±X	X	X	X	X	X	X		X	
MRSA												X							X	X	X	±X	X	X		CA-MRSA	
H influenzae			X[§]	X	X	X	X		X[§]	X	X	X	X	X	X	X	X	X[◊]				X	X	X	X		
M catarrhalis				X			X			X	X	X	X	X	X	X	X	X				X	X				
Neisseria	X		X	X	X	X	X		X	X	X	X		X	X	X	X	X				X	X	X			
E coli			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X				X	X	X		
Proteus			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X					X			
Klebsiella				X		±X	X	X	X	X	X	X	X	X	X	X	X		X				X	X	X		
Enterobacter					X	X	X			X	X	X	X	X	X	X	X		X				X	X	X		
Serratia						X	X			X	X	X	X	X	X	X	X		X					X			
Salmonella			X	X	X	X	X			X	X	X	X	X	X	X	X		X					X	X		
Pseudomonas					X	X	X			X[*]	X		X	X[**]	X	X	X[€]		X						X		
Stenotroph										X[φ]							X[ψ]						X	X	X		
ADA	X		X	X		X	X	X	X	X	X	X	X	X			X	X		X	X	X	X			X	X
BDA				X		±X	X		X[†]				X	X									X			±X	X
C difficile																				X							X
Legionella																X	X	X				X					
Treponema	X									X								X				X					

PSSP = Penicillin Susceptible *Streptococcus pneumoniae*
PRSP = Penicillin Resistant *Streptococcus pneumoniae*
VRE = Vancomycin Resistant *Enterococcus*
MSSA = Methicillin Susceptible *Staphylococcus aureus*
MRSA = Methicillin Resistant *Staphylococcus aureus*
ADA = Above the diaphragm anaerobes (*Peptococcus*)
BDA = Below the diaphragm anaerobes (*Bacteroides fragilis and Bacteroides fragilis group*)

Una = Unasyn (ampicillin/sulbactam)
Aug = Augmentin (amoxicillin/clavulanate)
Tim = Timentin (ticarcillin/clavulanate)
Zos = Zosyn (piperacillin/tazobactam)

§ β-lactamase negative strains only
†Cephamycin cephalosporins only (cefoxitin, cefotetan)
‡ Ceftriaxone and cefotaxime only
* Ceftazidime and cefoperazone only; φ Ceftazidime only
Not ertapenem; * Synercid only against VRE faecium; telavancin/dalbavancin vs some VRE
ƨ Levofloxacin with better Gram-negative activity;€ Not moxifloxacin; ψ Levofloxacin only
◊ Azithromycin and clarithromycin only

INTRODUCTION TO ANTIBIOTICS

Appropriate antimicrobial therapy for a given infectious disease requires knowledge of the potential site of infection; the infecting pathogen(s); the expected activity of the antibiotic(s) against the infecting pathogen(s); and host characteristics. Therefore, **appropriate diagnosis is crucial.** Specimens should be obtained from the suspected site of infection (optimally BEFORE antibiotics are initiated) for microscopy and culture to try and identify the causative pathogen(s).

I. **ESTABLISHING THE PRESENCE OF INFECTION** – Before initiating antibiotic therapy, it is important to first clearly establish the presence of an infectious process. The isolation of an organism from a clinical specimen does not always indicate the presence of infection or mandate anti-infective therapy.

A. **NORMAL FLORA, CONTAMINATION, COLONIZATION, OR INFECTION**

1. The human body harbors a number of microorganisms that colonize certain body systems called **"normal flora",** which are normally harmless bacteria that occur naturally on the skin, and in the respiratory, gastrointestinal, and genitourinary tracts.
   a. Normal flora bacteria are located in anatomic sites where pathogenic organisms can cause disease. They often compete with pathogenic organisms for nutrients, stimulate cross-protective antibodies, and suppress the growth of pathogenic organisms.
   b. Bacteria that comprise normal flora may become pathogenic when host defenses are impaired or when they are translocated to sterile body sites during trauma, intravenous line insertion, or surgery (necessitating skin disinfection before line insertion or surgery).
   c. Indiscriminate use of antibiotics can alter or eradicate the protective normal bacterial flora.
   d. Patients who are hospitalized for more than 48 hours can have their usual normal flora replaced by the "normal flora" of the hospital, which tend to be gram-negative aerobes.
   e. **SITES OF NORMAL FLORA COLONIZATION**

SKIN	**UPPER RESPIRATORY TRACT**
Diphtheroids (*Corynebacterium spp*.) *Propionibacteriaceae* *Bacillus spp.* Staphylococci (esp. coagulase-negative) Streptococci	*Bacteroides spp.* *Haemophilus spp.* *Neisseria spp.* Streptococci (anaerobic)
GASTROINTESTINAL TRACT	**GENITOURINARY TRACT**
Bacteroides spp. *Clostridium spp.* Enterobacteriaceae (*E. coli, Klebsiella spp*.) Streptococci (anaerobic) *Enterococcus spp.* *Fusobacterium spp.*	*Lactobacillus spp.* *Corynebacterium spp.* Enterobacteriaceae – especially *E.coli* Staphylococci (*S. saprophyticus*) Streptococci

2. **BODY SITES (FLUIDS) THAT ARE STERILE** include the bloodstream, cerebrospinal fluid, pleural fluid, peritoneal fluid, pericardial fluid, synovial fluid, bone, and urine (taken directly from the bladder).
3. The isolation of an organism from a clinical specimen does not always represent the presence of infection - clinicians must consider the clinical, laboratory and radiographic evidence available to differentiate between contamination, colonization, or infection.
   a. **Contamination** – an organism is introduced into the clinical specimen during the sample acquisition process
      i. *Example:* isolation of coagulase negative staphylococci in the blood of a patient where the blood was drawn via a peripheral stick and the patient does not have signs of infection (normal skin flora bacteria contaminated blood culture).
   b. **Colonization** – an organism is present at a body site but is not invading host tissue or eliciting host responses.
      i. *Example:* isolation of *Pseudomonas aeruginosa* from a sputum culture in a patient without fever, cough, or infiltrate on chest x-ray (pathogenic bacteria in patient without clinical/radiologic signs of pneumonia).
   c. **Infection** – a **pathogenic** organism is present at a body site and is damaging host tissues and eliciting host responses and symptoms consistent with infection.
      i. *Example:* isolation of *Streptococcus pneumoniae* in the cerebrospinal fluid of a patient with fever, headache, photophobia, and neck stiffness.
4. ***Clinical* signs of infection** (both localized and systemic) include:

LOCALIZED		**SYSTEMIC**	
pain	purulent discharge	**FEVER**	malaise
inflammation	sputum production	chills, rigors	hypotension
swelling	cough	tachycardia	mental status changes
erythema	abnormal discharge	tachypnea	

5. ***Laboratory*** signs suggestive of infection include:
   a. Elevated white blood cell count (peripheral {leukocytosis} and/or at site of infection) with a "left shift"
   b. Positive gram stain and culture
   c. Elevated erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP)
   d. pO2 - hypoxemia
   e. Positive antigen or antibody titers
6. ***Radiographic*** signs of infection
   a. Infiltrate on chest x-ray in patients with pneumonia
   b. Periosteal elevation and bony destruction on a bone x-ray in a patient with osteomyelitis
7. **Assessment of the Severity of Infection**
   a. The severity of a patient's infection is based on the degree of abnormality in the parameters above.

b. Significant alterations in cardiac, respiratory and central nervous system parameters may signify a serious, life-threatening infection.
c. The severity of infection may influence the choice, route of administration, and dose of antibiotics used.

8. **Common Bacterial Pathogens by Site of Infection**
   a. Certain bacteria have a propensity to commonly cause infection in particular body sites or fluids.
   b. This information is used to guide the choice of empiric antibiotic therapy before the results of the gram stain, culture, and susceptibility results are known. An antibiotic is empirically chosen that has a spectrum of activity that covers the most common causative bacteria at the patient's suspected infection site.

SUSPECTED ORGANISMS BY SITE OF INFECTION

Mouth	**Skin & Soft Tissue**	**Bone & Joint**
Peptococcus	*Staphylococcus aureus*	*Staphylococcus aureus*
Peptostreptococcus	*Staphylococcus epidermidis*	*Staph epidermidis*
Actinomyces israelii	*Streptococcus pyogenes*	*Neisseria gonorrhoeae*
Treponema pallidum	*Pasteurella multocida*	*Streptococcus spp.*
		Gram-negative bacilli
Abdomen	**Urinary Tract**	**Upper Respiratory Tract**
Escherichia coli	*Escherichia coli*	*Streptococcus pneumoniae*
Proteus spp.	*Proteus mirabilis*	*Haemophilus influenzae*
Klebsiella spp.	*Klebsiella spp.*	*Moraxella catarrhalis*
Enterococci	*Enterococcus spp.*	*Streptococcus pyogenes*
Bacteroides spp.	*Staphylococcus saprophyticus*	
Fusobacterium spp.		
Lower Respiratory Tract	**Lower Resp Tract**	**Meningitis**
Community-Acquired	**Hospital-Acquired**	
Streptococcus pneumoniae	*Staphylococcus aureus (MRSA)*	*Streptococcus pneumoniae*
Haemophilus influenzae	*Pseudomonas aeruginosa*	
Neisseria meningitidis	*Klebsiella pneumoniae*	
	Acinetobacter sp.	
Klebsiella pneumoniae	*Enterobacter spp.*	*Haemophilus influenzae*
Legionella pneumophila	*Citrobacter spp.*	*Group B Strep*
Mycoplasma pneumoniae	*Serratia spp.*	*Escherichia coli*
Chlamydophila pneumoniae	*Acinetobacter spp.*	*Listeria monocytogenes*
Moraxella catarrhalis	*Staphylococcus aureus*	

When selecting an antibiotic for a particular infection, one of the issues that will be considered is the result of antimicrobial susceptibility testing of the infecting pathogen, which typically takes 24 to 48 hours or more to perform. If the susceptibility results of the infecting pathogen are not yet known, an antibiotic is empirically selected based on the most likely infecting organism and current local susceptibility patterns. ***In most cases, therapy must be initiated at the suspicion of infection since infectious diseases are often acute, and a delay in treatment may result in serious morbidity or even mortality (e.g., meningitis, pneumonia).*** *Once the susceptibility results of the infecting bacteria are known, empiric antibiotic therapy should be streamlined to an antibiotic agent with more specific activity toward the infecting bacteria.*

II. ANTIMICROBIAL SUSCEPTIBILITY TESTING

A. **General Antimicrobial Spectrum of Activity -** the spectrum of activity for each antibiotic is a general list of bacteria that the antibiotic displays activity against. However, since bacteria may become resistant to antibiotics over time, recent national, local, and specific organism susceptibility data should be considered when selecting an antibiotic to treat a specific patient's infection.

1. **Narrow Spectrum:** the antibiotic has activity against a limited group of bacteria (e.g., penicillin has activity against some gram-positive and gram-negative cocci, but not gram-negative bacilli).
2. **Broad Spectrum:** the antibiotic has activity against a wide variety of bacteria, such as gram-positive and gram-negative bacteria (e.g., imipenem has activity against gram-positive and gram-negative aerobes and anaerobes).

B. **Susceptibility Definitions**

1. **Minimum Inhibitory Concentration or MIC**– the lowest concentration of an antibiotic that prevents visible growth (unaided eye) of a bacteria after 18 to 24 hours of incubation
2. **Minimum Bactericidal Concentration or MBC** – the lowest concentration of an antibiotic that results in a decrease of > 99.9% of the bacterial inoculum (MIC ≤ MBC)
3. **Susceptibility Breakpoints** – interpretive guidelines established by the Clinical and Laboratory Standards Institute (CLSI) that categorize the MIC values or zone sizes for each antibiotics against each bacteria as:
   a. **Susceptible (S)** – organism will most likely be eradicated during treatment of infection using normal doses of the specified antibiotic; concentrations of the antibiotic represented by the MIC are easily achieved in patient's serum with usual doses.
   b. **Intermediate (I)** – results are considered equivocal or indeterminate; MICs are higher, and treatment may be successful when maximum doses are used or if the drug concentrates at the site of infection.
   c. **Resistant (R)** – indicates less than optimal results are anticipated if the particular antibiotic is used; the MIC exceeds usual serum concentrations (even if maximal doses are used).
   d. The interpretive guidelines for S, I, and R of each antibiotic are often different because they are based on clinical PK of the individual drug (**achievable serum and tissue concentrations**), general activity of the antibiotic, site of infection, and data from clinical efficacy trials.
   e. Susceptibility breakpoints differ for each antimicrobial drug class and even between antibiotics within the same drug class – therefore, **MIC values often cannot be compared between antibiotics.**

C. **TESTING METHODS FOR SUSCEPTIBILITY -** once an organism is cultured in the microbiology lab, further testing is performed to determine the antibiotic susceptibility of the organism to serve as a guide to streamline antibiotic therapy.

1. **Broth Dilution** (macrodilution with test tubes, microdilution with automated microtiter plates or cassettes) – a quantitative determination of the *in vitro* activity of an antibiotic since an exact MIC or MIC range can be determined

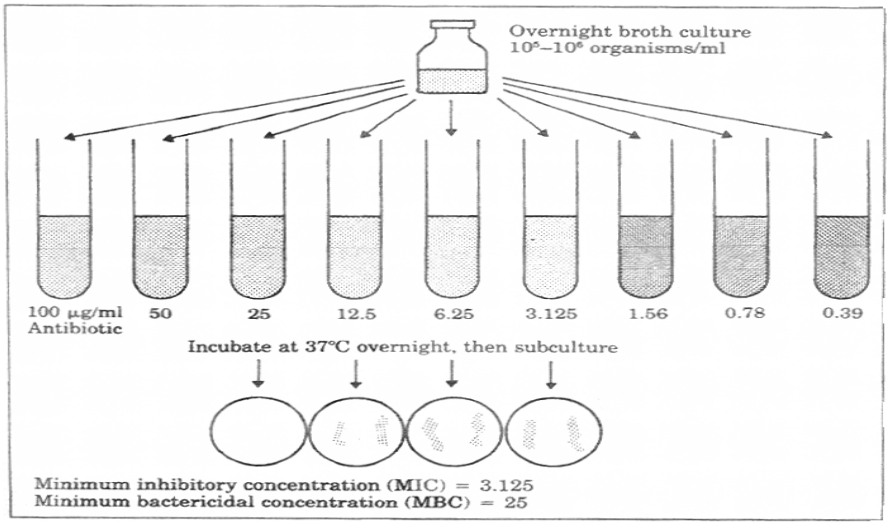
a. Dilutions of an antibiotic (based on achievable serum concentrations after usual doses) are placed in broth with a standard inoculum of the infecting bacteria and incubated for 18 to 24 hours.

b. **MIC** = the lowest concentration of an antibiotic that prevents visible growth of the infecting bacteria after 18 to 24 hours of incubation (clear to unaided eye with macrodilution; automated systems by the machine).

c. **Macrodilution testing** employs two-fold serial dilutions of an antibiotic (based on achievable serum concentrations after usual doses) incubated in test tubes with a standard inoculum of the patient's infecting bacteria; the exact MIC of the antibiotic is the first tube without visible growth; labor and resource intensive.

i. **MBC** – lowest concentration of the antibiotic that kills bacteria

- Test tubes without visible growth are cultured on agar plates. After incubation colonies counted - MBC is the concentration that reduced the original inoculum by 99.9% after 24 hours of incubation.
- MBC is only determined in limited circumstances such as in the treatment of certain infections where bactericidal activity may be more predictive of a favorable outcome (meningitis, endocarditis).



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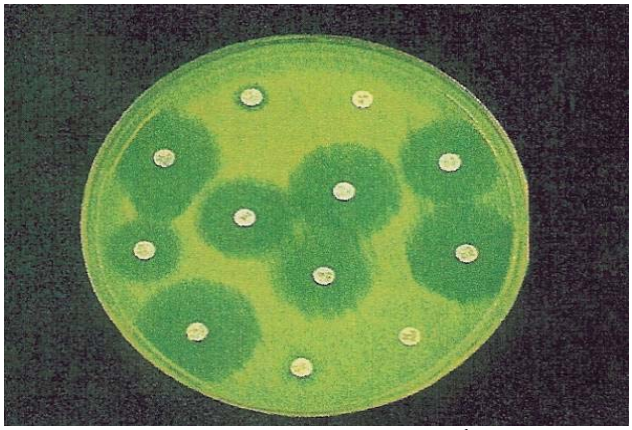
d. **Microdilution methods** employ microtiter plates or cassettes that contain wells with serial dilutions of **<u>several</u>** antibiotics that can be tested for susceptibility simultaneously in an automated system.

e. Size constraints of the plates or cassettes allow only a limited number of concentrations to be tested for each antibiotic (usually those representing the S, I, and R breakpoints), so that an MIC range may be reported instead of an exact MIC (for example ≤ 8 μg/ml, susceptible).

f. Automated microdilution systems are the **most common method** utilized in microbiology labs for susceptibility testing because less labor and resources are required for performance.

2. **Disk Diffusion (Kirby Bauer Method)** – a qualitative determination of the *in vitro* activity of an antibiotic
   a. Filter paper disks impregnated with a fixed concentration of an antibiotic are placed on agar plates inoculated with a standardized inoculum of the patient's infecting bacteria.
   b. Bacteria multiply on the plate while antibiotic diffuses out of the disk; bacterial growth occurs only in areas where drug concentrations are below those required to cause inhibition of bacterial growth.
   c. A clear zone of inhibition is then observed around the disk - the larger the diameter, the more active the drug against the bacteria. Zone diameters in millimeters (mm) for each drug have been correlated to susceptible and resistant interpretations; however, exact MICs cannot be determined.



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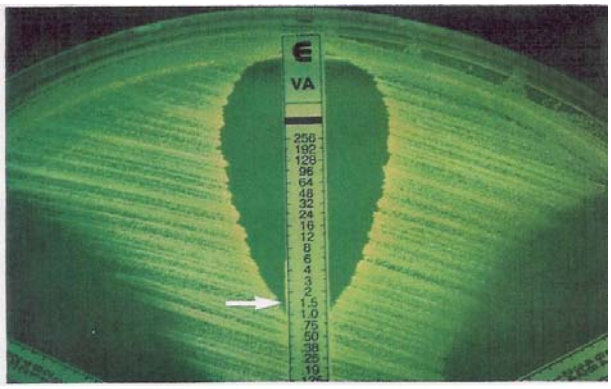
3. **E-Test® (Epsilometer Test) –** combines the quantitative benefits of microdilution with the ease of agar dilution
   a. A plastic strip impregnated with a known, prefixed concentration gradient of antibiotic is placed on an agar plate with a standardized inoculum of the patient's infecting bacteria.
   b. Bacteria multiply on the agar plate while antibiotic diffuses out of the strip according to the concentration gradient; bacterial growth occurs only in areas where drug concentrations are below those required to cause inhibition of bacterial growth.
   c. An elliptical zone of inhibition is then formed, and the MIC is measured where the ellipse crosses the antibiotic strip. An exact MIC can be determined.



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4. **Susceptibility Reports**
   a. For each patient's infecting bacteria, a susceptibility report will be generated that lists the antibiotics that were tested for activity against the organism, the exact MIC or zone size (or MIC range if automated systems are used) and CLSI interpretation (S, I, and R).
   b. This information is utilized with other clinical and patient-specific parameters (to be discussed later) to select an antibiotic regimen for the treatment of the patient's infection.
5. **Hospital Antibiograms**
   a. Susceptibility data from organisms cultured from patients (inpatients and/or outpatients) are compiled in an annual report called an **Antibiogram**.
   b. The susceptibility data in an antibiogram is typically used to help guide the choice of ***empiric*** antibiotic therapy before the infecting organism has been identified in the lab. Clinicians use the antibiogram to determine the most active antibiotic against specific organisms at that specific institution.

NUMBERS REFLECT PERCENT SUSCEPTIBLE

Gram Positive Cocci	Total No. Tested	Penicillin	Ampicillin	Ampicillin/ Sulbactam	Oxacillin	Cefazolin	Ceftriaxone	Vancomycin	Clindamycin	Erythromycin	Ciprofloxacin	Rifampin	Nitrofurantoin* For urine only	TMP/SMX	Tetracycline	Gentamicin	Gentamicin 500ug	Streptomycin 2000ug
Staph. aureus	853	11	—	100	100	100	—	100	93	70	87	100	100	96	94	99	—	—
Methicillin Resistant S. aureus	531	0	—	0	0	0	—	100	15	4	8	96	100	88	94	66	—	—
Staph.sp. coagulase negative	853	7	7	27	27	28	—	100	58	26	53	94	100	57	81	64	—	—
Group D Enterococcus	467	61	64	—	—	—	—	86	—	—	—	—	85	—	—	—	69	52
Streptococcus pneumoniae	87	56	—	—	—	—	75	100	90	67	—	—	—	63	85	—	—	—

14% Group D Enterococcus are vancomycin resistant.
38% S. aureus are methicillin resistant.
Oxacillin susceptibility predicts nafcillin susceptibility; cephalothin susceptibility predicts cefazolin susceptibility.
Haemophilus influenzae (184 tested) 64% were beta-lactamase negative.
Moraxella catarrhalis are beta-lactamase positive; consider resistant to penicillin, ampicillin, and amoxicillin.
No susceptibility testing performed on Group A Streptococcus and Group B Streptococcus; all are penicillin susceptible.

III. HOW ANTIBIOTICS ARE USED

A. The treatment of infectious diseases is quite different than other disease states requiring drug therapy in a number of ways:

1. Antibiotics can be used to ***treat*** a suspected or documented infection, or can be used to ***prevent*** an infection from occurring in high-risk patients.
2. Additionally, anti-infective therapy is typically given for a ***finite duration of therapy*** or a particular number of days based on previous clinical data for that infection type and/or infecting organism. Occasionally, some patients may receive anti-infective therapy for an infinite duration (such as that given for diabetes, CHF, or hypertension).

B. **Empiric Therapy –** Antibiotics are administered that have activity against the predicted or most likely pathogens causing a patient's infection based on the signs and symptoms of infection. The site of infection may or may not be known, and the culture results are pending, negative, or unobtainable.
1. *Examples* – antibiotics are started in a patient with community-acquired pneumonia who is unable to expectorate a sputum sample; a patient presents to the hospital with signs of bacterial meningitis and antibiotics are started immediately after a lumbar puncture is performed.
2. The initial antibiotic therapy is selected based on the known or probable site of infection, the most likely causative organism(s), the drug of choice for that particular organism and infection, and the local (hospital antibiogram) or regional susceptibility patterns of the suspected bacterial pathogens. Empiric antibiotic therapy usually covers a wide variety of bacteria ***(broad-spectrum)***.
3. Empiric therapy is usually administered until the culture and susceptibility results are available. If an organism is not isolated, empiric therapy may be continued until the finite duration of antibiotic therapy has been completed for that infection type, assuming the patient is improving.

