# PHARMACOLOGY/THERAPEUTICS I BLOCK III HANDOUTS – 2017-18

20/21 Introduction to Antibiotics & General Principles of Antimicrobial Therapy I & II – **ON LINE ONLY**

22. Cell Wall Inhibitors I - Penicillins - **Reid**

23. Cell Wall Inhibitors II: Cephalosporins, Carbapenems and Monobactams – **Reid**

24. Aminoglycosides – **Reid**

25. Vancomycin, Linezolid and Daptomycin – **Reid**

26. Tetracyclines, Glyclines, sulfonamides, Chloramphenicol, etc – **Reid**

27. Marcrolides, Ketolides, Streptogramins, etc – **Scardina**

28. Fluoroquinolones & Metronidazole – **Labuszewski**

29. Clinical Applications of Antibiotics - **Reid**

S. Erdman, Feb 2016

# SPECTRUM OF ACTIVITY SUMMARY CHART

| Antibiotic / Organism | Penicillins | | | | | | | Cephalosporins | | | | | | Carb | Mon | FQ | | Mac | AG | Vanc | Syner | Tet | Tige | TMP-SMX | Col | Clin | Met |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Pen G | Naf | Amp | Una Aug | Tic | Pip | Tim Zos | 1st | 2nd | 3rd | 4th | Anti-MRSA ceftar | Ceftol -Tazo, Ceftaz-Avi° | Imip Mero Erta Dori | Aztre | Cip | Levo[ƨ] Moxi | Eryth Clari Azith | Gent Tobra Amik | | Linez Tediz Dapt Tela Dalb Orita | 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*** | | | | | | | | | | Xφ | | | | | | | Xψ | | | | | | 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, ° including some ESBL- or AmpC-producing Gram negatives (Avycaz™ also covers some KPCs)
†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*.)<br>*Propionibacteriaceae*<br>*Bacillus spp.*<br>Staphylococci (esp. coagulase-negative)<br>Streptococci | *Bacteroides spp.*<br>*Haemophilus spp.*<br>*Neisseria spp.*<br>Streptococci (anaerobic) |
| **GASTROINTESTINAL TRACT** | **GENITOURINARY TRACT** |
| *Bacteroides spp*.<br>*Clostridium spp.*<br>Enterobacteriaceae (*E. coli, Klebsiella spp*.)<br>Streptococci (anaerobic)<br>*Enterococcus spp.*<br>*Fusobacterium spp.* | *Lactobacillus spp.*<br>*Corynebacterium spp.*<br>Enterobacteriaceae – especially *E.coli*<br>Staphylococci (*S. saprophyticus*)<br>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

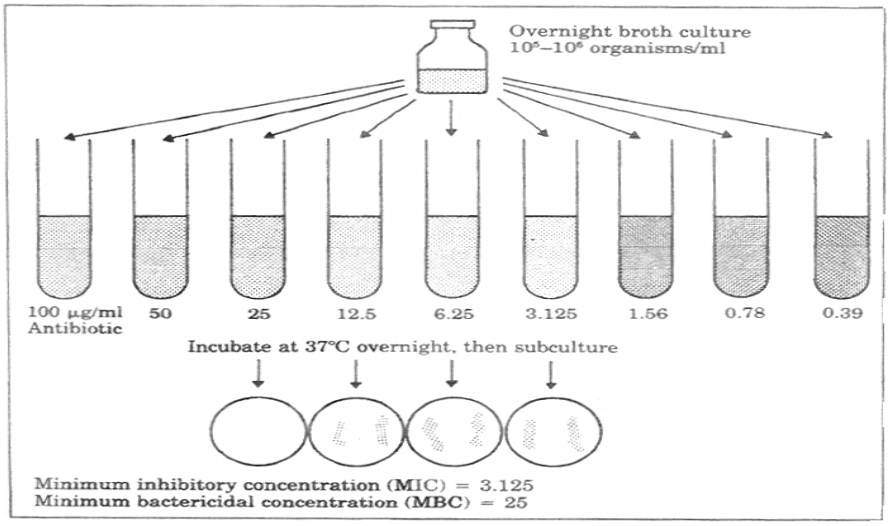
a. Dilutions of an antibiotic (based on achievable serum concentrations after usual doses) are placed in broth with a standard inoculum of the infecting bacteria and incubated for 18 to 24 hours.