C. **Directed or targeted therapy –** antibiotics are used to treat an **<u>established</u>** infection where the site of infection, causative pathogen, and antibiotic susceptibilities are known.
1. *Example* – a patient has bacteremia with methicillin-susceptible *Staphylococcus aureus* and is receiving intravenous nafcillin therapy.
2. Antibiotic therapy is selected based upon the susceptibility results of the infecting pathogen, and is typically changed from the empiric antibiotic originally chosen to a more narrow-spectrum agent directed toward the infecting organism.
3. Antibiotics are given for the finite duration of therapy as determined by the infection type. All effective antibiotics that have been administered for the infection count toward the effective days of therapy (empiric and directed).

D. **Prophylactic Therapy –** antibiotics are given to prevent the development of infection during a procedure or immunocompromised state when there is a considerable risk of infection
1. *Examples* – a patient with a prosthetic heart valve is given amoxicillin to prevent endocarditis at the time of a bacteremia-inducing dental procedure; an AIDS patient is given Bactrim to prevent *Pneumocystis carinii* pneumonia when the CD_4 count is less than 200 cells/mm^3; antibiotics are given prior to surgical procedures to prevent surgical site infections

2. Antibiotic therapy is selected based on the local and regional susceptibility patterns of the most likely infecting bacteria.
3. Prophylaxis is administered for as long as the patient is at risk, such as single dose antibiotic therapy for surgical/dental prophylaxis or longer durations of antibiotic therapy during immunosuppressive states.

E. **Combination Therapy**

1. Combination therapy may be selected in a limited number of circumstances for the treatment of infection:
   a. To provide coverage against all organisms in a mixed, polymicrobial infection where a single antibiotic does not cover all of the infecting organisms – used to broaden bacterial coverage.
   b. To take advantage of synergistic properties when the antibiotics are used together.
   c. To decrease the emergence of resistance – only for tuberculosis.
2. **Synergy** – the activity of the antimicrobial combination is greater than that expected from the additive activity of the individual antimicrobials
   a. $(A + B) > A + B$
   b. *Example:* ampicillin and gentamicin are administered together in the treatment of *Enterococcal* endocarditis in order to produce **bactericidal** activity and achieve successful eradication of the infection (alone each agent is bacteriostatic against *Enterococcus*)
3. **Additive** – the activity of the antimicrobial combination is no greater than the sum of the effects of each individual component (no greater and no worse)
   a. $(A + B) = A + B$
4. **Antagonism** – the activity of the antimicrobial combination is less than that expected from the additive activity of the individual antimicrobials
   a. $(A + B) < A + B$
   b. *Example:* azole antifungals and amphotericin B

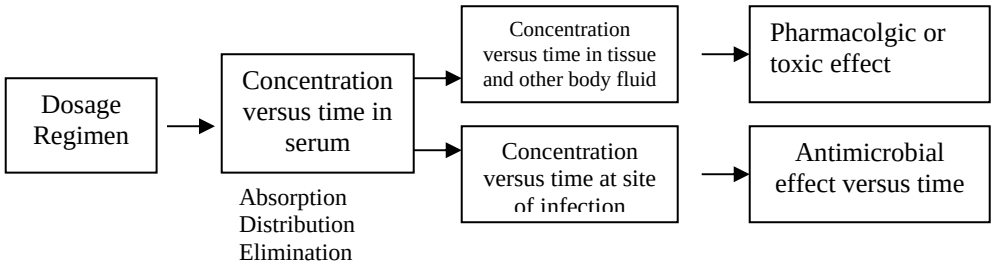
IV. PHARMACODYNAMIC CONSIDERATIONS

A. **Type of antibacterial activity – BACTERIOSTATIC or BACTERICIDAL?**

1. **Bacteriostatic** – antimicrobial agents that ***inhibit*** the growth of susceptible bacteria and rely on host defenses to help kill the bacteria and subsequently eradicate the infection
   a. Typically, normal host defenses are required for clinical success of bacteriostatic agents, so they should be used with caution in patients who are immunocompromised.
   b. *Examples*: macrolides, ketolides, streptogramins, oxazolidinones, tetracyclines, glycylcyclines, sulfonamides (alone), and clindamycin
2. **Bactericidal** – antimicrobial agents that ***kill*** susceptible bacteria in the absence of host defenses
   a. Bactericidal activity is considered essential in the treatment of infections located in sites where host defenses are not adequate including the meninges (meningitis), heart valves (endocarditis), and bone (osteomyelitis); as well as in patients with impaired host defenses (febrile neutropenia).

b. *Examples*: β-lactams, aminoglycosides, vancomycin, daptomycin, fluoroquinolones, metronidazole, and trimethoprim-sulfamethoxazole

B. **Pharmacodynamics (PD)** is the study of the time course or rate of bacterial killing relative to serum concentrations. The study of pharmacodynamic provides a rational basis for optimizing dosing regimens by describing the relationship between drug, host, and antimicrobial effect by integrating both pharmacokinetic and MIC data.



Pharmacokinetics **Pharmacodynamics**

C. PD studies have demonstrated ***marked differences*** in the time course of bacterial killing among different antibiotics, described by examining the relationship between pharmacokinetic parameters and the MIC.

D. On the basis of PD studies, antibiotics can generally be divided into 2 major groups on the basis of their bactericidal activity:

1. **Concentration-dependent** – the higher the serum concentration of the antibiotic, the more rapid and extensive the degree of bacterial killing. Concentration-dependent agents also appear to have prolonged persistent effects (post antibiotic effects or PAE) that allow for infrequent dosing**.**
   a. ***Examples*** of concentration-dependent antibiotics include the **aminoglycosides,** the **fluoroquinolones, daptomycin,** and **metronidazole**
   b. The major PD parameters that correlate with clinical and microbiologic outcome (efficacy) of concentration-dependent antibiotics are the **Peak/MIC ratio** and the **AUC/MIC ratio.**
   c. **Goal of dosing - infrequent dosing of large doses to maximize drug concentrations or magnitude of exposure for optimal bacterial killing.**
2. **Concentration-independent (time-dependent) –** higher serum concentrations of the antimicrobial do not produce enhanced bacterial killing. The extent of bacterial killing is largely dependent on the **time of exposure. These agents are not rapidly bactericidal, and typically have a short or nonexistent PAE.**
   a. ***Examples*** include the **β-lactams, clindamycin, macrolides, ketolides, vancomycin, tetracyclines, linezolid, Synercid**
   b. Goal of dosing - optimize the duration of exposure (Time>MIC). Maintain the serum concentrations of the antibiotic above the MIC for the infecting pathogen for at least 40-70% of the dosing interval, depending on the organism.

E. **Post-Antibiotic Effect (PAE)** – the time it takes for a bacteria to recover after exposure to an antibiotic, or the time it takes for bacteria to recover and begin regrowth after an antibiotic has been removed.
   1. The exact duration of the PAE is drug and organism specific.
   2. Agents with appreciable PAEs may be dosed to allow serum concentrations to fall below the MIC of the infecting bacteria since regrowth will not occur for a finite period (for as long as the antibiotic's PAE).
   3. All antibiotics produce some PAE against **gram-positive bacteria**; the PAE for β-lactams is approximately 2 hours.
   4. For **gram-negative bacteria**, prolonged PAEs are observed after exposure to protein synthesis inhibitors or nucleic acid synthesis inhibitors (fluoroquinolones and aminoglycosides); β-lactams have short or nonexistent PAE.

V. ANTIMICROBIAL REGIMEN SELECTION

A. Choosing an antibiotic to treat a patient's infection is more complicated than simply matching a drug to a known or suspected pathogen. The decision is typically based on the interrelationship between the patient, the infection, and the characteristics of the antibiotic.

B. When selecting an antibiotic for the treatment of an infection, a variety of factors must be considered:
   1. ***Infection-Specific Factors***
      a. **Severity of infection** (mild. moderate, severe, life-threatening) – influences the route of administration, dose, number of antibiotics
         Oral – for infections that are mild, or for those that are significantly improved and can be treated on an outpatient basis
         IV – used for infections that are serious or life-threatening, or for antibiotics with insufficient absorption from the GI tract.
      b. **Site of infection** – influences the antibiotic and dose, since adequate concentrations of the drug must reach the site of infection for efficacy. Special considerations must be made for the treatment of meningitis (cross blood-brain barrier), endocarditis, prostatitis, etc.
      c. **Infecting organism** – site of acquisition of the infection (community versus hospital, nursing home); exposure to ill family members, pets; employment; recent travel; known or anticipated susceptibility patterns; empiric versus directed therapy; drug of choice for particular organism/infection; need for combination therapy
   2. ***Host Factors*** – patient-specific characteristics should be considered in every patient in whom antimicrobial therapy will be instituted
      a. **Allergies** – careful assessment of allergy history should be performed to ascertain the potential antimicrobial agents that may be used for a patient's infection.
         i. A careful allergy history is necessary because many patients confuse common adverse effects with true allergic reactions (GI effects such as nausea, vomiting, or diarrhea).

ii. The most common antibiotic allergy is to the penicillins; must consider the allergic reaction as well as the degree of cross-reactivity to other β-lactam antimicrobials.
iii. Allergy to a specific antibiotic precludes the use of that antibiotic (and often antibiotic class) for the treatment of infection. Typically, allergy to one macrolide precludes the use of other macrolides, and the same holds true for other antibiotics among the same class.

b. **Age** – aids in identification of the causative pathogen, as well as assessing the patient's ability to eliminate antimicrobial agents.
i. The causative pathogen in meningitis varies markedly depending on the age of the patient.
ii. The pharmacokinetics (PK) of different antibiotics may be altered based on the age of the patient including protein binding, metabolism, or renal elimination of an antimicrobial agent, which may influence drug selection or drug dosing.
- Premature neonates develop kernicterus from sulfonamides due to displacement of bilirubin from albumin.
- Renal function (and elimination) declines with age.
- Age-related hepatotoxicity with isoniazid.

c. **Pregnancy and nursing** – the fetus is at risk for teratogenicity during pregnancy and adverse effects while nursing during antibiotic therapy with some agents. Also, PK parameters are altered during pregnancy (increased volume of distribution and clearance for some drugs) and must be taken into account when dosing.

d. **Renal and hepatic function** – patients with diminished renal or hepatic function will accumulate certain anti-infectives, which may lead to undue toxicity. Dosage adjustments are necessary ensure efficacy but avoid undue toxicity.
i. Antibiotics primarily eliminated by the kidney include most β-lactams (except nafcillin, oxacillin, ceftriaxone, cefoperazone); most fluoroquinolones, clarithromycin, aminoglycosides, vancomycin, daptomycin, Bactrim®, and tetracycline. Dosages can be adjusted according to predetermined guidelines.
ii. Some antibiotics may be removed during a hemodialysis session and require supplemental dosing.
iii. Liver dysfunction will alter the elimination of chloramphenicol, clindamycin, metronidazole, nafcillin/oxacillin, linezolid, Synercid®, erythromycin, azithromycin, doxycycline, tigecycline, and Bactrim®. Dosage adjustments in this setting are not well-studied.

e. **Concomitant drug therapy** may influence the antibiotic used, the dose, or monitoring (occurrence of a drug-drug interactions)
i. *Augmented toxicity* – coadministration of drugs may increase the likelihood of toxicity (vancomycin and gentamicin → nephrotoxicity; ganciclovir and zidovudine → neutropenia)
ii. *Altered PK* – coadministration may alter the A, D, M, and E of either agent (divalent cations decrease the absorption of fluoro-

quinolones and tetracyclines → ↓ concentrations and treatment failure)

f. **Underlying disease states** influence antibiotic selection by predisposing the patient to certain infections or particular causative pathogens related to their disease state.
   i. Patients with diabetes or peripheral vascular disease are prone to soft tissue infections of the lower extremities; patients with chronic lung disease are prone to pulmonary infections.
   ii. Underlying immunosuppression (malignancy, acquired immunodeficiencies) may lead to a wide variety of infections due to a number of etiologic agents.
   iii. Disruption of integumentary barriers from burns, trauma, or iatrogenic wounds (surgery, intravascular lines) may increase the risk of infection.

3. ***Drug Factors*** – the individual characteristics of each antibiotic must be considered when selecting the most appropriate agent
   a. ***In vitro* spectrum of activity and current susceptibilities** – antibiogram, national, regional, or local
   b. **Clinical efficacy** as demonstrated by FDA-approved indications or other clinical studies in the published literature
   c. **Drug of choice charts** – textbooks, treatment guidelines; the drug of choice for a specific infection is often based on the *in vitro* activity against the causative organisms, documented clinical efficacy of the agent against the causative organisms, PK properties of the drug (adequate concentration at site of infection), patient characteristics, etc
   d. **Dosage forms available** – oral (tablet, capsule, suspension), parenteral (intramuscular, intravenous), intrathecal
      i. The route of administration depends on the severity of illness of the patient (patient with hypotension should not receive oral therapy due to unreliable drug absorption); the age of the patient (can the patient swallow a tablet?); available dosage forms; etc.
      ii. Antibiotics that are only available orally should not be used for the treatment of meningitis
   e. **Pharmacokinetics (tissue penetration, route of elimination) -** choose an anti-infective that achieves adequate concentrations in the serum and the site of infection (with meningitis – agent must cross the blood brain barrier, etc.).

   f. **Pharmacodynamics**
      i. What type of activity is required to treat the patient's infection - bacteriostatic or bactericidal?
      ii. Consideration should be given to the type of bactericidal activity (concentration-dependent or time-dependent) the antibiotic provides and use this information to select an appropriate dose.

g. **Side effect profiles -** the potential adverse events associated with the use of each antibiotic must be carefully considered for each patient
   i. Nephrotoxic agents should be used with caution (e.g., aminoglycosides, amphotericin) in patients with underlying renal insufficiency.

h. **Cost –** antimicrobial agents are a major portion of hospital drug expenditures, and include more than just the obvious acquisition cost of the drug. Other considerations include the ancillary costs (preparation, storage, distribution, and administration of the drug), cost of frequent dosing, and the costs associated with monitoring and managing toxicity or serious adverse effects.

APPENDIX A: CLINICALLY-RELEVANT BACTERIA

GRAM-POSITIVE AEROBES

Gram-positive cocci in **clusters**
- *Staphylococcus aureus*
- *Staphylococcus epidermidis*
- *Staphylococcus saprophyticus*
- *Staphylococcus haemolyticus*
- *Staphylococcus hominis*
- *Staphylococcus capitis*
- *Staphylococcus saccharolyticus*

Gram-positive cocci in **pairs**
- *Streptococcus pneumoniae*

Gram-positive cocci in **chains**
- **Group Streptococcus**
  - Group A Strep - *Streptococcus pyogenes*
  - Group B Strep - *Streptococcus agalactiae*
  - Group C Strep - *Streptococcus equi*
  - Group D Strep – *S bovis, S. equinus*
  - Group F, G Strep
- **Viridans Streptococcus**
  - *Streptococcus mitis*
  - *Streptococcus milleri*
  - *Streptococcus mutans*
  - *Streptococcus sanguis*
  - *Streptococcus salivarius*
  - *Streptococcus intermedius*

Gram-positive cocci in **pairs AND chains**
- *Enterococcus faecalis*
- *Enterococcus faecium*
- *Enterococcus gallinarum*
- *Enterococcus casseliflavus*

Gram-Positive **BACILLI**
- *Bacillus anthracis*
- *Bacillus cereus*
- *Corynebacterium diphtheriae*
- *Corynebacterium jeikeium*
- *Lactobacillus spp.*
- *Listeria monocytogenes*
- *Nocardia asteroides*
- *Streptomyces spp.*

GRAM-NEGATIVE AEROBES

Gram-negative cocci
- *Moraxella catarrhalis*
- *Neisseria meningitidis*
- *Neisseria gonorrhoeae*

Gram-negative coccobacilli
- *Haemophilus influenzae*
- *Haemophilus parainfluenzae*

Gram-negative bacilli
- **Enterobacteriaceae**
  - *Citrobacter freundii*
  - *Enterobacter aerogenes* or *cloacae*
  - *Escherichia coli*
  - *Klebsiella pneumoniae*
  - *Morganella morganii*
  - *Proteus mirabilis* or *vulgaris*
  - *Providencia spp*
  - *Salmonella spp.*
  - *Shigella spp.*
  - *Serratia marcescens*
  - *Yersinia pestis*
- **Non-Enterobacteriaceae**
  - *Acinetobacter spp*
  - *Aeromonas hydrophila*
  - *Bordetella pertussis*
  - *Burkholderia cepacia*
  - *Campylobacter jejuni*
  - *Gardnerella vaginalis*
  - *Helicobacter pylori*
  - *Pasteurella multocida*
  - *Pseudomonas aeruginosa*
  - *Stenotrophomonas maltophilia*
  - *Vibrio cholerae*

ANAEROBES

"Above the Diaphragm"

Gram-positive cocci	**Gram-negative cocci**	**Gram-positive bacilli**
Peptococcus	*Prevotella*	*Actinomyces israelii*
Peptostreptococcus	*Veillonella*	*Prevotella*
		Porphyromonas
		Fusobacterium

"Below the Diaphragm"

Gram-positive bacilli	**Gram-negative bacilli**
Clostridium perfringens	*Bacteroides fragilis*
Clostridium difficile	*Bacteroides fragilis* group {"DOT" = **d**istasonis, **o**vatus, **t**hetaiotamicron)
Clostridium tetani	*Fusobacterium spp.*
	Prevotella

"Skin Anaerobes"
Propionibacterium acnes (a gram-positive bacilli)

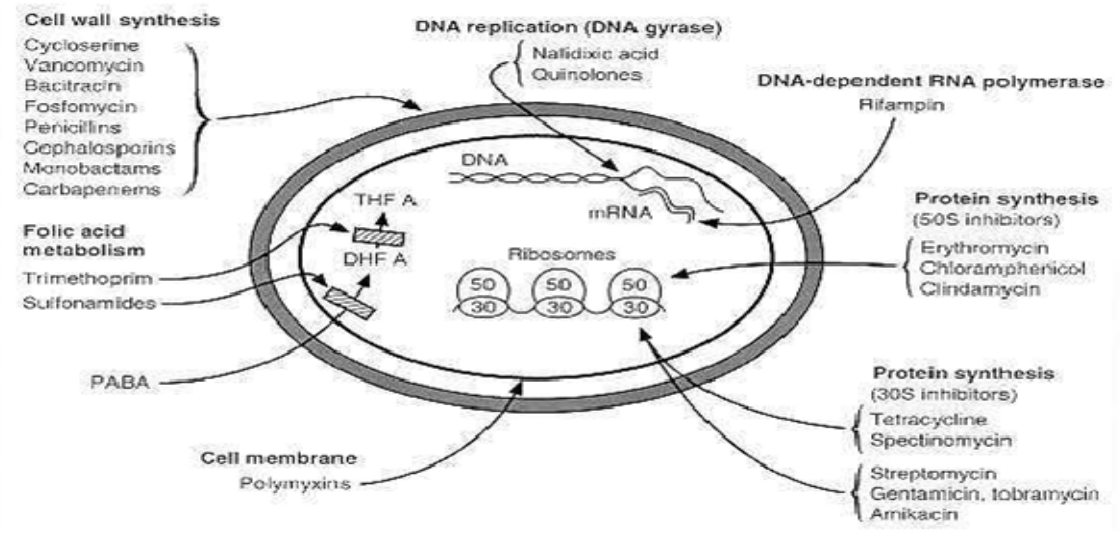
ATYPICAL BACTERIA
Chlamydophila pneumoniae
Chlamydia trachomatis
Legionella pneumophila
Mycoplasma pneumoniae

SPIROCHETES
Treponema pallidum (syphilis)
Borrelia burgdorferi (Lyme disease)
Leptospira interrogans

APPENDIX B: ANTIBIOTIC CLASS SUMMARY

Class	Group/ Name	Static or Cidal
CELL WALL SYNTHESIS INHIBITORS		
β-Lactams	Penicillins	Bactericidal
	Cephalosporins	Bactericidal
	Carbapenems	Bactericidal
	Monobactams (aztreonam)	Bactericidal
	β-lactam inhibitor combos (Zosyn®, Unasyn®)	Bactericidal
Glycopeptides	Vancomycin	Bactericidal
Lipopeptides*	Daptomycin	Bactericidal
PROTEIN SYNTHESIS INHIBITORS		
Aminoglycosides*	Gentamicin, tobramycin, amikacin	Bactericidal
Macrolides	Erythromycin, azithromycin, clarithromycin	Bacteriostatic
Tetracyclines, Glycylcyclines	Doxycycline, tetracycline, tigecycline	Bacteriostatic
Chloramphenicol		Bacteriostatic
Lincosamides	Clindamycin	Bacteriostatic
Streptogramins	Quinupristin/ dalfopristin (Synercid)	Bacteriostatic
Oxazolidinones	Linezolid	Bacteriostatic
NUCLEIC ACID SYNTHESIS INHIBITORS		
Fluoroquinolones*	Ciprofloxacin, levofloxacin, moxifloxacin	Bactericidal
Metronidazole*		Bactericidal
METABOLIC INHIBITORS		
Sulfonamides	Trimethoprim-sulfamethoxazole	Bactericidal

* Concentration-dependent bactericidal activity



Penicillins

Key Concepts and Learning Objectives
At the end of the lecture the learner will be able to:

1. Describe the differences in the spectrum of activity between the natural penicillins, the penicillinase-resistant penicillins, the aminopenicillins, the carboxypenicillins, the ureidopenicillins, and the β-lactamase inhibitor combinations with special emphasis on the specific penicillin agents that have activity against *Staphylococcus aureus*, *Pseudomonas aeruginosa*, and *Bacteroides fragilis*. List examples of commonly used agents within each of the penicillin classes.

2. Describe the distribution characteristics of the penicillins into the cerebrospinal fluid, urinary tract, lungs, skin/soft tissue, and bone. List the penicillins that are not primarily eliminated by the kidneys. List the penicillins that require dosage adjustment in renal insufficiency, and those that are removed by hemodialysis.

3. Discuss the main clinical uses of representative penicillins within each group of penicillins.

4. Describe the major adverse effects associated with the penicillin antibiotics.

#28 - PENICILLINS

Date: September 1, 2015

Suggested Reading:
Wright AJ. The penicillins. *Mayo Clinic Proceedings* 1999;74:290-307.

Learning Objectives:

1. Describe the differences in the spectrum of activity between the natural penicillins, the penicillinase-resistant penicillins, the aminopenicillins, the carboxypenicillins, the ureidopenicillins, and the β-lactamase inhibitor combinations with special emphasis on the specific penicillin agents that have activity against *Staphylococcus aureus*, *Pseudomonas aeruginosa*, and *Bacteroides fragilis*. List examples of commonly used agents within each of the penicillin classes.
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3. Discuss the main clinical uses of representative penicillins within each group of penicillins.
4. Describe the major adverse effects associated with the penicillin antibiotics.

Drugs Covered in this Lecture:

Natural Penicillins: Aqueous Penicillin G, Benzathine Penicillin, Procaine Penicillin G, Penicillin VK
Penicillinase-Resistant Penicillins: Nafcillin, Oxacillin, Dicloxacillin
Aminopenicillins: Ampicillin, Amoxicillin
Carboxypenicillins: Ticarcillin
Ureidopenicillins: Piperacillin
β-Lactamase Inhibitor Combinations: Ampicillin-Sulbactam (Unasyn®), Amoxicillin-Clavulanic Acid (Augmentin®), Ticarcillin-Clavulanic Acid (Timentin®)), Piperacillin-Tazobactam (Zosyn®)
β-LACTAMS (Penicillins, Cephalosporins, Carbapenems, Monobactams)

Six General Characteristics of β-Lactam Antibiotics (with a few exceptions)

1. ***Same mechanism of action*** - inhibitors of cell wall synthesis

2. ***Same mechanisms of resistance*** – destruction by β-lactamase enzymes; alteration in penicillin binding proteins (PBPs); decreased permeability of outer cell membrane in gram-negative bacteria

3. ***Pharmacodynamic properties*** – time-dependent bactericidal activity (**except against *Enterococcus* spp.**)

4. ***Short elimination half-life (< 2 hours)*** - repeated, frequent dosing is needed for most agents to maintain serum concentrations above the MIC of the infecting bacteria for an adequate amount of time (**except ceftriaxone, cefoperazone, cefotetan, cefixime, ertapenem**)

5. ***Renal elimination*** – primarily eliminated unchanged by glomerular filtration and tubular secretion (**except nafcillin, oxacillin, ceftriaxone, cefoperazone**)

6. ***Cross-allergenicity*** **- all except aztreonam**

#51 - PENICILLINS

I. INTRODUCTION

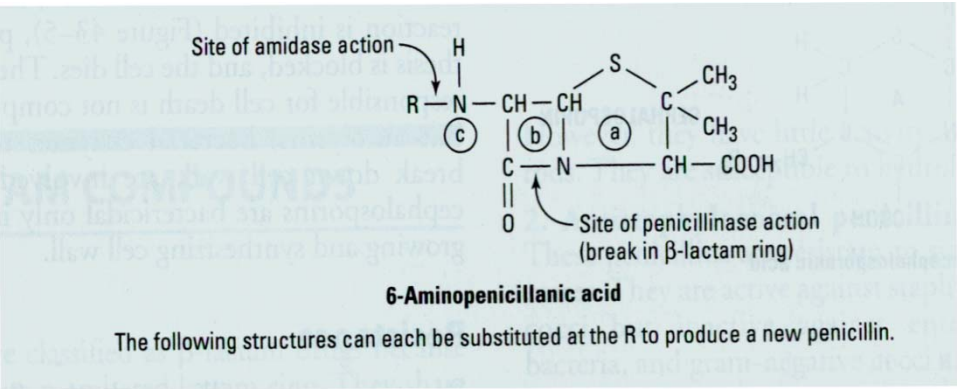
In 1928, penicillin was accidentally discovered by Dr. Alexander Fleming when he noted the antibacterial activity of a mold, *Penicillium notatum*, that was contaminating bacterial culture plates in his laboratory. Due to difficulties with purification and production, penicillin was not used in the treatment of infections until 1941 when it was utilized in the treatment of staphylococcal and streptococcal infections in seriously ill patients. Throughout the years, natural penicillin has remained a useful antibiotic for some of the bacteria for which it was initially introduced. The emergence of bacteria resistant to natural penicillin, as well as the need for agents with expanded antibacterial activity, led to the development of several groups of semisynthetic penicillins with varying side chains to enhance antibacterial activity and improve pharmacologic activity.

II. CHEMISTRY

A. All penicillins share the basic structure of a 5-membered thiazolidine ring connected to a β-lactam ring, with attached acyl side chains.

B. Manipulations of the side chain have led to agents with differing antibacterial spectrums, greater β-lactamase stability, and pharmacokinetic properties.

C. Bacterial β-lactamase enzymes may hydrolytically attack the β-lactam ring and render the penicillin inactive.



A = thiazolidine ring, B = β-lactam ring, C = acyl side chain

III. MECHANISM OF ACTION

A. Penicillins interfere with bacterial cell wall synthesis by binding to and inhibiting enzymes called penicillin-binding proteins (PBPs) that are located in the cell wall of bacteria.

B. PBPs are enzymes (transpeptidases, carboxypeptidases, and endopeptidases) that regulate the synthesis, assembly, and maintenance of peptidoglycan (cross-linking of the cell wall). The number, type, and location of PBPs vary between bacteria.

C. Inhibition of PBPs by β-lactam antibiotics leads to inhibition of the final transpeptidation step of peptidoglycan synthesis, exposing a less osmotically stable cell membrane that leads to decreased bacterial growth, bacterial cell lysis, and death.

D. Penicillins, like all β-lactam antibiotics, are **bactericidal**, except against *Enterococcus* spp. where they display bacteriostatic activity.

IV. MECHANISMS OF RESISTANCE

A. There are **3** primary mechanisms of resistance to penicillin antibiotics

1. Production of β-lactamase enzymes

a. The most important and most common mechanism of bacterial resistance where the bacteria produces a β-lactamase enzyme that hydrolyzes the cyclic amide bond of the β-lactam ring, inactivating the antibiotic.

b. Over 100 different β-lactamase enzymes have been identified. β-lactamase enzymes may be plasmid-mediated or chromosomally-mediated, constitutive or inducible.

c. Produced by many gram-negative (*H. influenzae, N. gonorrhoeae, M. catarrhalis, K. pneumoniae, E. coli, Proteus* spp., *P. aeruginosa, S. marcescens,* etc.), some gram-positive (*Staphylococcus aureus*), and some anaerobic (*Bacteroides fragilis)* bacteria.
   i. β-lactamase enzymes produced by gram-negative bacteria reside in the periplasmic space (very efficient).

d. β-lactamase inhibitors have been developed and combined with some penicillin agents to prevent the β-lactamase enzymes of *some* bacteria from hydrolyzing the penicillin.

2. Alteration in the structure of the PBPs, which leads to decreased binding affinity of penicillins to the PBPs (e.g., methicillin-resistant *Staphylococcus aureus*, penicillin-resistant *Streptococcus pneumoniae*).

3. Inability of the antibiotic to reach the PBP target due to poor penetration through the outer membrane of the bacteria (Gram-negative).

V. CLASSIFICATION AND SPECTRUM OF ACTIVITY

A. There are several groups of natural and semisynthetic penicillins currently available that have different spectrums of antibacterial activity. The different groups of semisynthetic penicillins were developed to provide extended antibacterial activity, including coverage against bacteria resistant to previous groups of penicillins.

B. **Natural Penicillins** - The first agents in the penicillin class to be used clinically. Examples of natural penicillins include **aqueous penicillin G, benzathine penicillin G, procaine penicillin G, penicillin VK**.

1. **Gram-Positive**: excellent activity against non-β-lactamase-producing gram-positive cocci and bacilli
   - Group Streptococci (groups A, B, C, F, G)
   - Viridans streptococci
   - Some *Enterococcus* spp.
   - Some *Streptococcus pneumoniae* (high level resistance ~ 15 to 20%)
   - **Very little activity against *Staphylococcus spp.*- due to penicillinase production**
   - *Bacillus* spp. (including *B. anthracis*)
   - *Corynebacterium* spp.

2. **Gram-Negative**: only against some gram-negative **cocci**
   - *Neisseria meningitidis*, non-β-lactamase-producing *Neisseria gonorrhoeae*, *Pasteurella multocida*

3. **Anaerobes**: good activity against gram-positive anaerobes
   - Mouth anaerobes (gram-positive cocci, "above the diaphragm") – such as *Peptococcus* spp, Peptostreptococcus spp., *Actinomyces* spp.
   - *Clostridium* spp. (gram-positive bacilli, "below the diaphragm"), with the exception of *C. difficile*

4. **Other**
   - *Treponema pallidum*

Penicillin G is still considered to be a DRUG OF CHOICE for the treatment of infections due to *Treponema pallidum (syphilis), Neisseria meningitidis, Corynebacterium diphtheriae, Bacillus anthracis (anthrax), Clostridium perfringens* and *tetani,* viridans and Group Streptococci.

C. **Penicillinase-Resistant Penicillins** - Developed to address the emergence of penicillinase-producing staphylococci that rendered the natural penicillins inactive. They contain an acyl side chain that sterically inhibits the action of penicillinase by preventing opening of the β-lactam ring. Examples include **nafcillin**, *methicillin* (no longer available in US), oxacillin, and **dicloxacillin**.

1. **Gram-Positive**

- **M**ethicillin **S**usceptible ***S**taphylococcus **a**ureus* **(MSSA) - NOT ACTIVE AGAINST MRSA**
- Viridans and Group streptococci (less activity than Pen G)
- No activity against *Enterococcus* spp. or *S. pneumoniae*

2. **Gram-Negative**: no activity

3. **Anaerobes**: limited

D. **Aminopenicillins** - Developed to address the need for penicillins with extended activity against gram-negative aerobic bacilli. Aminopenicillins were formulated by the addition of an amino group to the basic penicillin molecule. Examples include **ampicillin** and **amoxicillin**.

1. **Gram-Positive**: similar activity to the natural penicillins (also ineffective against *Staphylococcus aureus* because destroyed by penicillinase)
   - ***Better*** activity than natural penicillin against *Enterococcus* spp.
   - Excellent against *Listeria monocytogenes*, a gram-positive bacillus

2. **Gram-Negative**: better activity than natural penicillins
   - *H. influenzae* (only β-lactamase negative strains ~ 70%)
   - *E.coli* (45 to 50% of strains are resistant)
   - *Proteus mirabilis*
   - *Salmonella* spp., *Shigella* spp.

3. **Anaerobes**: activity similar to Pen G

Drug of Choice for infections due to *Listeria monocytogenes, Enterococcus*

E. **Carboxypenicillins** – Developed to address the emergence of more resistant gram-negative bacteria and the increasing frequency of *Pseudomonas aeruginosa* as a nosocomial pathogen. These agents were formulated by adding a carboxyl group to the basic penicillin molecule. **Ticarcillin** was the only available carboxypenicillin (discontinued 2004).

1. **Gram-Positive**: generally weak activity
   - Less active against *Streptococcus* spp.
   - Not active against. *Enterococcus* or *Staphylococcus* spp.

2. **Gram-Negative:** enhanced activity
   - Same gram-negative bacteria as aminopenicillins (including indole-positive *Proteus mirabilis*)
   - *Enterobacter* spp.
   - *Providencia* spp.
   - *Morganella* spp.
   - ***Pseudomonas aeruginosa***

**** NOT active against *Klebsiella* spp., *Serratia* spp., or *Actinobacter* spp.**

F. **Ureidopenicillins** – Developed to further enhance activity against gram-negative bacteria. These agents are derived from the ampicillin molecule with acyl side chain adaptations that allow for greater cell wall penetration and increased PBP affinity. The ureidopenicillins are the broadest-spectrum penicillins available without β-lactamase inhibitors. **Piperacillin** was the only available ureidopenicillin (discontinued 2011).

1. **Gram-Positive**
   - Good activity against viridans and Group Streptococci
   - Some activity against *Enterococcus* spp.
   - No activity against *Staphylococcus* spp.

2. **Gram-Negative**: improved activity
   - Displays activity against most Enterobacteriaceae
   - Active against *Klebsiella spp.* and *Serratia marcescens*
   - ***Pseudomonas aeruginosa* (piperacillin is the most active penicillin)**

3. **Anaerobes**:
   - Activity similar to Pen G against *Clostridium* and *Peptostreptococcus*

G. **β-lactamase Inhibitor Combinations**: Available as a combination product containing a penicillin and a β-lactamase inhibitor. The β-lactamase inhibitor irreversibly binds to the catalytic site of the β-lactamase enzyme, preventing the hydrolytic action on the penicillin. The β-lactamase inhibitors enhance the antibacterial activity of their companion penicillin in situations where the resistance is primarily the result of β-lactamase production.

Examples: **Amoxicillin / Clavulanate (Augmentin®) – PO**
Ampicillin / Sulbactam (Unasyn®) – IV
Ticarcillin / Clavulanate (Timentin®) – IV (discontinued 2014)
Piperacillin / Tazobactam (Zosyn®) – IV

1. These combination agents will retain the same activity of the parent penicillin against non β-lactamase producing organisms, and will have **enhanced activity against β-lactamase producing bacteria.**

2. **Gram-Positive**
   - Provide activity against β-lactamase producing strains of *Staphylococcus aureus* (they have activity against MSSA).

3. **Gram-Negative**
   - Enhanced activity against β-lactamase producing strains of *E. coli, Proteus spp., Klebsiella spp., H. influenzae, M. catarrhalis, and N. gonorrhoeae.*

- Not very active against the inducible β-lactamase enzymes produced by ***S****erratia marcescens,* ***P****. aeruginosa*, **i**ndole-positive *Proteus spp.,* ***C****itrobacter spp.*, and ***E****nterobacter spp.* (SPICE bacteria).
- **Ticarcillin/clavulanate is active against *Stenotrophomonas maltophilia***

4. **Anaerobes**
   - **Enhanced activity against β-lactamase producing strains of *B. fragilis* and *B. fragilis* group (DOT) organisms.**

VI. PHARMACOLOGY

A. Pharmacodynamic principles of dosing

1. Penicillins display **time-dependent** bactericidal activity.

2. The pharmacodynamic parameter that correlates with clinical efficacy of the penicillins is **Time above the MIC.**

3. PAE for gram-positive bacteria; no significant PAE for gram-negatives.

4. Penicillins are **bactericidal**, but only display ***bacteriostatic*** activity against *Enterococcus spp.* **Bactericidal activity (synergy) can be achieved against *Enterococcus spp*. by adding an aminoglycoside** (gentamicin or streptomycin)**,** which is used in the treatment of *Enterococcal* endocarditis.

B. General pharmacologic properties of the penicillins (see PK charts pages 9 and 10)

1. **Absorption**

   a. Many penicillins are degraded by gastric acid and are unsuitable for oral administration, so they must be administered parenterally.

   b. Orally-available penicillins are variably absorbed from the gastrointestinal tract (see PK charts). Concentrations achieved with oral dosing are lower than those achieved with parenteral dosing, so oral therapy should only be used for mild to moderate infections. Food typically delays the rate and/or extent of absorption.

   c. Special Absorption Considerations
      i. ***Natural penicillins*** – oral pen G is poorly absorbed so that phenoxymethyl penicillin is used orally (pen VK); IM benzathine and procaine penicillin G are formulated to delay absorption resulting in prolonged serum and tissue concentrations
      ii. ***Aminopenicillins*** – amoxicillin displays higher bioavailability than ampicillin; food delays ampicillin absorption
      iii. ***Penicillinase-Resistant Penicillins*** – oral dicloxacillin displays the best bioavailability

2. **Distribution**

   a. Penicillins are widely distributed into body tissues and fluids including pleural fluid, synovial fluid, bone, bile, placenta, and pericardial fluid, but do NOT penetrate the eye or prostate. The variation in distribution of various penicillins depends on their molecular configuration and protein binding.

   b. Adequate concentrations of penicillins in the cerebrospinal fluid (CSF) are attainable **only in the presence of inflamed meninges when high doses of parenteral penicillins are used.**

   c. Penicillin binding to serum proteins is variable, ranging from 15% for the aminopenicillins to **97%** for dicloxacillin.

3. Elimination

   a. **Most penicillins are eliminated primarily by the kidneys unchanged via glomerular filtration and tubular secretion**, and require dosage adjustment in the presence of renal insufficiency. **Exceptions include nafcillin and oxacillin, which are eliminated primarily by the liver, and piperacillin which undergoes dual elimination**.

   b. Probenecid blocks the tubular secretion of renally-eliminated penicillins and can increase their serum concentrations.

   c. Most penicillins are removed during hemodialysis or peritoneal dialysis, and require supplemental dosing after a hemodialysis procedure – the **exceptions are nafcillin and oxacillin**.

   d. **ALL penicillins have relatively short elimination half-lives** (< 2 hours) and require repeated daily dosing (4 to 6 times daily) or continuous infusion to maintain therapeutic serum concentrations.

4. Other Pharmacologic Considerations

   a. **Sodium Load** – several parenterally-administered penicillins (especially the carboxy- and ureidopenicillins) contain sodium in their parenteral preparations, which **must be considered in patients with cardiac or renal dysfunction**.

      - Aqueous Sodium Penicillin G contains 2.0 mEq per 1 million units
      - **Ticarcillin** contains **5.2** mEq per gram (also in Timentin®)
      - Piperacillin contains 1.85 mEq per gram (also in Zosyn®)

Table: Pharmacokinetic Characteristics of Natural Penicillins, Aminopenicillins, and Penicillinase-Resistant Penicillins

Drug	F (%)	Protein Binding	Half-life (hours)	Route of Excretion	Removal by HD	Dosing Change For RI	Route of Admin
Penicillin G	--	45-68	0.5	Renal	Yes	Yes	IM, IV
Penicillin V	**60-73**	75-89	0.5	Renal	Yes	Yes	Oral
Ampicillin	30-55	15-25	0.7-1.4	Renal	Yes	Yes	Oral, IV, IM
Amp/sulb	--	15-25	0.7-1.4	Renal	Yes	Yes	IV
Amoxicillin	**75-90**	17-20	0.7-1.4	Renal	Yes	Yes	Oral
Amox/clav	**75-90**	17-20	0.7-1.4	Renal	Yes	Yes	Oral
Dicloxacillin	**35-76**	95-97	0.3-0.9	**Renal, some hepatic**	**Minimal**	**No**	Oral
Nafcillin	--	70-90	0.5-1.5	**Hepatic**	**Minimal**	**No**	IV, IM
Oxacillin	30-35	89-94	0.3-0.9	**Hepatic**	**Minimal**	**No**	Oral, IV, IM

F = bioavailability
HD = hemodialysis
RI = renal insufficiency
IV = intravenous
IM = intramuscular

Table: Pharmacokinetic Characteristics of Carboxypenicillins and Ureidopenicillins

Drug	Sodium Content (mEq/g)	Protein Binding	Half-life (hours)	Route of Excretion	Removal by HD	Dosing Change For RI	Route of Admin
Ticarcillin	**5.2**	50-60	1.2	Renal	Yes	Yes	IV
Ticar/clav	**5.2**	50-60	1.2	Renal	Yes	Yes	IV
Piperacillin	1.85	15-20	1.0	**Renal and hepatic**	Yes	Yes	IV
Pip/tazo	1.85	15-20	1.0	**Renal and hepatic**	Yes	Yes	IV

HD = hemodialysis
RI = renal insufficiency
IV = intravenous
IM = intramuscular

VII. CLINICAL USES

A. Natural Penicillins

1. Intravenous aqueous penicillin G is often used for serious infections in hospitalized patients due to its rapid effect and high serum concentrations. Lower serum concentrations are achieved with oral penicillin VK so that its use is limited to the treatment of mild to moderate infections such as pharyngitis or prophylaxis in some circumstances.

2. Considered to be a **drug of choice** for infections due to:

    a. *S. pneumoniae* (IV or IM – for penicillin-susceptible or penicillin-intermediate strains)

    b. Other Streptococci, including *S. pyogenes* (benzathine pen or aqueous pen), viridans streptococci pharyngitis (PO or IM); bacteremia, endocarditis (with an aminoglycoside), meningitis (IV)

    c. *Neisseria meningitidis* - meningitis, meningococcemia (IV)

    d. *Treponema pallidum* – syphilis (benzathine pen or IV pen)

    e. *Clostridium perfringens* or *tetani*

    f. *Actinomycosis*

3. Other Uses:

    a. Endocarditis prophylaxis in patients with valvular heart disease undergoing dental procedures at high risk for inducing bacteremia

    b. Prevention of rheumatic fever

B. **Penicillinase-Resistant Penicillins (Antistaphylococcal Penicillins)**

1. Because of enhanced activity against *S. aureus,* these agents are useful for the treatment of infections due to methicillin-susceptible *Staphylococcus aureus* (MSSA) such as skin and soft tissue infections, septic arthritis, osteomyelitis, bacteremia, endocarditis, etc. Parenteral therapy should be used for moderate to severe infections.

2. Oral dicloxacillin is useful for the treatment of mild to moderate skin and soft tissue infections, and as follow-up therapy after parenteral therapy for the treatment of more serious infections such as osteomyelitis or septic arthritis.

C. **Aminopenicillins**

1. Because of activity against respiratory tract pathogens, oral ampicillin and amoxicillin are useful for the treatment of mild to moderate pharyngitis, sinusitis, bronchitis, and otitis media.

2. Oral ampicillin or amoxicillin are useful for uncomplicated urinary tract infections due to susceptible organisms.

3. Parenteral ampicillin is used for the treatment of **Enterococcal** infections (with an aminoglycoside for endocarditis) and *Listeria monocytogenes* meningitis.

4. Endocarditis prophylaxis in patients with valvular heart disease.

5. Treatment of *Salmonella* and *Shigella*.

D. **Carboxypenicillins and Ureidopenicillins**

1. Due to enhanced activity against gram-negative bacteria, these agents are (were) useful for the treatment of serious infections such as bacteremia, pneumonia, complicated urinary tract infection, peritonitis, intraabdominal infections, skin and soft tissue infections, bone and joint infections, and meningitis caused by gram-negative bacteria (**hospital-acquired infections**). **Piperacillin is the most active penicillin for infections due to *Pseudomonas aeruginosa*.**

E. **β-Lactamase Inhibitor Combination Products** – enhanced activity against β-lactamase-producing bacteria

1. **Amoxicillin-clavulanate (Augmentin® - PO)** is useful for the treatment of otitis media, sinusitis, bronchitis, lower respiratory tract infections, and human or animal bites

2. Due to expanded activity against gram-positive and gram-negative bacteria (including anaerobes), the parenteral combination agents are often utilized in the treatment of polymicrobial infections such as intraabdominal infections, gynecological infections, diabetic foot infections, etc.

a. **Ampicillin-sulbactam (Unasyn® – IV)** is useful for the treatment of mixed aerobic/anaerobic infections (limited gram-negative coverage).

b. **Ticarcillin-clavulanate (Timentin® --IV)** is (was) used as second line for treatment of infections caused by *Stenotrophomonas maltophilia*. It has similarly broad coverage to piperacillin-tazobactam but the latter is preferred due to tolerability (i.e., sodium load).

c. **Piperacillin-tazobactam (Zosyn® – IV)** is useful for the treatment of polymicrobial infections or other infections involving gram-negative bacteria including hospital-acquired pneumonia, bacteremia, complicated urinary tract infections, complicated skin and soft tissue infections, intraabdominal infections, and empiric therapy for febrile neutropenia.