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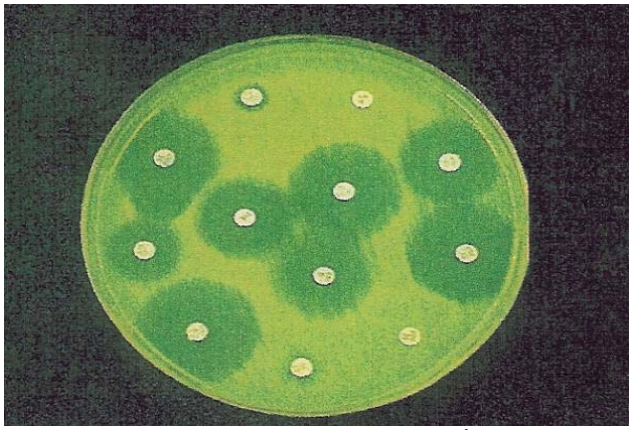
d. **Microdilution methods** employ microtiter plates or cassettes that contain wells with serial dilutions of **<u>several</u>** antibiotics that can be tested for susceptibility simultaneously in an automated system.

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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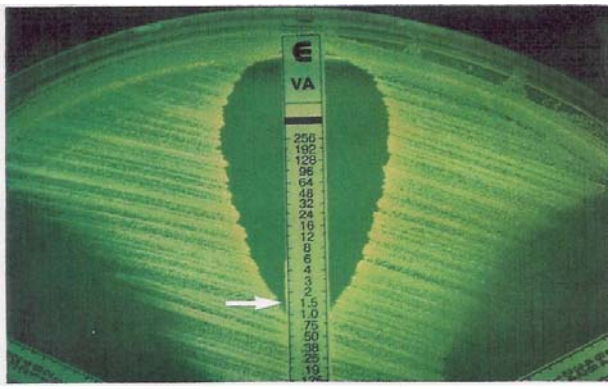
3. **E-Test® (Epsilometer Test) –** combines the quantitative benefits of microdilution with the ease of agar dilution
   a. A plastic strip impregnated with a known, prefixed concentration gradient of antibiotic is placed on an agar plate with a standardized inoculum of the patient's infecting bacteria.
   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 **established** 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

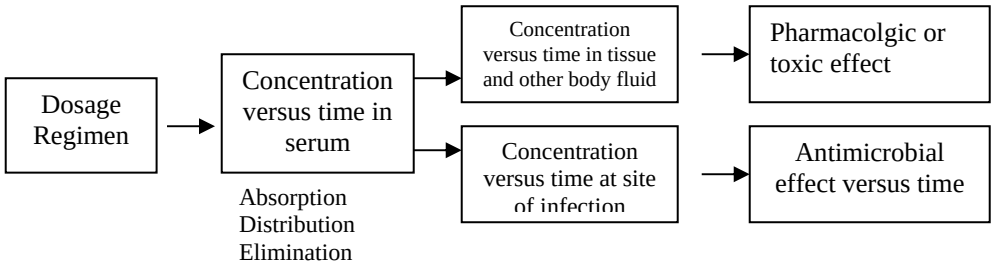
## IV. PHARMACODYNAMIC CONSIDERATIONS

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)

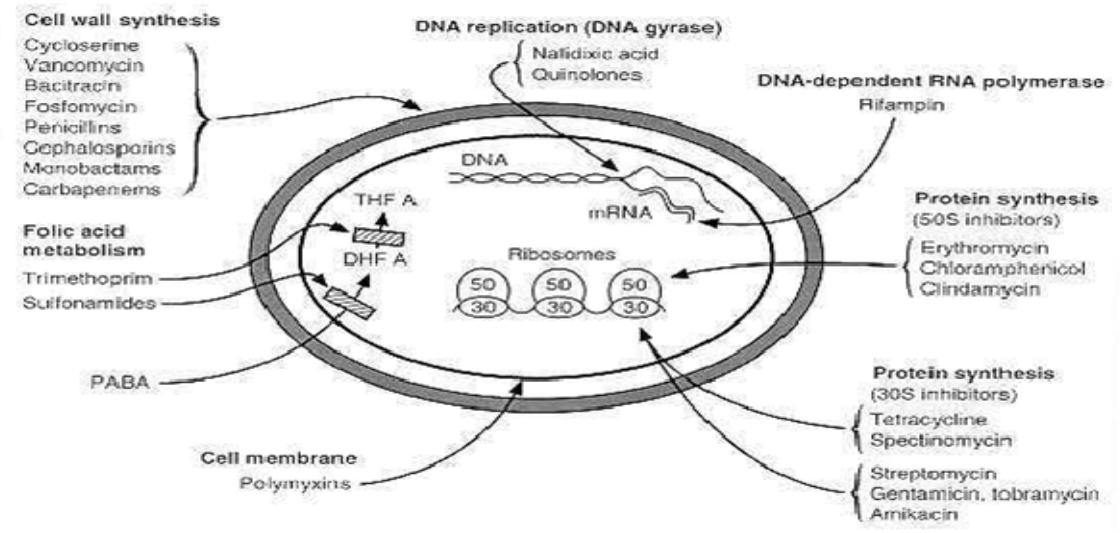
**ATYPICAL BACTERIA**
*Chlamydophila pneumoniae*
*Chlamydia trachomatis*
*Legionella pneumophila*
*Mycoplasma pneumoniae*