VIII. ADVERSE EFFECTS

A. **Hypersensitivity –** most frequently occurring side effect (3 to 10%)

1. Less frequent with oral administration, somewhat higher when administered intravenously.

2. Reactions include pruritus, rash (maculopapular, erythematous, or morbilloform), urticaria, angioedema, hypotension, vasodilation, shock, and anaphylaxis.

    a. Anaphylaxis is rare, occurring in 0.004-0.015% of patients.

    b. Mediated by antibodies produced against penicillin degradation products that become haptens when bound to tissue proteins.

    c. Penicillin skin testing – occasionally used to predict hypersensitivity reactions when a history of a hypersensitivity reaction is unclear.

    d. Desensitization is possible (oral or parenteral) in some patients.

3. **Cross-allergenicity is observed among natural and semisynthetic penicillins due to their common nucleus – patients allergic to one penicillin product should be considered allergic to other members of the penicillin family, and caution should be used with some other β-lactams.**

4. Other allergic reactions include drug fever, serum sickness, Stevens-Johnson syndrome, erythema multiforme, toxic epidermal necrolysis, and exfoliative dermatitis

B. **Neurologic**

1. Direct toxic effect observed primarily in patients who receive large intravenous doses of some penicillins in the presence of concomitant renal dysfunction.

2. Irritability, jerking, confusion, generalized **seizures**

C. **Hematologic**

1. β-lactam-specific cytotoxic IgG or IgM antibodies are developed that bind to circulating WBC or platelets; cause cell lysis when antigen (penicillin) encountered by activation of the complement system

2. Leukopenia, neutropenia or thrombocytopenia - especially in patients receiving long-term (> 2 weeks) therapy

D. **Gastrointestinal**

1. Transient increases in liver enzymes – especially oxacillin and nafcillin

2. Nausea, vomiting

3. Diarrhea – especially with amoxicillin-clavulanic acid

4. Pseudomembranous colitis (*Clostridium difficile* diarrhea)

E. **Interstitial Nephritis**

1. Immune-mediated damage to renal tubules (cell-mediated immunity or antigen-antibody reactions) where the penicillin acts as a hapten when bound to renal tubular cells - most commonly associated with **methicillin,** but can occur with **nafcillin** and other penicillins.

2. Initial manifestations may be fever, eosinophilia, pyuria, **eosinophiluria, and an abrupt increase in serum creatinine.**

3. May progress to renal failure

F. Other adverse effects include **phlebitis** (nafcillin); pain and induration with IM injection (benzathine penicillin, penicillin G, ampicillin); **hypokalemia** (ticarcillin because it acts as nonreabsorbable anions resulting in increased excretion of potassium); **sodium overload and fluid retention (ticarcillin, piperacillin)**

IX. DOSING

Table 43–1. Guidelines for dosing of some commonly used penicillins.

Antibiotic (Route of Administration)	Adult Dose	Pediatric Dose[1]	Neonatal Dose[2]	Adjusted Dose as a Percentage of Normal Dose for Renal Failure Based on Creatinine Clearance (Cl_{cr})	
				Cl_{cr} Approx 50 mL/min	Cl_{cr} Approx 10 mL/min
Penicillins					
Penicillin G (IV)	1–4 mU q4–6h	25,000–400,000 units/kg/d in 4–6 doses	75,000–150,000 units/kg/d in 2 or 3 doses	50–75%	25%
Penicillin VK (PO)	0.25–0.5 g qid	25–50 mg/kg/d in 4 doses		None	None
Antistaphylococcal penicillins					
Cloxacillin, dicloxacillin (PO)	0.25–0.5 g qid	25–50 mg/kg/d in 4 doses		None	None
Nafcillin (IV)	1–2 g q4–6h	50–100 mg/kg/d in 4–6 doses	50–75 mg/kg/d in 2 or 3 doses	None	None
Oxacillin (IV)	1–2 g q4–6h	50–100 mg/kg/d in 4–6 doses	50–75 mg/kg/d in 2 or 3 doses	None	None
Extended-spectrum penicillins					
Amoxicillin (PO)	0.25–0.5 g tid	20–40 mg/kg/d in 3 doses		66%	33%
Amoxicillin/ potassium clavulanate (PO)	500/125–875/125 mg bid–tid	20–40 mg/kg/d in 3 doses		66%	33%
Piperacillin (IV)	3–4 g q4–6h	300 mg/kg/d in 4–6 doses	150 mg/kg/d in 2 doses	50–75%	25–33%
Ticarcillin (IV)	3 g q4–6h	200–300 mg/kg/d in 4–6 doses	150–200 mg/kg/d in 2 or 3 doses	50–75%	25–33%

[1]The total dose should not exceed the adult dose.

[2]The dose shown is during the first week of life. The daily dose should be increased by approximately 33–50% after the first week of life. The lower dosage range should be used for neonates weighing less than 2 kg. After the first month of life, pediatric doses may be used.

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Class	**Antimicrobial Activity**			
Drug (Route)	**Gram-positive**	**Gram-negative**	**Anaerobes**	**Other**
Natural Penicillins Aqueous Pen G (IV) Benzathine Penicillin (IM) Procaine Penicillin G (IM) Penicillin VK (PO)	**Group A, B, C, F, G Streptococci** **Viridans streptococci** PCN-susceptible *S. aureus* (very limited) & *S. pnuemoniae* Some *Enterococcus* spp. *Bacillus* spp. *Corynebacterium* spp.	***Neisseria meningitidis*** B-lactamase negative *N. gonorrhoeae* *Pasteurella multocida*	*Peptostreptococcus* spp. *Actinomyces* spp. ***Clostridium* spp.** (not *C. difficile*)	***Treponema pallidum*** (syphilis)
Penicillinase-Resistant Penicillins **Nafcillin** (IV) Oxacillin (IV) **Dicloxacillin** (PO)	**Methicillin-susceptible *Staphylococcus aureus* (MSSA)**	None	Limited	
Aminopenicillins **Ampicillin** (**IV**, PO) Amoxicillin (**PO**)	Similar to the natural penicillins but better against ***Enterococcus*** ***Listeria monocytogenes***	B-lactamase negative *H. influenzae*, *E. coli*, *Proteus mirabilis*, *Salmonella* spp., *Shigella* spp	Similar to the natural penicillins	
Carboxypenicillins Ticarcilin (IV)	Minimal activity	Aminopenicillins plus: *Enterobacter* spp. *Providencia* spp. *Morganella* spp. ***Pseudomonas*** spp. ***Stenotrophomonas maltophilia***	Similar to the natural penicillins without *Actinomyces* spp.	
Ureidopenicillins **Piperacillin** (IV)	Group A, B, C, F, G Streptococci Viridans streptococci *Enterococcus* spp.	Carboxypenicillins plus: *Klebsiella* spp. & *Serratia marscescens* NOT active against *S. maltophilia* Used most for **broad Gram-negative coverage including *P. aeruginosa***	Similar to the natural penicillins	
B-lactamase Inh. Combinations **Ampicillin/ sulbactam** (Unasyn®, IV) **Amoxicillin/ clavulanate** (Augmentin®, PO) Ticarcillin/ clavulanate (Timent IV) **Piperacillin/ tazobactam** (Zosyn®, IV)	Same activity as parent penicillin plus: methicillin-susceptible *Staphylococcus aureus*	Enhanced activity against **β-lactamase producing strain** of *E. coli*, *Proteus* spp., *Klebsiella* spp., *H. influenzae* *M. catarrhalis*, *N gonorrhoe* Timentin and Zosyn have the broadest Gram-negative activity	**Enhanced** from natural pencillins to include: *Bacteroides fragilis* *Fusobacterium* spp.	

Cephalosporins, Carbapenems, Monobactams

Gen	Drug	SE/AEs	Spectrum	Indications	Misc
1st	Cephalothin IV Cephalexin PO Cefazolin IV Cefadroxil PO	Allergy, hives, anaphylaxis, rash 5-10% cross reactive with PCN allergy Cdiff	Gram + Some Gram – PEK	Skin infections Some UTIs	
2nd	Cefamandole IV Cefaclor PO Cefuroxime IV/PO Cefoxitin IV Cefotetan IV		Gram + More Gram – HEN-PEK		Anaerobes: cefotetan, cefoxitin MTT side chang of cefamandole, cefotetan affect Vit K clotting factor synthesis Interferes with EtOH metab
3rd	Ceftriaxone IV Ceftazidime IV Cefotaxime IV Cefpodoxime PO Cefperazone IV		More gram – No anaerobes Some Gram +	Meningitis pneumonia	Ceftaz & cefaperazone vs Pseudomonas Ceftriaxone – good CNS activity
4th	Cefepime IV		As above+ Pseudomonas	HCAP	No anaerobes
5th	Ceftaroline IV		Gram +, MRSA	SSSTI	Poor GNR activity
carb	Ertapenem IV	5-15% HS x rxn w/ PCN	G+, G-, anaerobes	Polymicrobial infxn, B lac GNRs, nosocomial, NOT MRSA, C diff, CNSt, VRE, Steno, atypicals	No Pseudomonas activity; longer T1/2
	Meropenem IV				
	Imipenem IV				Risk of seizures. Requires cilastatin
	Doripenem IV				
mon	Aztreonam IV	Hypersensitiv	Gram - only		Vs. Pseudomonas,

o		ity no Xreactive with PCN; GI, drug Fever, phlebitis,			pcn allergic, CNS penetratn

Antibiotics Against Gram-Positive Organisms

Vancomycin
Dalbavancin
Telavancin
Oritavancin
Linezolid
Tedizolid
Daptomycin
Quinupristin-Dalfopristin

Gram positive organisms

- *Staphylococcus*
- *Streptococcus*
- *Enterococcus*
- *Listeria*
- *Clostridium*
- *Bacillus*
- *Actinomyces*
- *Nocardia*

I. Glycopeptides

a. Vancomycin

A tricyclic glycopeptide first isolated in 1953 from soil samples and available since 1956. Contains two chlorine atoms. Initially used to treat PCN resistant *Staphylococcus aureus.*
Early versions had significant kidney damage and hearing impairment, but adverse events decreased with improved purification. Prior names: Mississippi Mud
Clinical use decreased with introduction of antistaphylococcal penicillins. However, more recently, use has increased due to more MRSA and PRSP (penicillin resistant *Strep pneumoniae*)

A. Mechanism of Action
   i. Inhibits bacterial cell wall synthesis at a site different than β-lactams
   ii. Inhibits synthesis and assembly of the second stage of cell wall synthesis
   iii. Binds firmly to D-alanyl-D-alanine portion of cell wall precursors to prevent cross-linking and further elongation of peptidoglycan;

B. Mechanism of Resistance
   i. Resistance in VRE and VRSA due to modification of D-alanyl-D-alanine binding site of peptidoglycan
   ii. Terminal D-alanine replaced by D-lactate
   iii. Loss of critical hydrogen bond
   iv. Loss of antibacterial activity
   v. 3 phenotypes - vanA, vanB, vanC

a. vanA resistance to vancomycin and teicoplanin with inducible exposure
b. vanB inducible by vancomycin but may be susceptible to teicoplanin (lower level resistance)
c. vanC least important, constitutive resistance to vancomycin only.

vi. VISA – thickened cell wall

C. Spectrum of Activity
i. *Gram-positive bacteria* - Methicillin-Susceptible AND Methicillin-Resistant *S. aureus* and coagulase-negative staphylococci*
ii. *Streptococcus pneumoniae* (including PRSP*), viridans streptococcus, Group streptococcus, *Enterococcus* spp.
iii. *Corynebacterium, Bacillus. Listeria, Actinomyces Clostridium* spp. (including *C. difficile**), *Peptococcus, Peptostreptococcus*
iv. *No activity vs gram-negative organisms*

D. Clinical Uses
i. Infections due to methicillin-resistant staph including bacteremia, empyema, endocarditis, peritonitis, pneumonia, skin and soft tissue infections, osteomyelitis, meningitis
ii. Serious gram-positive infections in β-lactam allergic patients
iii. Infections caused by multidrug resistant bacteria (PRSP)
iv. Endocarditis or surgical prophylaxis in select cases
v. Oral vancomycin for moderate to severe *C. difficile* colitis

E. Vancomycin Adverse Effects
i. Red-Man Syndrome
- Flushing, pruritus, erythematous rash on face, neck, and upper torso within 5 to 15 minutes of starting infusion due to Histamine release from mast cell degranulation;
- Related to RATE of intravenous infusion;
- Resolves spontaneously after discontinuation
- May lengthen infusion (over 2 to 3 hours) or pre-treat with antihistamines in some cases

ii. Nephrotoxicity and Ototoxicity
a. Rare with vancomycin monotherapy, more common when administered with other nephro- or ototoxins , such as aminoglycosides
b. Risk factors include renal impairment, prolonged therapy, high doses, ? high serum concentrations, use of other nephro- or ototoxins

iii. Dermatologic - rash
iv. Hematologic - neutropenia and thrombo-cytopenia with prolonged therapy
v. Thrombophlebitis – related to rate of infusion. Recommend slow infusion at least over 60 minutes.
vi. interstitial nephritis

b. Dalbavancin

A semisythetic lipoglycopeptide. Derived from teicoplanin.

A. Mechanism of Action
   i. binds to C terminal D-ala-D ala interfering with cross-linkage and polymerization. It can attach to the cell membrane from its lipophilic moiety, make it more portent than vancomycin.

B. Mechanisms of Resistance
   i. new on market, possibly different than vancomycin

C. Spectrum of Activity
   i. similar to vancomycin, but more potent
   ii. also has activity against VISA and Linezolid resistant SA as well as 1 of 2 VRSA
   iii. activity against VRE with vanB and vanC genes, but not vanA
   iv. streptococcus, including PRSP
   v. gram positive anaerobes, Corynebacterium.
   vi. not active against gram negative rods

D. Clinical Uses
   i. skin and skin structure infections due to MRSA and other drug resistant Gram positive organisms, including some resistant to vancomycin

E. Adverse effects
   vii. Nausea, vomiting
   viii. Pruritus, anaphylaxis, skin reactions
   ix. Increased ALT
   x. Flushing with rapid infusion

c. Telavancin

A. Lipoglycopeptide
   i. cell wall inhibition
   ii. affects cell membrane permeability/depolarization
   iii. affects transglycosilation/transpeptidation

B. Activity vs. MRSA and other GPOs

C. Clinical uses
   i. complicated Skin and skin structure infections
   ii. Staphylococcal Healthcare associated pneumonia and ventilator associated pneumonia

D. Adverse effects
   i. nausea, vomiting, constipation
   ii. headache
   iii. teratogenic in animals
   iv. higher rate of renal toxicity than vancomycin

d. Oritvancin

A. semisynthetic glycopeptide
   i. disrupts cell membrane – depolarization & permeability
   ii. Affects transglycosilation/transpeptidation

B. Sepctrum of Activity MSSA, MRSA< Enterococcus, Streptococcus, possible Bacillus antrhacis

II. Oxazolidinones

Linezolid (Zyvox®) is the first FDA approved agent (2000) PO and IV. Synthetic antibiotic developed in response to need for antibiotics with activity against resistant gram-positives (VRE, MRSA, VISA).

i. Mechanism of Action
- Binds to the 50S ribosomal subunit near the surface interface of 30S subunit – causes inhibition of 70S initiation complex (unique binding site), which inhibits protein synthesis
- Bacteriostatic (bactericidal against *Strep pneumoniae*)

ii. Mechanism of Resistance
- Alterations in ribosomal binding sites - rare
- Cross-resistance with other protein synthesis inhibitors is unlikely

iii. Spectrum of Activity
   a. *Gram-Positive Bacteria*
      i. Methicillin-Susceptible, Methicillin-Resistant AND Vancomycin-Resistant *Staph aureus** and coagulase-negative staphylococci
      ii. *Streptococcus pneumoniae* (including PRSP*), viridans streptococcus, Group streptococcus
      iii. *Enterococcus faecium AND faecalis* (including VRE)*
      iv. *Bacillus. Listeria, Clostridium* spp. (except *C. difficile*), *Peptostreptococcus, P. acnes*
   b. *Gram-Negative – inactive*

iv. *Atypical Bacteria* (some activity)
   a. *Mycobacteria*

v. Clinical Uses

reserved for serious/complicated infections caused by resistant gram-positive bacteria:
   a. VRE bacteremia, NOT urinary tract infections
   b. Complicated skin and soft tissue infections due to MSSA, MRSA or *Streptococcus pyogenes*
   c. Nosocomial pneumonia due to MRSA

vi. Adverse Effects
a. GI – nausea, vomiting, diarrhea (6 to 8 %)
b. Headache – 6.5%
c. Peripheral neuropathy - irreversible
d. (Bone marrow suppression)Thrombocytopenia or anemia: > 2-4%
i. Most often with treatment > 10- 14 days
ii. After therapy discontinued – counts will return to normal
e. Optic neuropathy possibly due to mitochondrial toxicity
f. lactic acidosis possibly due to mitochondrial toxicity

vii. Tedizolid
a. For acute bacterial skin and skin structure infections
b. Staphylococcus, Streptococcus, Enterococcus
c. More potent than linezolid
d. Oral or IV, once daily for six days
e. AE: neuropathy (peripheral and optic, hematologic, dizziness
f. No serotonin/MAOI interactions

III. Daptomycin

(Cubicin®) is a cyclic lipopeptide antibiotic with bactericidal activity against resistant gram-positives (VRE, MRSA, VISA). Naturally occurring in *Streptomyces roseosporus*. First discovered in late 1980s

i. Mechanism of Action
a. Binds to bacterial membranes → rapid depolarization of membrane potential → inhibition of protein, DNA, and RNA synthesis
b. Concentration-dependent bactericidal activity

ii. Mechanism of Resistance
a. Rarely reported in VRE and MRSA due to altered cell membrane binding
b. Full mechanism unknown.

iii. Spectrum of Activity
a. Gram-Positive Bacteria
- Methicillin-Susceptible, Methicillin-Resistant AND Vancomycin-Resistant *Staph aureus** and coagulase-negative staphylococci
- *Streptococcus 5neumonia* (including PRSP*), viridans streptococcus, Group streptococcus
- *Enterococcus faecium AND faecalis* (including VRE)*

b. Gram-Negatives – inactive

iv. Clinical uses
• reserved for serious/complicated infections caused by resistant bacteria:
- Complicated skin and soft tissue infections due to MSSA, MRSA, or *Streptococcus pyogenes*
- Bacteremia, including endocarditis, due to *Staphylococcus aureus*
- Daptomycin should NOT be used to treat pneumonia as it is inactivated by surfactant

v. Adverse Effects
    a. Gastrointestinal – nausea, diarrhea
    b. Headache
    c. Injection site reactions
    d. Rash
    e. Myopathy and CPK elevation –(2.8-10%). Must follow CK levels while on this drug.
    f. Eosinophilic pneumonia, usually in patients older than 60
vi. Drug Interactions
    a. HMG CoA-reductase inhibitors – may lead to increased incidence of myopathy

IV. Quinupristin-Dalfopristin (Synercid®)

a. two drugs synergistically acting
b. activity against Staphylococcus and VRE faecium
c. protein synthesis inhibition (static) of both drugs makes the combination cidal
d. dalfopristin enhances binding of quinupristin
e. cleared in the liver

Drug	Activity	Mechanism	AEs
Vancomycin	GPOs MRSA, CNSt, pcn Resistant gpcs	Cell wall synthesis inhibitor	Oto-/nephrotoxic Red man syndrome
Dalbavancin	GPOs MRSA, VISA, some VRE	Cell wall synthesis inhibitor	GI s/s Skin reactions and flushing
Telavancin	GPOs MRSA	Cell wall synthesis inhibitor	Teratogenic in animals nephrotoxic
Linezolid	GPOs esp MRSA, VRE, CNSt Pcn R gpcs; bacillus, listeria, clostridia	Binds to 50s rSU inhibiting protein synthesis	BM suppression h/a, Gi Serotonin syndrome neuropathy
Tedizolid	Staph, Strep, Enterococcus	Protein synthesis	Neuropathy, hematologic, nausea, vomiting, dizzy
Daptomycin	VRE, MRSA, VISA	Binds to membranes → inhibition of protein, RNA, DNA synthesis	GI, H/a Injection site rxn Rash myopathy
Qunupristin-Dalfopristin	Gram positive organisms	Protein synthesis inhibitors-synergistic effect	GI, headache, rash, jaundice, Flu like symptoms, myalgia, arthralgia

Aminoglycosides

Key Concepts and Learning Objectives
At the end of the lecture the learner will be able to:

1. Explain the mechanisms of action and resistance of the aminoglycosides.

2. Differentiate the spectrums of activity of gentamicin, tobramycin, amikacin, and streptomycin.

3. Describe the concept of synergy between cell wall active agents and aminoglycosides.

4. Explain the pharmacokinetics and pharmacodynamics of the aminoglycosides and apply this information to dosing strategies.

5. Compare traditional vs extended-interval aminoglycoside dosing strategies.

6. Describe and differentiate the clinical uses of the individual aminoglycosides.

7. Describe the most common and significant toxicities associated with the aminoglycosides.

The Aminoglycosides

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Despite the introduction of newer, less toxic antimicrobial agents, the aminoglycosides continue to serve a useful role in the treatment of serious enterococcal, mycobacterial, and gram-negative bacillary infections. Gentamicin, because of its low cost, remains the aminoglycoside of choice in hospitals with low levels of resistance among Enterobacteriaceae and *Pseudomonas aeruginosa*. Typically, it is administered in combination with β-lactam antibiotics, but it may also be used as monotherapy for urinary tract infections or tularemia. Amikacin is useful against gentamicin-resistant gram-negative bacilli and also in the treatment of infections caused by susceptible *Nocardia* and nontuberculous mycobacteria. Streptomycin serves an important role in the treatment of multidrug-resistant tuberculosis and may be useful in the treatment of some gentamicin-resistant enterococcal infections. Despite an alarming increase in aminoglycoside-resistant enterococci, most institutions have noted little change in patterns of resistance among gram-negative bacilli. Although the development of newer, less toxic aminoglycosides is unlikely in the near future, single daily dosing regimens have been proposed as a convenient, cost-effective strategy. In selected patients, this novel approach seems to be as safe and effective as traditional, multidose regimens.

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DW = dosing weight; IBW = ideal body weight; MIC = minimal inhibitory concentration; SDD = single daily dosing

Several aminoglycoside-aminocyclitol antibiotics have been introduced into clinical practice since Waksman's historic discovery of streptomycin in 1943. The formidable toxicity of neomycin precluded systemic administration, and kanamycin (isolated in 1957) became the aminoglycoside of choice until the discovery of the gentamicins in 1963, a breakthrough in therapy for gram-negative bacillary infections, including those caused by *Pseudomonas aeruginosa*. Subsequently, tobramycin (1968), amikacin (1972), and netilmicin (1975) were developed and marketed for clinical use; dibekacin, sisomicin, and isepamicin, although marketed worldwide, have not been and are unlikely to be released in the United States. Failure to identify less toxic yet efficacious agents during the past 10 years will undoubtedly curtail the development of new aminoglycosides, although further efforts will likely be directed toward a better understanding of antimicrobial resistance and toxicity.

STRUCTURE, MODE OF ACTION, AND MAIN PHARMACOLOGIC PROPERTIES

The aminoglycoside-aminocyclitol antibiotics are structurally defined by the presence of amino sugars bound by glycosidic linkage to a central hexose nucleus. The aminoglycosides bind irreversibly to the 30 S bacterial ribosome, interfere with reading of the genetic code, and inhibit synthesis of proteins. An essential prelude to ribosomal binding is an energy- and oxygen-dependent transport mechanism that is inhibited by anaerobiosis and low pH. The uptake of aminoglycosides for various organisms, especially gram-positive cocci, is facilitated by the presence of inhibitors of synthesis of the bacterial cell wall—that is, β-lactam antibiotics and vancomycin.[1,2] Despite continuing investigation,[3,4] the precise mechanism through which the aminoglycosides cause bacterial cell death remains elusive. Inhibition of synthesis of proteins in itself is clearly an insufficient explanation because other antibacterial agents (such as tetracycline and chloramphenicol) that inhibit synthesis of proteins are not bactericidal. Unlike the β-lactam antibiotics, aminoglycosides demonstrate concentration-dependent killing (that is, enhanced bactericidal effect with increasing drug concentration) as well as a prolonged postantibiotic effect, whereby bacterial killing continues even after serum concentrations decline below the minimal inhibitory concentration (MIC) of the bacterium.

All aminoglycosides share certain pharmacokinetic properties. Because of poor oral absorption, parenteral administration is necessary to achieve adequate serum concentrations. Poor gastrointestinal absorption has facilitated their use (especially neomycin) for preoperative sterilization of the aerobic gut flora, although even negligible gastrointestinal absorption may cause toxicity in patients with renal failure.[5] After parenteral administration, aminoglycosides have a volume of distribution that approximates the

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extracellular space.[6,7] Alterations in the extracellular fluid compartment (such as in the presence of ascites, congestive heart failure, or dehydration) result in a change in the volume of distribution that potentially necessitates dosage modification. Recently, Dager[8] reviewed the volume of distribution in specific subgroups of patients. Aminoglycosides have negligible protein binding.[9]

In adults with normal renal function, each aminoglycoside has a serum half-life of approximately 2 hours, but considerable variability exists among patients.[10] Dickson and colleagues[11] demonstrated that loading of dietary proteins increased the clearance of aminoglycosides, a response that suggests that variations in intake of proteins might partially explain observed differences in kinetics. The serum half-lives of these drugs increase with deteriorating renal function and may exceed 24 hours in patients with end-stage renal failure.[12] Aminoglycosides are removed efficiently by hemodialysis[13] and less efficiently by peritoneal dialysis.[14] Newer, high-efficiency hemodialyzers may more effectively clear aminoglycosides in comparison with earlier equipment.[15] Accordingly, more frequent dosing adjustments and monitoring may be necessary. Because of their highly polar structure, these drugs cross biologic membranes poorly; thus, their intracellular tissue concentrations are low except for the proximal renal tubule, where aminoglycosides are concentrated in excess of concomitant plasma levels.[16] Parenterally administered aminoglycosides cross the blood-brain barrier poorly, even in the presence of meningeal inflammation.[17,18] Therefore, the concentrations achieved are inadequate for the treatment of gram-negative bacillary meningitis in adults.

Drug levels in bronchial secretions, despite variations in technique, have been consistently poor. Although endotracheal administration results in higher bronchial levels, earlier studies[19] did not show appreciable differences in the clinical outcome of patients with gram-negative bacterial pneumonia. Several recent studies, however, have demonstrated improved pulmonary function and decreased hospitalization rates in patients with cystic fibrosis treated with inhaled tobramycin.[20-23] Systemic therapy results in unreliable or inadequate therapeutic levels in vitreous fluid,[24] prostate,[25] and bile;[26] low concentrations of aminoglycosides in purulent fluids (characterized by low pH and oxygen tension) are probably due to local inactivation by DNA released by leukocytes.[27] Aminoglycosides usually achieve reasonable concentrations in bone, synovial fluid, and peritoneal fluid. In patients with normal renal function, however, urinary concentrations may exceed serum levels by 100 times.

Aminoglycosides are rapidly excreted, predominantly by glomerular filtration. Reabsorption of a small but notable amount of drug by the proximal tubule results in accumulation within the renal cortex; this preferential binding is responsible for nephrotoxicity. Findings in animal models have suggested that, in comparison with the other aminoglycosides, amikacin and tobramycin have diminished affinity for the proximal tubule.[28] With sensitive assay techniques, urinary concentrations of gentamicin can be detected for days to weeks after completion of therapy.[29]

SPECTRUM OF ACTIVITY

Aminoglycosides are active in vitro against a wide range of aerobic gram-negative bacilli, many staphylococci, and certain mycobacteria. Susceptibility data for gentamicin and amikacin against selected gram-negative bacilli at Mayo Clinic Rochester in 1998 are shown in Table 1. In addition, 26% of enterococci demonstrated high-level resistance to gentamicin (MIC greater than 500 μg/mL), and 26% showed high-level resistance to streptomycin (MIC greater than 2,000 μg/mL). In general, resistance to aminoglycosides among Enterobacteriaceae and *P. aeruginosa* has not increased appreciably during the past 10 years. Against susceptible Enterobacteriaceae and Pseudomonadaceae, gentamicin, tobramycin, netilmicin, and amikacin have similar activity, except tobramycin is generally more active in vitro against most strains of *P. aeruginosa* and gentamicin is more active against *Serratia* species. Netilmicin is generally less active against *P. aeruginosa*. *Burkholderia* (formerly, *Pseudomonas*) *cepacia* and *Stenotrophomonas* (formerly, *Xanthomonas*) *maltophilia* are typically resistant to all aminoglycosides.

INDICATIONS

The introduction of extended-spectrum β-lactam antibiotics (cephalosporins, monobactams such as aztreonam, and carbapenems such as imipenem and meropenem) and fluoroquinolones, all of which have a greater safety profile than the aminoglycosides, has necessitated a critical reappraisal of the specific indications for aminoglycoside therapy. For example, whereas aminoglycosides were formerly used in combination regimens for the treatment of serious intra-abdominal infections, Ho and Barza[30] and Gorbach[31] were unable to demonstrate a clear advantage for aminoglycoside-containing regimens, except perhaps for a subgroup of patients whose initial cultures showed *P. aeruginosa* or *Enterobacter*. Moreover, Leibovici and coworkers,[32] in a recent prospective study of monotherapy versus β-lactam-aminoglycoside combination treatment of gram-negative bacteremia, found no advantage of combination therapy except in patients with neutropenia. They also noted a trend toward reduction in mortality with combination treatment in nonneutropenic patients with *P. aeruginosa* bacteremia.

Considerable controversy has existed regarding the initial empiric treatment of febrile patients with neutropenia. Recently, the Infectious Diseases Society of America published a comprehensive set of practice guidelines that address this question in detail.[33] On the basis of a review of published studies, monotherapy with ceftazidime or the imipenem-cilastatin compound seems to be as effective as the combination of antipseudomonal penicillins with aminoglycosides. Of importance, the initial antimicrobial program should be modified on the basis of clinical response and microbiologic data. In a large study of gram-negative bacteremia in patients with severe neutropenia (that is, less than 100 neutrophilic leukocytes/mm^3), the European Organization for Research and Treatment of Cancer[34] found a more favorable response in patients who received ceftazidime plus amikacin for 9 days than in those who received amikacin for only 3 days.

Gentamicin

In general, gentamicin continues to be the aminoglycoside of choice for serious hospital-acquired infections caused by Enterobacteriaceae and *P. aeruginosa* in institutions that have minimal background resistance (Table 1). Typically, it is used in combination with β-lactam antibiotics, but it may be used independently for the treatment of urinary tract infections or tularemia.[35] The following additional indications for the use of gentamicin are proposed: (1) in combination with ampicillin, penicillin, or vancomycin for the treatment of endocarditis due to gentamicin-susceptible enterococci or viridans streptococci; (2) in conjunction with ampicillin (or vancomycin in penicillin-allergic patients) for endocarditis prophylaxis in high-risk patients before genitourinary or gastrointestinal procedures; (3) combined with antistaphylococcal penicillins for right-sided endocarditis caused by *Staphylococcus aureus* in injection drug users;[36] (4) in association with penicillin for the treatment of endocarditis caused by susceptible *Corynebacterium* species; (5) combined with vancomycin and rifampin in the treatment of prosthetic valve endocarditis due to coagulase-negative staphylococci; (6) in combination with antipseudomonal penicillins for treatment of serious infections caused by *P. aeruginosa* other than those confined to the urinary tract (for example, bacteremia, endocarditis, and initial treatment of malignant external otitis); (7) in association with doxycycline for the treatment of brucellosis;[37] and (8) in combination with ceftriaxone for treatment of penicillin-susceptible streptococcal endocarditis.[38]

Tobramycin

As will be discussed in the section on adverse reactions, in comparison with gentamicin, tobramycin may be somewhat less nephrotoxic (although not of sufficient magnitude to be clinically significant) and has greater activity against some strains of *Acinetobacter* species and *P. aeruginosa* but has less activity against *S. marcescens*. These minor in vitro differences, however, have not necessarily correlated with clinical success. Several clinical trials[20-23] have shown the benefit of maintenance treatment with aerosolized tobramycin in patients with cystic fibrosis and chronic pulmonary *P. aeruginosa* infection or colonization; improvement in results of pulmonary function studies and reduction in frequency of hospitalization have been substantiated. Unfortunately, the pharmacokinetics of aerosolized delivery have been inadequately studied, and the associated dosing and mechanics of administration are not well standardized.

In general, most gentamicin-resistant strains are also resistant to tobramycin—that is, both are affected by the same aminoglycoside-modifying enzymes. In susceptibility studies at our institution in which 1,065 strains of *P. aeruginosa* were tested with use of a concentration of 4 μg/mL, 93% of strains were inhibited by gentamicin and 96% of strains were inhibited by tobramycin. In addition, the combination of tobramycin with cell wall-active antibiotics is not synergistic against *Enterococcus faecium* even in the absence of high-level tobramycin resistance and should not

Table 1.—**Percentage of Gram-Negative Bacilli Susceptible to Gentamicin and Amikacin at Specified Concentrations—Mayo Clinic Rochester, 1998**

Organism	Gentamicin (≤4 μg/mL)	Amikacin (≤16 μg/mL)
Acinetobacter species	95	95
Alcaligenes species	67	75
*Burkholderia cepacia**	100†	50
Citrobacter diversus	100	100
C. freundii	94	100
Enterobacter aerogenes	100	100
E. agglomerans	100	100
E. cloacae	99	99
Escherichia coli	98	100
Klebsiella oxytoca	100	100
K. pneumoniae	100	100
Morganella morganii	97	100
Proteus mirabilis	95	100
P. vulgaris	100	100
Providencia rettgeri	100	100
P. stuartii	100	100
Pseudomonas aeruginosa	88	94
Serratia marcescens	100	100
Stenotrophomonas maltophilia‡	9	9
Yersinia enterocolitica	100	100

*Formerly, *Pseudomonas cepacia.*
†Based on only 6 strains tested.
‡Formerly, *Xanthomonas maltophilia.*

be used in the treatment of infective endocarditis caused by this organism. Furthermore, tobramycin is considerably more expensive than gentamicin.

Amikacin

When organisms are susceptible to gentamicin, amikacin offers no therapeutic advantage and is considerably more expensive. Amikacin, however, offers definite advantages for treating infections caused by organisms resistant to other aminoglycosides; it is affected by relatively few aminoglycoside-modifying enzymes. Interestingly, no appreciable increase in resistance to amikacin has been noted during the past 10 years,[39-42] even with extensive and exclusive use. It remains the aminoglycoside of choice for the treatment of gentamicin-resistant gram-negative bacilli. Finally, amikacin is useful in the treatment of infections caused by *Nocardia asteroides*,[43-45] *Mycobacterium avium-intracellulare*,[46] and certain species of "rapid-growing" mycobacteria (that is, *M. chelonae* and *M. fortuitum*).[47] Of note, neither tobramycin nor amikacin demonstrates synergy against *E. faecium* when combined with β-lactam antibiotics.

Netilmicin

Netilmicin has a spectrum of activity similar to that of gentamicin and tobramycin but may be active against some gentamicin-resistant Enterobacteriaceae; it is less active against *P. aeruginosa*. Recently, Francioli and associates[38] demonstrated the efficacy of netilmicin in combination with ceftriaxone for 2 weeks in the treatment of endocarditis due to penicillin-susceptible streptococci. Although netilmicin was the aminoglycoside used in that study, gentamicin would be equally effective.[48] Even though some studies have shown netilmicin to be less ototoxic than other aminoglycoside agents,[49] the definition and detection of ototoxicity are both vague and poorly standardized.

Streptomycin

As a single agent, streptomycin has previously been used for the treatment of tularemia and plague; as discussed in the foregoing material, gentamicin may be substituted for streptomycin in the treatment of these infections. Otherwise, streptomycin is used exclusively in combination with other antimicrobial agents as follows: (1) with tetracycline for the treatment of brucellosis; (2) in association with other antituberculous drugs for the treatment of tuberculosis, especially for infections caused by multidrug-resistant organisms; and (3) in combination with penicillin, ampicillin, or vancomycin for the treatment of endocarditis due to those strains of enterococci exhibiting high-level resistance to gentamicin but preserved susceptibility to streptomycin. Clinical microbiology laboratories should always determine susceptibility to both aminoglycosides in the setting of enterococcal endocarditis.

DOSAGE AND MEASUREMENT OF SERUM CONCENTRATIONS

Multiple Daily Dosing

The recommended traditional, multiple daily dosing regimens and serum concentrations for the commonly used aminoglycosides are outlined in Table 2. Administration of a "loading dose" (that is, 1.5 to 2 mg/kg for gentamicin, tobramycin, and netilmicin and 7.5 to 15 mg/kg for amikacin) is advisable in critically ill patients. The loading dose is calculated on the basis of ideal body weight (IBW), which can be derived by using the following formulas:

IBW for male patients =
50 kg + 2.3 kg (height in inches – 60 inches)

IBW for female patients =
45 kg + 2.3 kg (height in inches – 60 inches)

For obese patients (more than 30% above IBW), calculate a dosing weight (DW), based on a reduced volume of distribution in adipose tissue:[50]

$$DW = IBW + 0.4 \text{ (actual weight in kg} - IBW)$$

Various published nomograms[51,52] can be used to calculate the daily maintenance dose, based on age and creatinine. The following Cockcroft-Gault equation will yield a rough estimate of creatinine clearance for male patients (multiply results by 0.85 for female patients), although O'Connell and associates[53] found that this equation was inaccurate in 33% of patients studied:

$$\text{Creatinine clearance (mL/min)} = (140 - \text{age}) \times \text{IBW (kg)} \div \text{serum creatinine} \times 72$$

As an example, if this formula yields a calculated clearance of 50 mL/min, this result represents 50% of normal renal function; hence, the maintenance dose can be decreased by 50%, either by reducing each dose or by lengthening the dosage interval.

Because of interpatient variability in volume of distribution, renal function, and disease state, monitoring of aminoglycoside serum concentrations has been the standard of care in patients receiving the traditional, multiple daily dosing regimens to ensure adequacy of peak concentrations of the drug (previously thought to correlate with therapeutic success)[54-57] and to avoid toxicity. Considerable controversy exists regarding the normal therapeutic

Table 2.—**Recommended Dosages and Serum Concentrations of the Aminoglycosides: Traditional Multiple Daily Dosing**

Drug	Route	Daily dosage*		Serum concentration† (μg/mL)	
		Total (mg/kg)	Divided into doses given	Peak‡	Trough
Gentamicin	Intravenous or intramuscular	3-5§	Every 8 h	4-6	1-2
Tobramycin	Intravenous or intramuscular	3-5	Every 8 h	4-6	1-2
Netilmicin	Intravenous or intramuscular	3-5	Every 8 h	4-6	1-2
Amikacin	Intravenous or intramuscular	15	Every 8 h	20-30	5-10
Streptomycin	Intramuscular//	15 (not to exceed 2 g/day)¶	Every 12 h	20-30	<5

*Recommendations based on normal renal function. Adjustments of dosage based on age and impaired renal function are described in the text.

†"Peaks" shown are *expected* levels. Higher peak serum concentrations are desirable in the treatment of life-threatening disease (for example, endocarditis) or less susceptible organisms. When aminoglycosides are used for synergistic therapy, lower serum levels are needed.

‡Serum specimen obtained 30 minutes after completion of 30-minute intravenous infusion or 1 hour after intramuscular administration.

§For serious infections, 5 mg/kg should be administered. In special situations (for example, endocarditis caused by *Pseudomonas aeruginosa* in a young patient who has illicitly used drugs intravenously), 8 mg/kg per day of gentamicin or tobramycin has been recommended; considerable toxicity affecting cranial nerve VIII has been reported with use of this high dosage.

//Although approved only for intramuscular use, streptomycin has safely been administered intravenously in situations in which intramuscular therapy is impractical (for example, prolonged therapy, thrombocytopenia, or small muscle mass).

¶Except in patients with plague. For tuberculosis, streptomycin may be administered once daily (1 g/day in patients with normal renal function).

range of serum concentrations, and McCormack and Jewesson,[58] after a critical review of the literature, concluded that insufficient evidence was available to support the traditionally accepted "normal therapeutic range." The development of rapid automated assays for the determination of drug concentrations has vastly facilitated the ability to individualize and monitor therapy. The timing of administration of the drug and collection of serum specimens is critical. Peak concentrations should be determined from specimens obtained 30 minutes after completion of a 30-minute intravenous infusion or 1 hour after intramuscular injection; trough concentrations should be measured immediately before the next dose is administered. Serum concentrations of aminoglycosides should be determined frequently (and appropriate dosage modifications should be implemented) for patients undergoing prolonged therapy, those with fluctuating renal function or on dialysis, and those with life-threatening infections. Some patients may not require rigorous measurement of aminoglycoside levels. Massey and colleagues[59] demonstrated that monitoring was unnecessary in young patients unless therapy was prolonged, renal function was impaired, or higher than normal doses of the drug were administered. Nevertheless, even when serum concentrations of the aminoglycosides are carefully controlled, toxicity may still develop in some patients.

Single Daily Dosing

The basis of single daily dosing (SDD) for aminoglycosides was initially derived from studies in experimental animals. Bennett and colleagues[60] demonstrated reduced nephrotoxicity (with decreased renal cortical accumulation) and ototoxicity without sacrificing antibacterial efficacy in animals receiving large SDD versus traditional multiple dosing regimens. The pharmacodynamic rationale for SDD is based on the following concepts: (1) aminoglycosides display concentration-dependent bactericidal action—that is, higher doses and serum concentrations result in more rapid bacterial killing; (2) aminoglycosides exhibit a long postantibiotic effect, resulting in persistent bacterial suppression even when serum concentrations decline below the MIC and thereby allowing less

frequent drug administration; and (3) large, single daily doses result in prolonged periods with negligible serum concentrations, potentially reducing renal cortical and auditory accumulation of the drug. In addition, SDD has the potential of reducing costs associated with drug administration and monitoring; patient convenience and outpatient administration are also facilitated by SDD. Two recent, excellent articles provide a comprehensive review of the subject,[61,62] and three meta-analyses of clinical trials comparing traditional dosing with SDD[63-65] suggest that SDD is at least as effective as traditional dosing and may be somewhat less toxic.

SDD administration of aminoglycosides is reasonable in most patients, with the following exceptions: (1) those with enterococcal endocarditis, for which multiple dosing regimens have been found superior in experimental animals;[66] (2) pregnant patients; (3) children; (4) patients with severe renal insufficiency; and (5) patients with neutropenia, unless the aminoglycoside is used in combination with a β-lactam antibiotic agent. Conventional multiple daily dosing regimens should also be considered for the treatment of serious *P. aeruginosa* infections (other than those confined to the urinary tract) because published studies have included relatively few of these cases.

Although cumulative published data for more than a decade support the efficacy of SDD, specific dosage recommendations have not been standardized (dosages of gentamicin, tobramycin, and netilmicin have ranged from 4 to 7 mg/kg daily), methods for dose modification in patients with renal insufficiency have varied, and strategies for the frequency and interpretation of serum concentrations have also differed. Several nomograms for SDD have been published.[63,67] The SDD guidelines for aminoglycosides at our institution are outlined in Table 3.[68]

Table 3.—**Recommendations for Single Daily Dosing of Aminoglycosides**

Estimated creatinine clearance (mL/min)*	Dose (mg/kg)†‡		Dose interval (h)
	Gentamicin or tobramycin	Amikacin	
>80	5.0	15.0	24
60-79	4.0	12.0	24
50	3.5	7.5	24
40	2.5	4.0	24
<30	Use conventional dosing		

*See text ("Multiple Daily Dosing") for formula for estimation of creatinine clearance.
†See text ("Multiple Daily Dosing") for formulas for determination of ideal body weight (IBW) and dosing weight (DW).
‡Suggested monitoring: assess 18-hour serum concentration after second dose. Suggested "trough" levels: 0.6 to 2.0 μg/mL for gentamicin or tobramycin; 2.5 to 5.0 μg/mL for amikacin.
Data from Gilbert.[68]

RESISTANCE: GENERAL CONCEPTS AND TRENDS

A lengthy discussion of resistance to aminoglycosides is beyond the scope of this article, and this topic has previously been reviewed in detail.[69,70] Microbial resistance is mediated through the following three mechanisms: a ribosomal mutation that results in reduced affinity for the 30 S subunit (primarily demonstrated for streptomycin), reduced transport into the cell (particularly for staphylococci and *Pseudomonas* species), and plasmid-mediated aminoglycoside-modifying enzymes, the most frequent and important of the three mechanisms of resistance. These enzymes include three acetyltransferases, four adenyltransferases, and five phosphotransferases. Aminoglycoside-modifying enzymes are substrate specific; gentamicin and tobramycin are susceptible to at least five enzymes, and the result is considerable cross-resistance between these two agents. Netilmicin is susceptible to only four modifying enzymes. In contrast, amikacin is modified by only one of these enzymes; thus, it has activity against a substantial percentage of gentamicin-resistant Enterobacteriaceae and many resistant strains of *P. aeruginosa*.