**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

**Original Handout written by Shellee Grim, PharmD. presented by G. Reid, M.D.**

**Date:** September 1, 2017

**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.
2. Describe the distribution characteristics of the penicillins and 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.

**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**

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## PENICILLINS

## I. INTRODUCTION

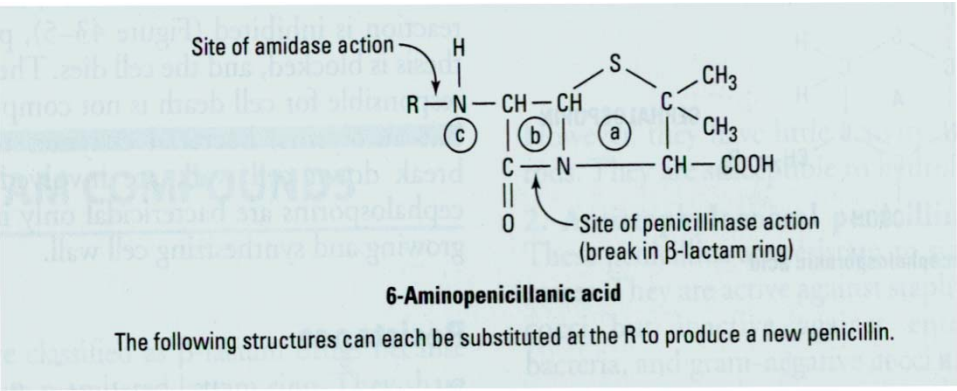
In 1928, penicillin was accidentally discovered by Dr. Alexander Fleming when he noted the antibacterial activity of a mold, *Penicillium notatum*, that was contaminating bacterial culture plates in his laboratory. Due to difficulties with purification and production, penicillin was not used in the treatment 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 VK** | **60-73** | 75-89 | 0.5 | Renal | Yes | Yes | Oral |
| **Procaine Penicillin G** | -- | ~65 | **1.4 – 3.2** | Renal/hepatic | Yes | No recs | IM |
| **Benzathine Penicillin G** | -- | ~60 | **>300** | Renal | Minimal | No recs | IM |
| **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 (0-5%)** | **No recs** | Oral |
| **Nafcillin** | -- | 70-90 | 0.5-1.5 | **Hepatic** | **Minimal** | **No recs** | IV, IM |
| **Oxacillin** | 30-35 | 89-94 | 0.3-0.9 | **Hepatic** | **Minimal** | **No recs** | 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.

From: Basic and Clinical Pharmacology, 10th edition, 2007, page 732

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

# 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 and 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.

Cephalosporins, Carbapenems, Monobactams

| Gen | Drug | SE/AEs | Spectrum | Indications | Misc |
|---|---|---|---|---|---|
| **1st** | Cephalothin IV<br>Cephalexin PO<br>Cefazolin IV<br>Cefadroxil PO | Allergy, hives, anaphylaxis, rash<br>5-10% cross reactive with PCN allergy<br>Cdiff | Gram +<br>Some Gram –<br>PEK | Skin infections<br>Some UTIs | |
| **2nd** | Cefamandole IV<br>Cefaclor PO<br>Cefuroxime IV/PO<br>Cefoxitin IV<br>Cefotetan IV | | Gram +<br>More Gram –<br>HEN-PEK | | Anaerobes: cefotetan, cefoxitin<br>MTT side chang of cefamandole, cefotetan affect Vit K clotting factor synthesis<br>Interferes with EtOH metab |
| **3rd** | Ceftriaxone IV<br>Ceftazidime IV<br>Cefotaxime IV<br>Cefpodoxime PO<br>Cefperazone IV | | More gram –<br>No anaerobes<br>Some Gram + | Meningitis<br>pneumonia | Ceftaz & cefaperazone vs Pseudomonas<br>Ceftriaxone – good CNS activity |
| **4th** | Cefepime IV | | As above+<br>Pseudomonas | HCAP | No anaerobes |
| **5th** | Ceftaroline IV<br>Ceftolozane-tazo IV | | Gram +, MRSA<br>Resistant GNRs | SSSTI<br>IAIs | |
| **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 | | | | |