The prevalence of aminoglycoside-modifying enzymes exhibits considerable geographic, and also interhospital, variability. Among gram-negative bacilli, investigators have noted essentially no increase in resistance to amikacin[39-42] and a trend toward a decrease in resistance to gentamicin and tobramycin.[71-73] These national trends are reflected at our own institution, where aminoglycoside resistance among gram-negative bacilli has remained stable for at least 10 years (Table 1). In contrast, aminoglycoside resistance among enterococci has increased appreciably. By 1977, 48% of enterococcal isolates at Massachusetts General Hospital displayed high-level resistance to streptomycin (MIC of more than 2,000 μg/mL),[74] although none of these strains showed resistance to gentamicin (MIC of more than 500 μg/mL). Resistance of enterococci to gentamicin was first reported in the United States 10 years ago, and a survey of eight US tertiary-care hospitals demonstrated that 25% of enterococci had high-level resistance to gentamicin.[75] As mentioned earlier, 26% of enterococci isolated at Mayo Clinic Rochester in 1998 showed high-level resistance to gentamicin. Enterococci with high-level resistance to gentamicin are usually resistant to all other aminoglycosides but occasionally are susceptible to streptomycin.[76] Zervos and associates[77] described the nosocomial acquisition and interhospital spread of these strains. These trends are even more worrisome

because of an apparent increase in the rate of hospital-acquired enterococcal infections.[78] This situation creates many therapeutic dilemmas. Although cell wall-active agents (ampicillin, penicillin, or vancomycin) may be used alone in the treatment of certain enterococcal infections—that is, those confined to the urinary tract—they must be used in combination with aminoglycosides in the treatment of enterococcal endocarditis. Unfortunately, combinations of cell wall-active agents with aminoglycosides are not bactericidal against aminoglycoside-resistant enterococci.

Table 4.—**Toxicity Associated With Use of Aminoglycosides***

Major
Ototoxicity
Vestibular
Auditory
Nephrotoxicity
Neuromuscular block
Minor
Drug fever
Rash

*See text for more details.

ADVERSE REACTIONS

Unlike the β-lactam and quinolone antimicrobial agents, aminoglycosides have considerable intrinsic toxicity (Table 4). Recently, Barclay and Begg[79] provided a comprehensive review of the risk factors for and mechanisms of aminoglycoside toxicity. Comparative studies[80-82] of aminoglycoside-induced nephrotoxicity suggest that all these agents are potentially nephrotoxic (neomycin the most and streptomycin the least). Although a few investigations have shown tobramycin to be somewhat less nephrotoxic than gentamicin, others have not; furthermore, definitions of nephrotoxicity have been arbitrary, and no published studies have documented clinically significant differences.

The basic mechanism of nephrotoxicity is likely related to inhibition of intracellular phospholipases in the proximal tubule, where aminoglycosides preferentially accumulate.[83] Clinical nephrotoxicity usually occurs after at least a week of therapy, is nonoliguric, and is characterized by a reduction in glomerular filtration rate; the degree of renal impairment is generally mild but may be moderate or even severe. Although typically reversible, nephrotoxicity can substantially increase morbidity and patient costs.[84] Bertino and coworkers[85] reviewed the risk factors for aminoglycoside-induced nephrotoxicity, including hypotension, duration of therapy, associated liver disease, increased trough serum concentrations, advanced age, and coadministration of other nephrotoxic drugs. Investigators have suggested that aminoglycoside-related renal toxicity may be potentiated by concomitant administration of vancomycin.[86,87] Although individualized pharmacokinetic calculation of dosing regimens has been proposed in an attempt to decrease the occurrence of nephrotoxicity, Leehey and colleagues[88] were unable to correlate a reduction in toxicity with use of such regimens.

Unlike nephrotoxicity, ototoxicity (either vestibular or auditory) is irreversible. The actual incidence of this complication is controversial, as is the issue of differential ototoxicity of the various aminoglycosides. Clinical assessment of ototoxicity is difficult for the following reasons: (1) hearing loss typically affects high-tone frequencies and consequently is not readily detectable at the bedside; (2) no universally accepted standard for defining drug-induced ototoxicity is available; and (3) clinical assessment of vestibular dysfunction in ill, hospitalized patients is almost impossible. Not unexpectedly, few studies of ototoxicity have been reported during the past 10 years. In a risk factor and comparative study of auditory toxicity, Gatell and coworkers[89] found netilmicin the least ototoxic of the aminoglycosides (but see related comments under previous "Netilmicin" heading); these investigators also determined that advanced age, especially beyond 60 years, was the only independent risk factor for auditory toxicity.

Neuromuscular block, a rare but potentially serious complication, occurs almost exclusively as a result of copious peritoneal irrigation or rapid intravenous administration. It is enhanced by underlying conditions or drugs that affect the neuromuscular junction (such as myasthenia gravis or concomitant administration of neuromuscular relaxant drugs). Aminoglycoside-associated neuromuscular block is treated primarily by supportive measures (for example, airway protection and possible control of ventilation). The prompt administration of calcium may also be useful.[90]

Despite the unavailability of newer, less toxic aminoglycosides, investigators have tried various methods to minimize the toxicity associated with these agents. A novel approach to the prevention of experimental aminoglycoside nephrotoxicity was described by Gilbert and associates;[91] the coadministration of polyaspartic acid with gentamicin successfully prevented all anatomic and functional evidence of nephrotoxicity in comparison with the findings in rats that received only gentamicin. This promising finding may prompt future clinical trials in humans. The concept of using SDD for aminoglycosides was originally proposed as a theoretical means for decreasing nephrotoxicity and ototoxicity; several published studies on this subject reflect a statistically insignificant trend toward reduced toxicity.

Table 5.—**Representative Acquisition Costs of Various Aminoglycosides**

Drug	Dose (for 70-kg patient)* and frequency	Cost/day (AWP)†
Gentamicin		
Conventional dosing	1.5 mg/kg (100 mg) every 8 h	$4.10
Single daily dosing	5 mg/kg (350 mg) daily	$4.56
Tobramycin		
Conventional dosing	1.5 mg/kg (100 mg) every 8 h	$32.80
Single daily dosing	5 mg/kg (350 mg) daily	$36.45
Amikacin		
Conventional dosing	7.5 mg/kg (500 mg) every 12 h	$130.60
Single daily dosing	15 mg/kg (1,000 mg) daily	$130.60

*With normal renal function.

†AWP = average wholesale price. Note that most hospitals can acquire these agents at prices lower than AWP through contracting agreements. In addition, this cost does not include the cost of supplies (such as intravenous piggyback bags and tubing). The cost of intravenous piggyback bags would be more for the conventional dosing (multiple daily doses) than for the single daily dosing regimen.

COST

The current fiscal crisis in health care necessitates consideration of cost factors in the use of antimicrobial agents. Representative acquisition costs of selected aminoglycosides are shown in Table 5. Acquisition costs do not include fees for mixing and administration of these agents, which typically are at least $15 per dose in most hospitals. Furthermore, aminoglycoside therapy has previously been associated with many "hidden costs"—such as the measurement of peak and trough serum concentrations as well as the potential cost of toxicity. Eisenberg and colleagues[84] estimated the mean total additional cost of aminoglycoside-related nephrotoxicity to be $2,500. The use of SDD for aminoglycosides has clearly been shown to decrease the costs. For example, Hitt and coworkers,[92] who performed a retrospective cost analysis comparing hospital costs for standard administration versus SDD, demonstrated a 58% reduction in aminoglycoside-associated hospital costs with SDD. At our institution, we estimate a 60% reduction in per-patient charges when aminoglycosides are administered once daily in comparison with multiple daily dosing. Further studies on the economic ramifications of SDD are needed.

CONCLUSION

Recent trends suggest that use of aminoglycosides continues to decline. Specifically, use of gentamicin at our institution decreased by almost 70% between 1987 and 1990 because of the introduction of newer, less toxic agents; use has also decreased by 56% during the 4-year period from 1995 through 1998. Nonetheless, these drugs serve a useful, although changing, role in the treatment of serious enterococcal and gram-negative infections. Although the introduction of newer, less toxic aminoglycosides into clinical practice is unlikely, future efforts may continue to be directed toward the understanding and prevention of aminoglycoside-related toxicity.

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End of **Symposium on Antimicrobial Agents,** Part VIII.
Part IX will appear in the June issue.

AMINOGLYCOSIDES
Drugs covered: gentamicin, tobramycin, amikacin, streptomycin

Date: September 10, 2015

Suggested Reading:
Edson RS, Terrell CL. The aminoglycosides. Mayo Clinic Proceedings 1999;74:519-28.

Learning Objectives:
1. Describe the mechanisms of action and resistance of the aminoglycoside antibiotics.
2. Differentiate the spectrums of activity of gentamicin, tobramycin, amikacin, and streptomycin.
3. Describe the concept of synergy between cell wall active agents and aminoglycosides.
4. Explain the pharmacokinetics and pharmacodynamics of the aminoglycosides and apply this information to dosing strategies.
5. Compare traditional and extended-interval aminoglycoside dosing strategies.
6. Describe and differentiate the clinical uses of the individual aminoglycosides.
7. Describe the most common and significant toxicities with the aminoglycosides.

I. INTRODUCTION

The aminoglycosides were first introduced in 1943 with streptomycin and the last of the currently used aminoglycosides became available in 1972 (amikacin). Despite the broad antibacterial (especially gram-negative) activity, the use of these agents declined in the 1980-90s due to the development of broad-spectrum beta-lactam antibiotics with more favorable toxicity profiles. Given the challenge of increasing antimicrobial resistance, aminoglycosides remain an important component of the antibacterial armamentarium given their synergy with beta-lactam antibiotics and their activity against gram-negative organisms. This is the first group of antibiotics that are *dosed individually for each patient* and require serum concentration monitoring which is important for efficacy and safety.

II. CHEMISTRY

A. The aminoglycosides consist of two or more amino sugars linked to an aminocyclitol ring by glycosidic bonds, hence the name aminoglycosides.

B. The aminoglycosides are polar compounds that are polycationic, highly water soluble (distribute primarily into extracellular fluid; renally eliminated), and incapable of crossing lipid-containing cellular membranes (poor PO absorption; poor penetration through meninges).

III. MECHANISM OF ACTION

A. The mechanism of action of the aminoglycosides is inhibition of protein synthesis.

B. Aminoglycosides **irreversibly** bind to the 30S ribosomal subunit (some to 50S subunits), which results in a disruption in the initiation of protein synthesis, a measurable decrease in protein synthesis, and misreading of messenger RNA.

1. The aminoglycosides must first bind to cell surface, not energy dependent.

2. Transported across the bacterial cytoplasmic membrane by energy dependent mechanism.

3. Ribosomal binding inhibits the synthesis of proteins, which disrupts the structure of the cytoplasmic membrane.

4. Aminoglycosides require aerobic energy to enter the cell and bind to ribosomes. (They are inactive against anaerobic bacteria)

IV. MECHANISMS OF RESISTANCE

A. Synthesis of aminoglycoside-modifying enzymes

1. Plasmid-mediated resistance factor that enables the resistant bacteria (usually gram-negative) to enzymatically modify the aminoglycoside by acetylation, phosphorylation, or adenylation. The modified aminoglycoside displays poor uptake and binds poorly to ribosomes, leading to high-level resistance.

2. More than 50 enzymes have been identified, and cross-resistance may occur. Gentamicin and tobramycin are generally susceptible to the same modifying enzymes, while amikacin is resistant to many enzymes.

B. Alteration in aminoglycoside uptake

1. Chromosomal mutations that influence any part of the binding and/or electrochemical gradient that facilitates aminoglycoside uptake – leads to decreased penetration of aminoglycoside inside the bacteria.

   a. Loss of porin channel

   b. Efflux pump

C. Alteration in ribosomal binding sites

1. Ribosomal binding site alterations rarely occur as a mechanism of resistance to gentamicin, tobramycin, and amikacin.

IV. SPECTRUM OF ACTIVITY

A. Gentamicin

1. Gram-negative: *E. coli* (less against ESBL-producers), *K. pneumoniae* (less against ESBL-producers), *Proteus, Moraxella, Citrobacter, Enterobacter, Morganella, Providencia, Serratia, Salmonella, Shigella, Pseudomonas* (less than tobramycin and amikacin)

2. Gram-positive (in combination with cell wall active agent): *S. aureus*, *Enterococcus*, Viridans *Streptococcus*, *Streptococcus pyogenes*

B. Tobramycin

1. Gram-negative: Most active aminoglycoside against *Pseudomonas* and slightly less active than gentamicin against other gram-negative bacteria (especially enterics)

C. Amikacin

1. Gram-negative: With the exception of tobramycin for *Pseudomonas*, most active aminoglycoside against nosocomial gram-negative pathogens (especially *Acinetobacter*)

2. Gram-positive/partially acid-fast: *Nocardia*

3. Mycobacterial: *M. tuberculosis*, M. bovis, *M. marinum, M. avium,* and some strains of *M. chelonae* and *M. fortuitium*. Less active against *M. kansasii* and *M. chelonae*.

D. Streptomycin

1. Gram-positive (in combination with cell wall active agent): *Enterococcus*

2. Mycobacterial: *M. tuberculosis* and some strains of *M. kansasii*, *M. marinum*, and *M. avium*.

E. Synergy

1. Synergy exists between the aminoglycosides and cell wall active agents, such as β-lactams and vancomycin. Synergy is demonstrated when the effect of the drugs in combination is greater than the anticipated results based on the effect of each individual drug; the effects are more than additive.

2. Possibly due to enhanced uptake of aminoglycoside into bacteria whose cell walls have been damaged by cell wall synthesis inhibitors.

3. Synergy has been demonstrated for:

Enterococcus - with ampicillin, penicillin or vancomycin (gent or strep)
S. aureus, viridans streptococci- with β-lactams or vancomycin (gent)
P. aeruginosa and other gram-negative aerobes - with β-lactams (gentamicin, tobramycin or amikacin)

V. PHARMACOLOGY

A. Absorption

1. Aminoglycosides are very poorly absorbed from the gastrointestinal tract (<1%).

2. Aminoglycosides are well absorbed after IM administration (80-90%), however, rarely used via this route.

3. Intravenous infusion is the preferred route of administration.

4. Tobramycin is often given via inhalation (10-20% systemic absorption).

B. Distribution

1. Volume of distribution that approximates extracellular space, low protein binding (~10%).

2. Minimal penetration into the CSF (more with inflamed meninges), bronchial secretions, bile (30% of serum), vitreous humor (40%).

3. Pleural, pericardial, ascetic, and synovial fluids ~50% of serum; high concentrations in urine.

C. Metabolism

1. None

D. Elimination

1. Rapidly excreted, primarily by glomerular filtration. Reabsorption into the proximal tubule may lead to accumulation in the renal cortex which is responsible for nephrotoxicity. High urinary concentrations.

2. 30 – 40% removed by hemodialysis

E. Pharmacodynamics

1. Concentration-dependent killing (against gram-negatives)

2. PD parameter: Peak/MIC (goal of ≥ 8-10)

3. Post-antibiotic effect (PAE)

a. Persistent suppression of bacterial growth after drug concentration falls below MIC of targeted organism.

b. May be impacted by:
   i. Organism
   ii. Drug concentration
   iii. Duration of drug exposure
   iv. Antimicrobial concentrations

c. PAE ranges from ~ 0.5 – 7.5 hours

F. Dosing

1. Gram-negative infections

   a. Gentamicin/tobramycin

      i. Traditional dosing: **2 – 2.5 mg/kg q8h** (normal renal function; renal impairment requires substantial dose adjustment)
         a. Goal peak ~ 6 -10
         b. Goal trough < 2

      ii. Extended-interval dosing (also called once-daily dosing): **5-7 mg/kg/once daily** to optimize PK/PD (also requires renal dose adjustment)
         a. Goal peak ~ 15 - 20
         b. Goal trough < 1

   b. Amikacin

      i. Traditional dosing: **5 mg/kg q8h** (normal renal function; renal impairment requires substantial dose adjustment)
         a. Goal peak ~10 - 20
         b. Goal trough <4-5

      ii. Extended-interval dosing (also called once-daily dosing): **15 - 20 mg/kg/once daily** to optimize PK/PD (also requires renal dose adjustment)
         a. Goal peak ~30 - 40
         b. Goal trough < 2

2. Gram-positive infections

a. Gentamicin
    i. **1 mg/kg q8h** (normal renal function; renal impairment requires substantial dose adjustment)
        a. Goal peak ~3-4
        b. Goal trough < 1

b. Streptomycin
    i. Dose less well defined but may range from **5 - 10 mg/kg q12 – 24h** (normal renal function; renal impairment requires substantial dose adjustment)
        a. Goal peak and trough concentrations not defined (my opinion is that high peaks are not needed and would prioritize low troughs to optimize safety)

3. Mycobacterial infections

a. Amikacin/streptomycin

    i. Standard dose: **15 mg/kg once daily** (normal renal function; renal impairment requires substantial dose adjustment)
        a. Goal peak ~ 30 - 40
        b. Goal trough < 2

    ii. High dose (preferred): **25 mg/kg three times weekly** to optimize PK/PD (also requires renal dose adjustment)
        a. Goal peak ~ 70 - 80
        b. Goal trough < 1

4. Rational for extended-interval dosing

a. Concentration-dependent activity

b. Post-antibiotic effect

c. Adaptive resistance

d. Minimize toxicities

e. Cost savings

f. Improve efficacy

VII. CLINICAL USES

A. Gram-negative infections (gent, tobra, amikacin)

1. Used in combination with beta-lactams to treat *Pseudomonas aeruginosa* and other highly resistant gram negative bacilli

2. Often used for sepsis, especially from a urinary source; may be used for bloodstream, intraabdominal and skin and soft tissue infections. Given low pulmonary penetration, consider giving high-dose.

3. Rarely used as monotherapy (only for urinary tract infections)

B. Gram-positive infections (mostly gent, some streptomycin)

1. Used in combination with beta-lactams (ampicillin or nafcillin) or vancomycin for severe gram-positive infections (e.g., enterococcal or staphylococcal endocarditis)

C. Mycobacterial infections (amikacin or streptomycin)

1. Used in combination with multiple antimycobacterial agents

VIII. ADVERSE EFFECTS

A. Nephrotoxicity

1. Manifested as nonoliguric azotemia secondary to proximal tubular damage, leading to an increase in BUN and serum creatinine.

2. Reversible if the aminoglycoside dose is adjusted or the drug is discontinued early enough.

3. The risk factors for the development of nephrotoxicity include **prolonged high trough concentrations**, prolonged therapy > 2 weeks, the presence of underlying renal insufficiency, advanced age, hypovolemia, and the use of concomitant nephrotoxins (vancomycin, amphotericin B, cisplatin, CT contrast, etc.).

4. Comparative nephrotoxicity-gentamicin most nephrotoxic

   a. Gentamicin>tobramycin>amikacin>streptomycin

B. Ototoxicity - auditory and vestibular

1. Due to eighth cranial nerve damage.

   a. Damage is ***irreversible***, and must be caught early.

   b. Auditory toxicity tinnitus, hearing loss.

c. Vestibular symptoms include dizziness, nystagmus, vertigo and ataxia.

2. Auditory toxicity is more common with amikacin>gentamicin>tobramycin.

3. Vestibular toxicity is more common with streptomycin>gentamicin>amikacin>tobramycin.

4. The risk factors for the development of ototoxicity include prolonged therapy > 2 weeks, the presence of renal insufficiency, advanced age, ?prolonged high trough concentrations, and ?genetic factors.

C. Other rare adverse effects of the aminoglycosides include neuromuscular blockade by preventing presynaptic internalization of Ca++ which must occur prior to ACh release.

	Antimicrobial Activity		
Aminoglycoside	**Gram-Positive**	**Gram-Negative**	**Other**
Gentamicin	*S. aureus*, *Enterococcus* Viridans Streptococci, *S. pyogenes*	*E. coli*, *K. pneumoniae*, *Proteus*, *Moraxella*, *Citrobacter*, *Enterobacter*, *Serratia*, *P. aeruginosa* (less than tobra or amikacin)	
Tobramycin		Most active AG against *P. aeruginosa*; slightly less active than gent for most other Gram-negative bacteria	
Amikacin		Broadest Gram-negative coverage especially against *Acinetobacter baumannii*	*Nocardia* Mycobacterial
Streptomycin	Enterococcus		Mycobacterial (less than amikacin)

Protein and TH4 synthesis inhibitors, and UTI drugs

Drug	SE/AEs	Spectrum	Indications	Misc
Tetracycline IV/PO **Doxycycline IV/PO**	GI, photosensi, hepatotoxic Discolor teeth Fanconi syndrome if outdated	Rickettsia Chlamydia Mycoplasma Spirochetes strep	Atypical pneumonia	Avoid with cations, Mg, Ca, Fe.
Minocycline IV/PO	Same as tet & doxy	Same as tet & doxy		
Tigecycline IV	GI	GNR, GPO, anaerobes	SSSI	Not Pseudomonas, Proteus +MRSA, VRE, not bacteremia
SMX-TMP IV/PO	GI, rash, BM supprxn, renal	Strep, Haemoph, Shigella, Salmonella, chlamydia,	PJP	Tree mouth pee
Chloramphenicol IV/PO	BM supprxn Gray Baby	GPC, GNRs, anaerobies	Infant Meningitis w/ pcn allergy Rickettsia in kids and preg	
Nitrofurantion PO	GI, rash, acute pulmonary symptoms		Cystitis	Avoid in elderly and impaired renal function
Methenamine PO	Gi, rash, prutitus, cystitis, neuropathy anemia	No antimicrobial activity	Uti prophylaxis	

Protein Synthesis Inhibitors II: MISCELLANEOUS ANTIBIOTICS

Suggested Readings:

Kasten MJ. Clindamycin, metronidazole, and chloramphenicol. Mayo Clinic Proceedings 1999;74:825-33.

Mandell, Douglas and Bennett. Principles and Practice of Infectious Diseases, 7th Edition. Chapter 25 Tetracyclines and Choramphenicol and Chapter 34. Urinary Tract Agents: Nitrofurantoin and Methenamine.

Learning Objectives:

1. Describe the mechanisms of action and mechanisms of resistance of the tetracyclines, sulfonamides, chloramphenicol and agents used for urinary tract infection (nitrofurantoin, methenamine)
2. List the spectrum of activity of the tetracyclines, sulfonamides, chloramphenicol and agents used for urinary tract infection (nitrofurantoin, methenamine).
3. Describe the pharmacokinetic characteristics of the tetracyclines, sulfonamides, chloramphenicol and agents used for urinary tract infection (nitrofurantoin, methenamine).
4. List the major clinical uses of the tetracyclines, sulfonamides, chloramphenicol and agents used for urinary tract infection (nitrofurantoin, methenamine).
5. List the major adverse effects associated with the tetracyclines, sulfonamides, chloramphenicol and agents used for urinary tract infection (nitrofurantoin, methenamine)
6. List the major drug interactions associated with the tetracyclines, sulfonamides.
7. List the potential therapeutic advantages of the glycylcycline antibiotics.

Prototypical Drugs:

Tetracyclines: Tetracycline, Doxycycline, Minocycline

Glycylcyclines: Tigecycline (Tygacil)

Sulfonamides: Sulfadiazine, Sulfisoxazole, Trimethoprim-Sulfamethoxazole

Chloramphenicol

Urinary Tract Agents Nitrofurantoin, Methenamine

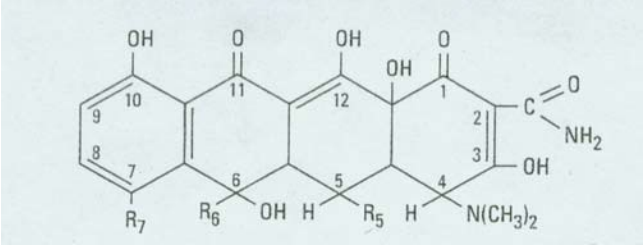
TETRACYCLINES and GLYCYLCYCLINES

I. INTRODUCTION

The tetracycline antibiotics were originally discovered through systematic screening of soil samples worldwide for antibiotic-producing organisms. Chlortetracycline was the first tetracycline antibiotic introduced in 1948. Currently, doxycycline, minocycline, and (rarely) tetracycline are the tetracycline antibiotics that are used in clinical practice. To address the emergence of resistance to the tetracycline class of antibiotics, structural modifications were made to the minocycline molecule to produce the glycylcycline antibiotics, of which tigecycline (Tygacil®) is the only approved agent of this class.

II. CHEMISTRY

A. The name "tetracycline" refers to antibiotics of either natural or semisynthetic origin that are comprised of a system of **four** linearly annelated six-membered rings. Tigecycline, a glycylcycline antibiotic, contains a glycylamido moiety attached to the 9-position of minocycline, which imparts enhanced activity against tetracycline-resistant bacteria.



III. MECHANISM OF ACTION:

A. Tetracyclines and glycylcyclines inhibit bacterial protein synthesis by reversibly binding to the 30S ribosome, blocking binding of amino-acyl tRNA to the acceptor (A) site on the mRNA-ribosomal complex. This prevents the addition of amino acid residues to the elongating peptide chain and inhibits protein synthesis.

B. Tetracyclines and glycylcyclines are usually **bacteriostatic** in action, but may be bactericidal in high concentrations or against highly susceptible organisms.

IV. MECHANISMS OF RESISTANCE

A. There are 3 main mechanisms of resistance to the tetracycline antibiotics:

1. Decreased accumulation of tetracycline within the bacteria due to either altered permeability or the presence of tetracycline-specific efflux pumps.

2. Decreased access of the tetracycline to the ribosome due to the presence of ribosomal protection proteins.

3. Enzymatic inactivation of the tetracycline.

B. Tigecycline does **NOT** appear to be affected by the 2 major tetracycline resistance mechanisms, namely tetracycline-specific efflux and ribosomal protection.

C. Cross-resistance is usually observed among the tetracycline antibiotics, with the exception of minocycline, which may retain susceptibility. Also, cross-resistance to tigecycline has not been observed in most tetracycline-resistant bacteria.

V. SPECTRUM OF ACTIVITY

A. The tetracyclines display activity against gram-positive and gram-negative aerobic bacteria, as well as unusual bacteria. However, the emergence of resistance to tetracyclines in conjunction with the introduction of new and improved antibiotics has limited the therapeutic usefulness of the tetracyclines.

1. **Gram-Positive Aerobes –** minocycline and doxycycline most active

Some *Staphylococcus aureus* (primarily **MSSA,** 80% susceptible)
Streptococcus pneumoniae (PSSP, doxycycline □ 80% susceptible)
Other Strep species
Bacillus, Listeria, Nocardia

2. **Gram-Negative Aerobes –**were initially useful for gram-negative aerobes, but many *Enterobacteriaceae* are relatively resistant

Haemophilus influenzae (90% susceptible)
Haemophilus ducreyi (chancroid)
Campylobacter jejuni
Helicobacter pylori

3. **Anaerobes**

Gram-positive: *Actinomyces, Proprionibacterium spp.*

4. **Miscellaneous organisms**

Bartonella, Bordetella, Brucella, Pasteurella,
Atypical bacteria such as ***Legionella pneumophila***, ***Chlamydophila pneumoniae*** *and* ***psittaci****; Chlamydia trachomatis, Mycoplasma hominis* and *pneumoniae, Ureaplasma sp.*
Spirochetes including *Borrelia, Leptospira,* and *Treponema*
Rickettsia such as *Rickettsia, Coxiella*
Doxycycline and tetracycline have demonstrated in vitro activity against *Mycobacterium fortuitum*

B. Tigecycline is active against a broad range of gram-positive and gram-negative aerobic and anaerobic bacteria, with an expanded spectrum that includes tetracycline-resistant strains.

1. **Gram-Positive Aerobes**

Staphylococcus aureus (**MSSA and MRSA**)
Group streptococci including *S. pyogenes and S. agalactiae*
Viridans streptococci
Enterococcus faecalis (vancomycin susceptible isolates)
Listeria monocytogenes

2. **Gram-Negative Aerobes**

Acinetobacter baumannii
Aeromonas hydrophila Citrobacter freundii and *koseri Enterobacter cloacae* and *aerogenes Escherichia coli*
Klebsiella pneumoniae and *oxytoca*
Serratia marcescens
Stenotrophomonas maltophilia

Tigecycline is NOT active against *Proteus mirabilis* or *Pseudomonas aeruginosa.*

3. **Anaerobes**

Gram-Positive**:** *Actinomyces, Proprionibacterium, Peptostreptococcus, Clostridium perfringens*

Gram-Negative: *Bacteroides spp., Prevotella spp.*

4. **Miscellaneous organisms**

Pasteurella multocida and *Mycobacterium fortuitum, chelonae, abscessus*

VI. PHARMACOLOGY

A. **Absorption** – tigecycline is only available IV; doxycycline is IV and PO, tetracycline and minocycline are only available PO

1. Tetracycline, demeclocycline – 60 to 80% absorbed from the GI tract

2. Doxycycline, minocycline – 90 to100% absorbed from the GI tract

3. Tetracyclines are absorbed best when taken on an empty stomach.

4. **Absorption of the tetracyclines is impaired by the concurrent ingestion of dairy products, aluminum hydroxide gels, calcium, magnesium, iron, zinc, and bismuth subsalicylate due to chelation with divalent or trivalent cations.**

B. **Distribution**

1. Tetracyclines and tigecycline are widely distributed into body tissues and fluids including pleural fluid, bronchial secretions, sputum, saliva, ascitic fluid, synovial fluid, aqueous and vitreous humor, and **prostatic** and seminal fluids.

2. Only small amounts of tetracyclines diffuse into the CSF.

C. **Elimination**

1. Demeclocycline and tetracycline are excreted unchanged mainly in the urine by glomerular filtration, and require dosage adjustment in renal insufficiency.

   Tetracycline half-life = 6 to 12 hours
   Demeclocycline half-life = 16 hours

2. Doxycycline and minocycline are excreted mainly by nonrenal routes, and do not require dosage adjustment in renal insufficiency – elimination half-lives ranges from 16 to 18 hours

3. Tigecycline is mainly eliminated by biliary/fecal excretion of unchanged drug and its metabolites (59%), with only 20% of the dose excreted as unchanged drug in the urine. The half-life of tigecycline is 27 to 42 hours. Dosage adjustments of tigecycline are required in patients with severe hepatic impairment (Child Pugh C), but are not required in patients with renal impairment or in patients undergoing hemodialysis.

4. Tetracyclines and tigecycline are not appreciably removed during hemodialysis or peritoneal dialysis.

VII. **CLINICAL USES** – the tetracyclines are primarily used for the treatment of infections due to unusual organisms

A. The emergence of bacterial resistance and the availability of more potent and useful antibiotics have limited the therapeutic usefulness of the tetracyclines in the treatment of gram-positive and gram-negative infections.

1. **Community-acquired pneumonia (doxycycline)** – due to penicillin-susceptible *S. pneumoniae*, *Mycoplasma spp, Chlamydophila spp.*

2. Treatment of **rickettsial infections** including Rocky Mountain spotted fever, epidemic and endemic typhus, Brill-Zinsser disease, scrub typhus, Q fever (*Coxiella burnetti*), rickettsial pox (doxycycline, tetracycline)

3. **Chlamydial infections** including psittacosis, lymphogranuloma venereum, and **nongonococcal urethritis*** (doxycycline)

4. *Brucellosis, bartonellosis* (doxycycline)

5. Acne (minocycline)

6. Useful as either primary or alternative therapy for the treatment of Plague (*Yersinia pestis*), Tularemia, Chancroid, Pertussis, Clostridial infections, Anthrax, Listeria, Syphilis, Lyme disease, *H pylori* , *Ehrlichia,* Cholera, prevention of Malaria (doxycycline)

7. Chronic syndrome of inappropriate antidiuretic hormone secretion – SIADH (demeclocycline)

B. Because of an expanded spectrum of activity, tigecycline is approved for the treatment of polymicrobial infections caused by susceptible bacteria (**not caused by *Proteus* or *Pseudomonas)*** in the following conditions:

1. Complicated skin and skin structure infections

2. Complicated intra-abdominal infections

VIII. ADVERSE EFFECTS

A. **Gastrointestinal** – **nausea (up to 29% with tigecycline), vomiting (up to 19% with tigecycline)**, diarrhea, flatulence, epigastric burning, oral candidiasis, antibiotic-associated pseudomembranous colitis

B. **Hypersensitivity** - rash, pruritus, urticaria, angioedema, anaphylaxis, serum sickness, Stevens-Johnson syndrome

C. **Dermatologic** – photosensitivity, manifested as exaggerated sunburn - most severe with demeclocycline, less frequently with doxycycline, tetracycline, and oxytetracycline, rarely with minocycline and tigecycline

D. **Renal** - Fanconi-like syndrome with outdated tetracycline; reversible dose-related diabetes insipidus with demeclocycline

E. **Hepatic** - elevations of liver function tests

F. **Central Nervous System** - lightheadedness, dizziness, vertigo, ataxia, headache

G. **Other** - vaginal candidiasis**,** thrombophlebitis with IV administration

H. **Pregnancy Category D - all tetracyclines and tigecycline are contraindicated during pregnancy because they cause permanent tooth discoloration of primary dentition (yellow-gray-brown) in children with developing teeth. They also appear to form a complex in bone-forming tissue, leading to decreased bone growth. For this reason, tetracyclines are also contraindicated for use during pregnancy and in children < 8 years of age.**

IX. DOSING

Agent	Adult Dosing	Pediatric Dosing (> 8 years of age)
Tetracycline (PO only)	250 to 500 mg every 6 hours	25 to 50 mg/kg daily in 2 to 4 divided doses
Demeclocycline (PO only)	150 mg every 6 hours or 300mg every 12 hours	6 to 12 mg/kg daily in 2 to 4 divided doses
Doxycycline (PO and IV)	100 mg every 12 hours	4 to 5 mg/kg daily in 2 divided doses
Minocycline (PO only)	100 mg every 12 hours	4 mg/kg initially followed by 2 mg/kg every 12 hours
Tigecycline (IV only)	100 mg followed by 50 mg every 12 hours	Not recommended

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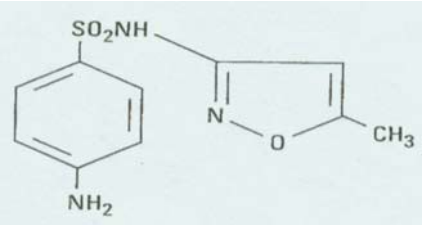
TRIMETHOPRIM-SULFAMETHOXAZOLE (SULFONAMIDES)

I. INTRODUCTION

The sulfonamides were the first effective antimicrobial agents to be used systemically in the treatment and prevention of bacterial infections. The introduction of the sulfonamides led to a dramatic reduction in the morbidity and mortality of treatable infectious diseases. Today, sulfonamides are rarely used alone in the treatment of infection. The combination of trimethoprim-sulfamethoxazole (**TMP-SMX, Bactrim**, co-trimoxazole) was introduced in the mid-1970s, and represented a significant and clinically useful therapeutic option that is still commonly used today.

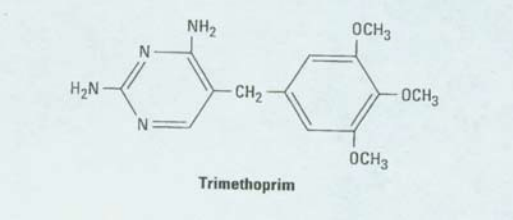
II. CHEMISTRY

A. Sulfonamide antibiotics are derivatives of para-aminobenzenesulfonamide (sulfanilamide).



Sulfamethoxazole

B. Trimethoprim is a diaminopyrimidine.



III. MECHANISM OF ACTION – TMP and SMX produce sequential blockade of microbial folic acid synthesis

A. **Sulfamethoxazole:** a sulfonamide that competitively inhibits the incorporation of p-aminobenzoic acid (PABA) into folic acid (inhibits dihydropteroate synthetase, which inhibits the formation of dihydrofolic acid)

B. **Trimethoprim:** competitively inhibits the activity of bacterial dihydrofolate reductase to prevent the reduction of dihydrofolate to tetrahydrofolate

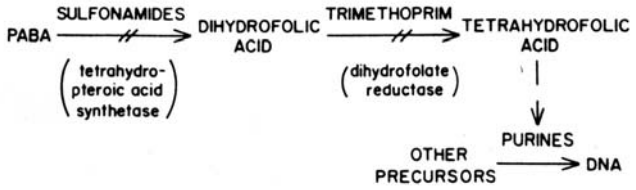


FIG. 3. Action of sulfonamides and trimethoprim on the metabolic pathway of bacterial folic acid synthesis.

C. Together, these two agents produce sequential inhibition of the synthesis of folate (necessary for microbial production of DNA) producing a synergistic **bactericidal** effect against many gram-positive and gram-negative aerobic bacteria that may not be present with each agent when used alone.

IV. MECHANISMS OF RESISTANCE

A. Resistance to trimethoprim-sulfamethoxazole occurs, but appears to develop more slowly to the combination than each individual agent.

B. Resistance has been reported in *E. coli, Klebsiella spp., Proteus mirabilis*, *H. influenzae, Salmonella spp,* and *Staphylococcus aureus.*

C. Bacterial resistance is mediated by **point mutations in dihydropteroate synthase** and/or **altered production or sensitivity of bacterial dihydrofolate reductase.**

V. SPECTRUM OF ACTIVITY

A. **Gram-Positive Aerobes:** *S. aureus* (including some **MRSA**, especially **CA-MRSA**), *S. pyogenes*, and *Nocardia*

B. **Gram-Negative Aerobes:** most Enterobacteriaceae including *Acinetobacter baumannii, Enterobacter spp., E. coli, K. pneumoniae, P. mirabilis, Salmonella, Shigella*, ampicillin-resistant *H. influenzae, H. ducreyi*, *N. gonorrhoeae*, and ***Stenotrophomonas maltophilia***.

1. **TMP-SMX is NOT active against *P. aeruginosa***

C. **Anaerobes:** little or no activity

D. **Other Organisms:** ***Pneumocystis carinii/ jiroveci*** (drug of choice)

VI. PHARMACOLOGY

A. The optimal synergistic ratio of trimethoprim (TMP) to sulfamethoxazole (SMX) in serum and tissue against most susceptible bacteria is approximately 1:20. Steady-state serum concentrations of 1:20 (TMP:SMX) are achieved by using a fixed oral or intravenous combination of 1:5 (TMP:SMX).

B. Absorption

1. Co-trimoxazole is rapidly and well absorbed after oral administration.

2. Peaks are higher and more predictable after parenteral administration.

C. Distribution

1. TMP-SMX concentrates in most tissues, including the CSF in the presence of inflamed meninges. CSF concentrations are 30 to 50% and 20%, respectively, of concomitant plasma concentrations.
2. Concentrates well into saliva, breast milk, urine, uninflamed prostatic tissue, seminal fluid, inflamed lung tissue, and bile.

D. Elimination

1. About 60% of TMP and 25 to 50% of SMX is excreted in the urine in 24 hours.

2. In patients with normal renal function, the half-lives of TMP and SMX are 11 and 9 hours, respectively.

3. Doses should be adjusted in patients with CrCl < 30 ml/min.

VII. CLINICAL USES

A. **Acute, chronic or recurrent infections of the urinary tract**

B. **Acute or chronic bacterial prostatitis**

C. Acute bacterial exacerbations of chronic bronchitis (ABECB)

D. ***Pneumocystis carinii/jiroveci*** **pneumonia** – TMP-SMX is **the** drug of choice for both treatment and prophylaxis

E. **Skin and soft tissue infections due to CA-MRSA**

F. Acute otitis media (sulfisoxazole), sinusitis (co-trimoxazole)

G. *Nocardia* infections – sulfisoxazole or TMP-SMX

H. ***Stenotrophomonas maltophilia*** **infections**

I. Listeria meningitis if patient is allergic to penicillins

J. Toxoplasmosis – sulfadiazine (with pyrimethamine)

VIII. ADVERSE EFFECTS

A. **Gastrointestinal:** nausea, vomiting, anorexia, glossitis, abdominal pain, diarrhea

B. **Hematologic:** leukopenia, thrombocytopenia, eosinophilia, megaloblastic anemia, acute hemolytic anemia, aplastic anemia, agranulocytosis

C. **Hypersensitivity reactions:** rash, urticaria, epidermal necrolysis, Steven's Johnson syndrome, erythema multiforme, exfoliative dermatitis, drug fever, malaise, pruritus, serum sickness

D. **CNS:** headache, insomnia, depression, fatigue, aseptic meningitis, seizures, tremor, hallucinations

E. **Others:** chills, myalgias, hepatitis (cholestatic and hepatic necrosis), renal failure, crystalluria (especially with older, less soluble sulfonamides)

IX. DRUG INTERACTIONS

A. **Warfarin –** potentiated anticoagulant effects due to inhibition of metabolism and possible displacement from albumin binding sites

X. DOSING

A. **Oral tablets**
Single Strength (SS) = 80mg TMP and 400mg SMX
Double Strength (DS) = 160mg TMP and 800mg SMX

B. **Oral Suspension = 40mg TMP and 200mg SMX per 5 ml**

C. **IV solution = 16mg TMP and 80mg SMX per ml**

Indication	Adult Dose
Urinary tract infections	One DS tablet twice daily
Prostatitis	One DS tablet twice daily
GI Infections	One DS tablet twice daily
Skin and sift tissue infections due to CA-MRSA	Two DS tablets twice daily
***Pneumocystis carinii/jiroveci* pneumonia**	**Treatment:** 15 to 20 mg/kg TMP daily divided every 6 to 8 hours (PO or IV) **Prophylaxis:** one DS tablet daily

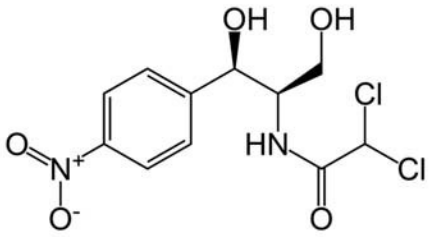
Chloramphenicol

I. Introduction

Chloramphenicol was discovered by screening organisms for antimicrobial activity and released in the United States for clinical use in 1949. The chemical was isolated from a mulched field and from compost. The organism producing the active compound was named *Streptomyces venezuelae*. Due to its association with aplastic anemia, this agent is

infrequently used in the United States. However its use is common in the developed world. Thiamphenicol is an analogue in which the *p*-nitro group on the benzene ring is)replaced by a methyl-sulfonyl group. It has the same spectrum of activity as chloramphenicol but has not been reported to cause aplastic anemia. Thiamphenicol is not available in the U.S.

II. Chemistry



III. Mechanism of action

A. Chlorampheicol enters the cell b an energy-dependent process. It inhibits protein synthesis by reversibly binding to the larger 50S subunit of the 70S ribosome.

B. Binding to the ribosome prevents attachment of the amino acid-containing end of the aminoacyl-tRNA to its binding region preventing peptide bond formation.

C. This mechanism produces a static effect against most bacteria except *Haemophilus influenza*, *Streptococcus pneumoniae* and *Neisseria meningitidis*.

IV. Spectrum of activity

A. Bacteria
- **i.** Gram positives
  1. Active against *Streptococcus pyogenes*, Group B Stretococcus, *Streptococcus pneumoniae,* Viridans streptococci
  2. Unreliable against *Staphylococcus aureus*
  3. Not active against Enterococci
- **ii.** Gram negatives
  1. Active against *Haemophilus influenza*, *Neisseria meningitidis*, *Neisseria gonorrhea*, *Salmonella sp* (including typhi), *Brucella sp*, *Shigella sp.*
  2. Not active against *Pseudomona aeruginosa*
- **iii.** Anaerobes
  1. Active against Gram positive (*Peptostreptococcus, Propionibacterium, Clostridium sp*) and Gram negative (*Veillonella, Bacteroides fragilis, Prevotella, Fusobacterium*)

B. Spirochetes

C. Rickettsiae

D. Chlamydiae

E. Mycoplasmas

V. Pharmacology

A. Absorption
- **i.** Encapsulated form well absorbed from the GI tract.
- **ii.** Intravenous administration produces active chloramphenicol levels in serum that are 70% of those obtained after oral administration due to incomplete hydrolysis. The iv preparation is the soluble but inactive chloramphenicol succinate ester that is rapidly hydrolyzed within the body to become biologically active.
- **iii.** Intramuscular injection produces levels similar to iv administration but may have delayed absorption from the injection site.

B. Distribution
- **i.** Due to high degree of lipid solubility, low protein binding (20 - 50%) and small molecular size, chorampheicol diffuses well into tissues and body fluids. Levels in cerebrospinal fluid 30-50% of the serum concentration (even in the absence of inflamed meninges).

C. Elimination
- **i.** Chloramphenicol is primarily metabolized by the liver (90%) where it is conjugated with glucuronic acid forming monoglucoronide. Due to wide variation in the metabolism and excretion in children, dosage requirements vary by age with lower daily doses in newborns.
- **ii.** Monoglucoronide is excreted in the bile into the small intestine, hydrolyzed by bacterial enzymes to aglycone, reabsorbed and conjugated with glucuronic acid again. This enterohepatic circulation results in about 80-90% of the monoglucoronide being excreted by the kidney.

D. Drug monitoring – because of the narrow therapeutic-to-toxic ratio, serum levels must be monitored especially in newborns and premature infants, in patients with hepatic disease and in patients taking interacting drugs. Peak serum levels should be maintained between 15-25 □g/mL and trough levels between 5-15 □g/mL in patients with meningitis, 10-20 □g/mL in patients with other infections. Toxicity occurs in those with levels □ 40 □g/mL.

E. Dose adjustment
- **i.** Renal insufficiency – not required
- **ii.** Hepatic failure – decrease dose

VI. Clinical Indications

A. Not indicated as first line therapy for treatment of infections in the U.S.

B. In developing nations, due to the low cost of this agent, chloramphenicol continues to be used for bacterial meningitis (in areas without high rates of *Hemophilus influenza* resistance), pneumonia, typhoid fever

VII. Adverse Effects

A. Hematologic

i. Reversible bone marrow depression from inhibition of mitochondrial protein synthesis. This reaction is rare occurring during the course of therapy and is dose related. It is more likely to occur in patients receiving 4 g/day or more and in patients with serum levels >25 □g/mL

ii. Aplastic anemia – rare but generally fatal reaction. This occurs in 1 in 24,500 to 40,800 patients who receive chloramphenicol (13 times greater than the occurrence of aplastic anemia in the general population). The mechanism is unknown but is not dose dependent and is different from bone marrow suppression from chloramphenicol. Can occur weeks to months after completion of therapy.