| | | | | | |
|---|---|---|---|---|---|
| **mono** | Aztreonam IV | Hypersensitivity no Xreactive with PCN; GI, drug Fever, phlebitis, | Gram - only | | Vs. Pseudomonas,<br>pcn allergic, CNS penetratn |
| | | | | | |

# CEPHALOSPORINS

**Original Handout written by S. Erdman, Pharm.D. presented by G. Reid, M.D.**

## I. INTRODUCTION

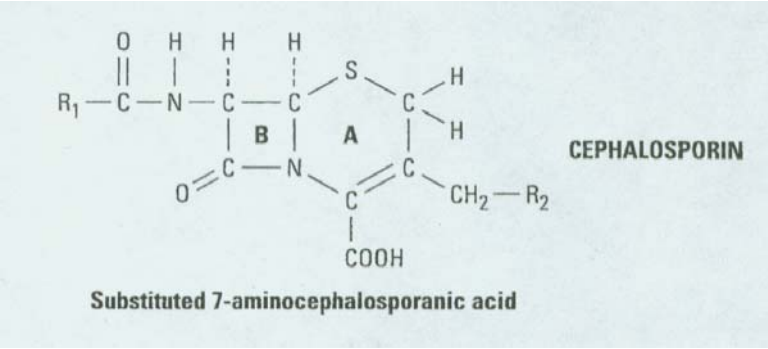
Cephalosporins are semisynthetic β-lactam antibiotics that are structurally and pharmacologically related to the penicillins. The first source of cephalosporins, a fungus named *Cephalosporium acremonium*, was isolated in 1948. The crude filtrates from this fungus were found to inhibit the *in vitro* growth of *Staphylococcus aureus*, as well as treat staphylococcal infections and typhoid fever in humans.

## II. CHEMISTRY

A. Cephalosporins contain a β-lactam ring where the 5-membered thiazolidine ring of the penicillins is replaced by a 6-membered dihydrothiazine ring. This structural difference **provides stability against many β-lactamase enzymes that render the penicillins inactive**.

B. Structural modifications at position 7 of the β-lactam ring are associated with changes in antibacterial activity, while changes at position 3 of the dihydrothiazine ring are associated with changes in the pharmacokinetic properties of the cephalosporins.

C. Cephamycins are cephalosporins with a methoxy group at position 7 of the β-lactam ring (confers activity against anaerobes such as *Bacteroides* spp.).




A = dihydrothiazine ring, B = β-lactam ring, R = acyl side chain

## III. MECHANISM OF ACTION

A. Cephalosporins, like penicillins, interfere with 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 include transpeptidases, carboxypeptidases, and endopeptidases that are responsible for peptidoglycan cross-linking. 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 wall that leads to decreased bacterial growth, bacterial cell lysis, and death.

D. Cephalosporins, like all β-lactam antibiotics, are **bactericidal**.

## IV. MECHANISMS OF RESISTANCE

A. There are **3** primary mechanisms of resistance to cephalosporins

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.

d. ***Cephalosporins have variable susceptibility*** to β-lactamases; 3rd and 4th generation cephalosporins are the most resistant to hydrolysis by β-lactamase enzymes produced by gram-negative aerobic bacteria.

e. Some bacteria (SPICE) have the ability to produce β-lactamase enzymes when exposed to antibiotics that induce their production – these are called inducible β-lactamases (such as during treatment of *Enterobacter spp.* infections with ceftazidime).

2. Alterations in PBPs that lead to decreased binding affinity of cephalosporins to PBPs (e.g., methicillin-resistant *S. aureus*, penicillin-resistant *S. pneumoniae*).

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

## V. CLASSIFICATION AND SPECTRUM OF ACTIVITY

A. Currently-available cephalosporins are divided into 4 major groups, called "generations", based primarily on their antimicrobial activity and stability against β-lactamase enzymes.