B. Gray Baby Syndrome of neonates – abdominal distention, vomiting, flaccidity, cyanosis, circulatory collapse, death. This syndrome is due to the neonate's diminished ability to conjugate chloramphenicol and to excrete the active form in the urine.

C. Optic Neuritis with decreased visual acuity

D. Other – hypersensitivity reactions, anaphylaxis (rare), Herxheimer-like responses during therapy for syphilis, brucellosis, typhoid fever, nausea, vomiting, diarrhea, glossitis, stomatitis, bleeding, acute attacks of porphyria, interference during development of immunity and should not be given during active immunization.

VIII. Drug interactions

A. Phenobarbital reduces serum concentrations of chloramphenicol by 30-40% with increased concentrations of Phenobarbital by 50%.

B. Cyclosporine concentrations increased by chlorampnenicol increasing the risk for renal dysfunction, cholestasis, paresthesias.

C. Decreased effectiveness of cyclophosphamide due to decreased metabolism to active cyclophosphamide.

D. Rifampin/rifabutin decreases chloramphenicol levels

E. Reduces tacrolimus blood concentrations.

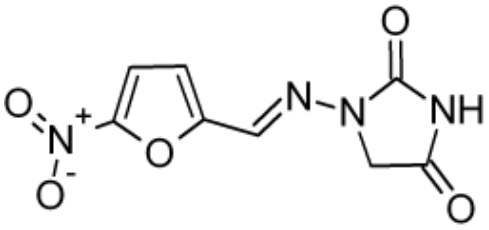
Urinary Tract Agents (Nitrofurantoin and Methenamine)

I. Introduction

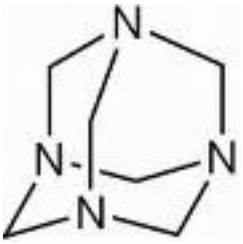
Nitrofurantoin is a weak acid and s amember of a group of synthetic nitrofuran compounds. Along with Methenamine, these two agents are used almost exclusively for treatment or prophylaxis of urinary tract infections.

II. Chemistry

Nitrofurantoin Structure:



Methenamine Structure:



III. Mechanism of action

A. Nitrofurantoin – the mechanism of action is poorly understood. May require enzymatic reduction within the bacterial cell wall. The reduced compounds are capable of binding to ribosomal proteins. Nitrofurantoin has also been shown to inhibit synthesis of inducible enzymes by blocking translation and also to inhibit bacterial respiration and pyruvate metabolism.

B. Methenamine – this compound itself has very little antimicrobial activity but at an acid pH (< 6), methenamine is hydrolyzed to generate ammonia and formaldehyde, the active product. Formaldehyde is a non-specific denaturant of proteins and nucleic acids with broad-spectrum antimicrobial activity.

IV. Mechanisms of resistance

A. Nitrofurantoin – Emergence of resistance to this agent from initially susceptible strains is rare. *E. coli* with chromosomal or plasmid-mediated resistance is associated with inhibition of nitrofuran reducase activity leading to decreased production of the active derivative.

B. Methenamine – alkaline urine will prevent conversion of methenamine to formaldehyde. No antimicrobial resistance to formaldehyde has been described.

V. Spectrum of activity

A. Nitrofurantoin

i. *E. coli, Citrobacter* sp, Group B streptococci, *Staphylococcus saprophyticus, Enterococcus faecalis*, *Enterococcus faecium*, and many VRE strains are susceptible. Organsims not associate with UTI but are susceptible to nitrofurantoin include *Salmonella* sp., *Shigella* sp.,

Coagulase negative staphylococci, *Streptococcus pneumoniae, Streptococcus pyogenes, Corynebacterium* sp, and *Bacteroides* sp.

ii. Unreliable activity against *Enterobacter, Klebsiella*

iii. *Proteus, Providencia, Morganella, Serratia, Acinetobacter* and *Pseudomonas* are resistant.

B. Methenamine

i. Broad-spectrum antimicrobial activity and microbial resistance to formaldehyde has not been described. Organisms that produce urease (*Proteus*) may alkalinize the urine and prevent conversion of methenamine to the active compound (formaldehyde).

VI. Pharmacology

A. Absorption

i. Nitrofurantoin – 40-50% absorption following oral administration. Absorption occurs rapidly in the small intestine and is enhanced with food.

ii. Methenamine – rapidly absorbed after oral absorption with 82-88% recovery in urine. May be partially degraded in the presence of gastric aid before absorption. Enteric-coated formulations reduce degradation but delays absorption.

B. Distribution

i. Nitrofurantoin – urine concentrations are substantial (50 – 250 □g/mL). Low to undetectable serum concentrations after standard oral doses. Serum half-life after intravenous administration ≤ 30 minutes. Therapeutic concentrations are not detected in prostatic secretions.

ii. Methenamine – Broad distribution in tissue, crosses the placenta and concentration in breast milk is similar to serum.

C. Excretion

i. Nitrofurantoin – eliminated predominantly in the kidneys involving glomerular filtration, tubular secretion, and tubular reabsorption. In patients with reanal failure, nitrofurantoin excretion is decreased in proportion to decreases in creatinine clearance and urinary drug concentrations become subtherapeutic. Should not be used in patients with renal insufficiency (creatinine clearance < 40 mL/min).

VII. Clinical uses

A. Nitrofurantoin is indicated only for the treatment and prophylaxis of acute, uncomplicated urinary tract infections. Should not be used in patients with pyelonephritis or complicated urinary tract infections. Can be used in pregnancy but discouraged at term. Not recommended for use in neonates.

B. Methenamine is indicated for suppression or prophylaxis of recurrent lower urinary tract infections. Should not be used for treatment of established urinary tract infection or pyelonephritis. Not effective in preventing urinary tract infection in patients with chronic, indwelling urinary catheters.

VIII. Adverse Effects

A. Nitrofurantoin –

- **i.** Gastrointestinal intolerance
- **ii.** Rashes
- **iii.** Acute pulmonary reaction (reversible hypersensitivity phenomena) occurring within hours to weeks of drug exposure. Rapid onset of fever, cough, dyspnea, myalgia with peripheral blood eosinophilia and lower lobe infiltrates.
- **iv.** Subacute and chronic pulmonary reactions presenting with gradual onset of progressive, non-productive cough and dyspnea with interstitial infiltrates on chest radiographs. May have positive antinuclear antibodies. Usually reversible but may lead to irreversible pulmonary fibrosis. A pattern of bronchiolitis obliterans and organizing pneumonia has been reported.
- **v.** Hepatitis
- **vi.** Hemolytic anemia has occurred rarely and is associated with deficiency of glucose-6-phosphate dehydrogenase. Folic acid responsive megaloblastic anemia. Eosinophilia, leucopenia, aplastic anemia rarely reported.
- **vii.** Peripheral sensorimotor neuropathy

B. Methenamine – well tolerated with few, mild, reversible side effects comparable with placebo. GI (nausea, vomiting), rashes and pruritis. Symptoms of bladder irritation. With higher doses, increased GI intolerance and hemorrhagic cystitis. Methenamine salts may predispose to development of urate crystals in urine of patients with gout. Should be avoided in patients with hepatic insufficiency.

IX. Dosing

A. Nitrofurantoin – 50 to 100 mg four times daily for 7 days for the treatment of established acute, uncomplicated cystitis. 50-100 mg once daily as prophylaxis for recurrent urinary tract infections.

B. Methenamine

- **i.** For adults and children older than 12 years – 1 gram orally twice daily up to 4g/day (1g four times daily).
- **ii.** Children 6-12 years old – 500 mg to 1 g twice daily
- **iii.** Children < 6 years old – 250 mg per 30 lbs body weight orally four times daily.

FLUOROQUINOLONES

Suggested Reading Assignment:
Walker RC. The fluoroquinolones. *Mayo Clinic Proceedings* 1999;74:1030-7.

Learning Objectives:

1. Describe the mechanism of action of the fluoroquinolones.
2. Describe the mechanisms by which bacteria develop resistance to the fluoroquinolone antibiotics.
3. List the spectrum of activity of the older and newer/respiratory fluoroquinolones. List the fluoroquinolones that have the best activity against *Staphylococcus aureus, Streptococcus pneumoniae, Pseudomonas aeruginosa*, atypical bacteria, and anaerobes.
4. Discuss the main clinical uses of ciprofloxacin, levofloxacin, and moxifloxacin.
5. List the major adverse effects associated with fluoroquinolone therapy.
6. Explain the major drug interactions that may occur with the fluoroquinolone antibiotics.

Drugs Covered in this Lecture:

Ciprofloxacin, Levofloxacin, Moxifloxacin, Gemifloxacin

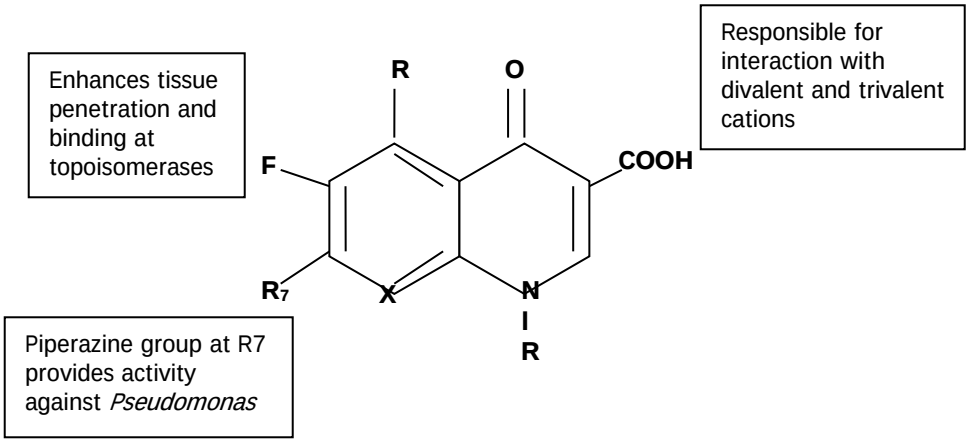
FLUOROQUINOLONES

I. INTRODUCTION

The fluoroquinolone antibiotics are a novel group of synthetic antibiotics developed in response to the need for antibiotics with activity against resistant bacteria. All of the quinolones available today are structural derivatives of the original prototype agent of this class, **nalidixic acid**. The usefulness of nalidixic acid was hindered by the rapid development of bacterial resistance (even during therapy) and limited therapeutic utility. The introduction of the fluorinated 4-quinolones (hence the name ***fluoroquinolones*** {FQs}: ciprofloxacin, levofloxacin, moxifloxacin, gemifloxacin) represents a particularly important therapeutic advance as these agents have broad antimicrobial activity, excellent oral bioavailability, extensive tissue penetration, and relatively long serum half-lives. Like other antibiotic classes, the main disadvantage of the FQs is the emergence of resistance in certain organisms.

II. CHEMISTRY

A. Currently available fluoroquinolones have two six-membered rings containing a nitrogen at position 1, a carboxylic acid moiety at position 3, a carbonyl group at position 4, a fluorine at position 6, and a piperazine moiety or other group at position 7.



III. MECHANISM OF ACTION

A. The FQs have a unique mechanism of action that includes **inhibition of DNA synthesis** by binding to and inhibiting bacterial topoisomerases, which are enzymes needed for maintaining cellular DNA in an appropriate state of supercoiling in both the replicating and nonreplicating regions of the bacterial chromosome.

B. The FQs target bacterial **DNA gyrase** (topoisomerase type II) and **topoisomerase IV**:

1. Inhibition of ***DNA gyrase*** prevents the relaxation of positively supercoiled DNA that is required for normal transcription and replication. The FQs form a stable complex with DNA and DNA gyrase, which blocks the replicating fork leading to a sudden and lethal cessation of DNA replication. **For many gram-negative bacteria, DNA gyrase is the primary target of the FQs.**

2. Inhibition of ***topoisomerase IV*** interferes with separation of replicated chromosomal DNA into the respective daughter cells during cell division that are the product of DNA replication, causing a cessation in DNA replication. **For many gram-positive bacteria (*S. aureus*), topoisomerase IV is the primary target of the FQs.**

C. The FQs display **concentration-dependent bactericidal activity**.

IV. MECHANISMS OF RESISTANCE

A. **Altered binding sites** – chromosomal mutations in the genes that code for the subunits of topoisomerase IV or DNA gyrase lead to **decreased binding affinity** of the FQs to these target sites.

1. *S. aureus* and *P. aeruginosa* require only a single mutation in the genes encoding for the topoisomerases to become resistant.

2. *E. coli* and *S. pneumoniae* often require more than one mutation to become resistant to the newer FQs.

B. **Expression of active efflux** – efflux pump is turned on that **enhances the transfer of FQs out of the cell**; reported in *P. aeruginosa* and *S. pneumoniae.*

C. **Altered cell wall permeability** – chromosomal mutations cause decreased expression of porin proteins that are responsible for FQ transit inside the cell leading to **decreased FQ accumulation within the cell (rare).**

D. **Cross-resistance is usually observed between the FQs.**

V. SPECTRUM OF ACTIVITY – older (ciprofloxacin) versus newer/respiratory FQs (levofloxacin, moxifloxacin, gemifloxacin)

A. **Gram-positive aerobes** – **ciprofloxacin** has ***poor*** activity against gram-positive bacteria; the **newer FQs** (**levofloxacin**, **moxifloxacin**, **gemifloxacin**) **have enhanced activity against gram-positive bacteria**

- Methicillin-susceptible *S. aureus* (**not MRSA**)
- *Streptococcus pneumoniae* (**including PRSP**)
- Viridans streptococci, *Enterococcus spp.* – limited activity

B. **Gram-negative aerobes** – some FQs have excellent activity against Enterobacteriaceae (**ciprofloxacin**=**levofloxacin**> moxifloxacin) and *H. influenzae*, *M. catarrhalis*, and *Neisseria* species

Haemophilus influenzae	*Moraxella catarrhalis*
Citrobacter spp.	*Enterobacter spp.*
Escherichia coli	*Klebsiella pneumoniae*
Proteus spp.	*Morganella morganii*
Providencia spp.	*Serratia marcescens*
Salmonella spp.	*Shigella spp.*
Campylobacter spp	*Neisseria spp.*

***Pseudomonas aeruginosa* (cipro > levo; NOT moxi or gemi)**

C. **Anaerobes** – moxifloxacin has some activity

D. **Atypical Bacteria** – **against *Legionella***, *Chlamydophila*, *Mycoplasma*, and *Ureaplasma*

E. **Other Organisms** – have activity against *Mycobacterium tuberculosis* (levo, moxi) and *Bacillus anthracis* (cipro, levo)

VI. PHARMACOLOGY

A. FQs exhibit **concentration-dependent bactericidal activity** (AUC/MIC {30 to 50 for *S. pneumoniae*; 100 to 125 for gram-negatives} or Peak/MIC correlate with clinical efficacy) and display a **PAE** against both gram-positive (2 hours) and gram-negative aerobic bacteria (2 to 4 hours).

B. **Absorption**

1. FQs are well absorbed after oral administration (except for norfloxacin, F = 50%); oral bioavailability is 70 to75% for ciprofloxacin and > 90% for levofloxacin and moxifloxacin – allows for early conversion to oral therapy.

2. Tmax is achieved within 1 to 2 hours; co-ingestion with food delays peak serum concentrations.

C. **Distribution**

1. Most of the FQs display extensive tissue penetration obtaining therapeutic concentrations in the **prostate**, liver, **lung, bronchial mucosa, sputum**, bile, saliva, skin and soft tissue, **bone** and into alveolar macrophages.

2. **Most FQs achieve high urinary concentrations (except for moxifloxacin, and gemifloxacin) making them useful for the treatment of urinary tract infections and prostatitis.**

3. Moxifloxacin achieves good penetration into the CSF.

D. Elimination

1. FQs are eliminated by various pathways

a. *Renal elimination* – levofloxacin is eliminated primarily by the kidney (glomerular filtration and tubular secretion); dosage adjustment is necessary in the presence of renal insufficiency

b. *Hepatic metabolism and elimination* – moxifloxacin

c. Ciprofloxacin and gemifloxacin undergo both renal and hepatic elimination; doses of both agents should be adjusted in the presence of renal insufficiency

d. NONE of the FQs are removed during hemodialysis

E. DOSING (for your reference)

	Parenteral (IV)	**Oral**
CIPROFLOXACIN (Cipro®)	200 to 400 mg q8-12h	250 to 750 mg BID
LEVOFLOXACIN (Levaquin®)	250 to 750 mg QD	250 to 750 mg QD
MOXIFLOXACIN (Avelox®)	400 mg QD	400 mg QD
GEMIFLOXACIN (Factive®)		320 mg QD

VII. CLINICAL USES

A. **Community-acquired pneumonia** – levofloxacin, moxifloxacin, and gemifloxacin

B. **Acute exacerbations of chronic bronchitis and sinusitis** – ciprofloxacin, levofloxacin, moxifloxacin, and gemifloxacin

C. **Bacterial exacerbations in cystic fibrosis** (*P. aeruginosa*) - ciprofloxacin

D. **Nosocomial pneumonia** – ciprofloxacin and levofloxacin (anti-pseudomonal FQ's)

E. **Urinary tract infections (cystitis, pyelonephritis)** – ciprofloxacin, levofloxacin;
F. **Chronic Bacterial Prostatitis** – ciprofloxacin and levofloxacin

G. **Bone/Osteomyelitis** – ciprofloxacin, levofloxacin, moxifloxacin

H. **Other** – intraabdominal infections (ciprofloxacin, levofloxacin or moxifloxacin with metronidazole); traveler's diarrhea (ciprofloxacin); tuberculosis (ciprofloxacin, levofloxacin, moxifloxacin); STDs

VIII. ADVERSE EFFECTS – many FQs have been removed from the market due to adverse effects. The FQs still available are well tolerated. **The MOST COMMON adverse effects are GI and CNS.**

A. **Gastrointestinal (5%)** – nausea, vomiting, diarrhea, dyspepsia, *Clostridium difficile* colitis

B. **CNS –** headache, confusion, agitation, insomnia, dizziness, rarely hallucinations and seizures

C. **Hepatotoxicity** – transaminase elevation; moxifloxacin has been associated with a few cases of liver failure

D. **Phototoxicity** – patients should to avoid exposure to sunlight or UV light. Sunscreen containing UVA blockers may help.

E. **Cardiac** – FQs may cause slight prolongation in QTc interval, excessive prolongation can lead to Torsades. **FQs should be used with caution in patients with hypokalemia or in patients who already have a prolonged QTc interval. Avoid concomitant use with class III antiarrhythmics (amiodarone, sotalol), or with other drugs that can prolong the QTc.**

F. **Articular Damage –** arthropathy (articular cartilage damage, arthralgias and joint swelling) observed in young experimental animals led to the **contraindication in pediatric patients and the warning to avoid their use in pregnant or breastfeeding patients**; FQs have been used in a substantial number of pediatric patients without apparent arthropathy (risk versus benefit)

G. **Tendonitis and Tendon Rupture** – Higher risk in patients over 60 years of age receiving corticosteroids, or who have undergone a renal, heart or lung transplant; patient should avoid exercise if tendon pain develops while on therapy

H. **Other:** hypersensitivity, rash (highest with gemifloxacin: 14% in women under 40 receiving the drug for 7 or more days).

IX. DRUG INTERACTIONS

A. **Divalent and trivalent cations** (**Zinc, Iron, Ca, Al, Mg**– including **antacids, ddI, Sucralfate, enteral feeds**) may **impair the absorption of ANY ORAL fluoroquinolones** through chelation leading to clinical failure; doses should be administered at least 2 to 4 hours apart (tube feedings must be stopped for several hours surrounding FQ administration); give FQ first

B. **Warfarin** – idiosyncratic interaction leading to increased prothrombin time and potential bleeding; has been reported with most FQs

C. **Theophylline** – inhibition of theophylline metabolism leading to increased serum theophylline concentrations and potential toxicity; may occur with **ciprofloxacin**, but does not occur with levofloxacin or moxifloxacin

D. **Cyclosporine** – **ciprofloxacin** may inhibit cyclosporine metabolism leading to increased cyclosporine levels and potential toxicity

Spectrum of activity	Ciprofloxacin	Levofloxacin	Moxifloxacin	Gemifloxacin
Gram + bacteria		X	X	X
Gram – bacteria	X	X	X	X
Pseudomonas (gram -)	X	X		
Anaerobic bacteria			X	
Atypical bacteria	X	X	X	X
Therapeutic Use				
Community acquired pneumonia		X	X	X
Health care associated Pneumonia	X	X		
Urinary tract infection	X	X		
Prostatitis	X	X		
Bone infection (osteomyelitis)	X	X	X	
Intra-abdominal infection (add metronidazole)	X	X	X	
Travelers Diarrhea	X			

Drug Class/Name	Spectrum of Activity	Indication/Clinical Use	Mechanism of Action	Adverse Effects
Drug name: Clindamycin **Drug Class**: Lincosamide	-Gram-positive aerobes -Anaerobes	Anaerobic infections excluding the CNS Skin and soft tissue infection (PCN allergic, CA-MRSA)	-Inhibits protein synthesis by binding to 50S subunit -Generally bacteriostatic	**Most common**: Nausea, vomiting, diarrhea, dyspepsia **Rare**: hepatotoxicity, neutropenia, thrombocytopenia
Drug name: Erythromycin Clarithromycin Azithromycin **Drug Class**: Macrolide	-Gram-positive aerobes -Gram negative aerobes -Anaerobes -Atypical	Respiratory tract infections Uncomplicated skin infections STDs MAC Alternative for PCN-allergic patients	-Inhibits protein synthesis by binding to 50S subunit -Generally bacteriostatic	**Most common**: Nausea, vomiting, diarrhea, dyspepsia **Rare**: Allergic reaction Cholestatic hepatitis Thrombophlebitis Prolonged QTc Transient/reversible tinnitus
Drug name: Quinupristin/Daltopristin **Drug Class**: Streptogramin	-Gram-positive bacteria	VRE bacteremia	-Inhibits protein synthesis by binding to 50S subunit -Generally bacteriostatic	**Most common**: Venous irritation Nausea, vomiting, diarrhea **Rare**: Rash Myalgias Arthralgias

Protein Synthesis Inhibitors

Marcrolides, Ketolides, Streptogramins & Locosamides

1. At the conclusion of the lecture, the audience should be able to meet the following objectives regarding protein synthesis inhibitors:
2. Identify the mechanism of action
3. Compare and contrast the appropriate clinical uses between each antibiotic
4. Describe the most common side effects associated with each medication
5. Categorize their spectrum of activity