B. **In general, 1st generation cephalosporins are best for gram-positive aerobes with activity against a limited number of gram-negative aerobes. As you move down the generations to 2nd and 3rd, gram-positive activity decreases with an increase in activity against gram-negative aerobes. Fourth generation cephalosporins are active against gram-positive and gram-negative aerobes**. **Also see greater stability against β-lactamase enzymes as you move through the generations.**

1. **First Generation Cephalosporins**

a. Excellent activity against gram-positive aerobes - the **best activity of all cephalosporins**

Methicillin-susceptible *Staphylococcus aureus* (**MSSA**)
Penicillin-susceptible *Streptococcus pneumoniae*
Group A (*S. pyogenes*) and Group B streptococci (*S. agalactiae*)
Viridans streptococci

b. Also have activity against a limited number of gram-negative aerobes (**PEK**):

***P****roteus mirabilis*
***E****scherichia coli*
***K****lebsiella pneumoniae*

c. Examples of 1st generation cephalosporins (*most often used)

| Generic Name | Brand Name | Route of Administration |
|---|---|---|
| **cefazolin*** | Ancef®, Kefzol® | intravenous |
| cephalothin | Keflin®, Seffin® | intravenous |
| cephradine | Velosef®, Anspor® | intravenous, oral |
| cephapirin | Cefadyl® | intravenous |
| **cephalexin*** | Keflex®, Keftab®, Biocef® | oral |
| cefadroxil | Duricef®, Ultracef® | oral |

2. **Second Generation Cephalosporins** (includes cephamycins and carbacephems)

a. Differences exist in the spectrum of activity among 2nd generation agents because of their structural variability.

b. In general, are slightly less active than 1st generation agents against gram- positive aerobes such as staphylococci and streptococci (MICs are higher), but are more active against gram-negative aerobes, and for some 2nd generation agents (cephamycins), anaerobes.

c. Gram-positive aerobes - 2nd generation agents have activity against the **same** bacteria as 1st generation agents, with MICs similar to or slightly higher than 1st generation agents. Cefprozil and cefuroxime have the best gram-positive coverage; cefoxitin and cefotetan have the worst.

d. Gram-negative aerobes - display activity against ***P.*** *mirabilis,* ***E.*** *coli*, and ***K.*** *pneumoniae* like the 1st generation cephalosporins, but they have expanded coverage including:

***H****aemophilus influenzae*
*Moraxella catarrhalis*
***N****eisseria spp.*

In addition, may be active against some strains of *Citrobacter* and ***E****nterobacter* that are resistant to 1st generation agents (**HENPEK**).

e. Anaerobes - only **cefoxitin, cefotetan** and **cefmetazole** (the cephamycins) are active against anaerobes including *Bacteroides fragilis* (cefoxitin is the best).

f. Examples of 2nd generation cephalosporins (* most common)

| Generic Name | Brand Name | Route of Administration |
|---|---|---|
| **cefuroxime*** | Kefurox®, Zenacef® | intravenous and oral |
| cefamandole | Mandol® | intravenous |
| cefonicid | Monocid® | intravenous |
| cefaclor | Ceclor® | oral |
| **cefprozil*** | Cefzil® | oral |
| ***Carbacephems*** | | |
| loracarbef | Lorabid® | oral |
| ***Cephamycins*** | | |
| **cefoxitin*** | Mefoxin® | intravenous |
| cefotetan | Cefotan® | intravenous |
| cefmetazole | Zefazone® | intravenous |

3. **Third Generation Cephalosporins**

a. In general, are less active than 1st or 2nd generation agents against gram-positive aerobes, but have enhanced activity against gram-negative aerobes.

b. Gram-positive aerobes - **ceftriaxone** and **cefotaxime** have the best activity (among the only cephalosporins that have activity against **penicillin-resistant *S. pneumoniae***), which is thought to be less than 1st or 2nd generation agents; other 3rd generation cephalosporins have relatively poor activity.

c. Gram-negative aerobes - expanded spectrum of activity than the 2nd generation agents (**HENPECKSSS and more**) including:

***P****. mirabilis,* ***E****. coli,* ***K****. pneumoniae* (better than 1st and 2nd generation agents)
***H****. influenzae, M. catarrhalis,* ***N****eisseria gonorrhoeae* (**even β-lactamase producing strains**)
*Neisseria meningitidis*
***C****itrobacter spp.,* ***E****nterobacter spp.* (less with oral agents)
*Morganella spp., Providencia spp*., ***S****erratia marcescens*
***S****almonella spp.,* ***S****higella spp.*
***Pseudomonas aeruginosa*** **- only ceftazidime and cefoperazone**

d. Anaerobes - very limited activity (ceftizoxime has marginal activity)

e. Select 3rd generation cephalosporins (especially ceftazidime) are strong inducers of extended spectrum β-lactamases (type 1 or Class C) in gram-negative aerobic bacteria (*Enterobacter spp)*

f. Examples of 3rd generation cephalosporins (* most commonly used)

| Generic Name | Brand Name | Route of Administration |
|---|---|---|
| cefotaxime | Claforan® | intravenous |
| **ceftriaxone*** | Rocephin® | intravenous |
| **ceftazidime*** | Fortaz®, Tazidime®, Tazicef® | intravenous |
| cefoperazone | Cefobid® | intravenous |
| ceftizoxime | Cefizox® | intravenous |
| moxalactam | no longer commercially available | |
| cefixime | Suprax® | oral |
| **cefpodoxime*** | Vantin® | oral |
| ceftibuten | Cedax® | oral |
| cefdinir | Omnicef® | oral |

4. **Fourth generation cephalosporins**

a. Considered a 4th generation cephalosporin for 2 reasons

i. Extended spectrum of activity, including many gram-positive and gram-negative aerobes (NOT anaerobes)

**Gram-positive aerobes**: coverage against staphylococci and streptococci similar to ceftriaxone and cefotaxime

**Gram-negative aerobes**: displays similar coverage against gram-negative aerobes as 3rd generation agents, including:

***Pseudomonas aeruginosa***
**β-lactamase producing *Enterobacter* and *E. coli***

ii. Excellent stability against β-lactamase hydrolysis; is a relatively **poor inducer** of extended spectrum β-lactamases (type 1 or Class C) in gram-negative aerobic bacteria.

b. 4th generation cephalosporin example

| Generic Name | Brand Name | Route of Administration |
|---|---|---|
| **cefepime*** | Maxipime® | intravenous |

5. **Fifth Generation cephalosporins**

a. Extended activity against respiratory pathogens, MRSA, MDROs. Both intravenous.

i. Ceftaroline: activity against MRSA

a. Skin & skin structure infections
b. Community acquired bacterial pneumonia

ii. Ceftolozane-tazobactam: Beta-lactam resistant GNRs, including Pseudomonas;

a. complicated UTI including pyelonephritis

b. complicated intra-abdominal infections, with metronidazole

C. Overall, cephalosporins are **not active** against **methicillin-resistant *Staphylococcus aureus* (MRSA)** and coagulase-negative staphylococci, ***Enterococcus spp.,*** *Listeria monocytogenes*, *Legionella pneumophila*, *Clostridium difficile*, *Stenotrophomonas maltophilia*, and *Campylobacter jejuni*.

## VI. PHARMACOLOGY (see Table on page 9)

A. General pharmacologic properties of cephalosporins

1. Orally-available cephalosporins are well absorbed from the gastrointestinal tract; however, serum concentrations are lower than those achieved with parenteral dosing. The influence of food on the absorption of individual agents is listed in the pharmacokinetic table.

2. Most cephalosporins are widely distributed into tissues and fluids including pleural fluid, synovial fluid, bone, bile, placenta, pericardial fluid and aqueous humor. Adequate concentrations in the cerebrospinal fluid (CSF) are **NOT** obtained with 1st and most 2nd generation cephalosporins. Therapeutic concentrations of **parenteral cefuroxime, parenteral 3rd, and 4th generation** cephalosporins are attained in the CSF, especially in the presence of inflamed meninges.

3. Most cephalosporins are eliminated unchanged by the kidneys via glomerular filtration and tubular secretion, and require dosage adjustment in the presence of renal insufficiency. The **exceptions** include **ceftriaxone** and **cefoperazone,** which are eliminated by the biliary system and the liver, respectively. Most cephalosporins are removed during hemodialysis and require supplemental dosing after a hemodialysis procedure, with the exception of **ceftriaxone.**

4. Most cephalosporins have relatively short elimination half-lives (< 2 hours), and require repeated daily dosing (3 to 4 times daily) to maintain therapeutic serum concentrations. **Exceptions** include **ceftriaxone (8 hours),** cefonicid (4.5 hours), cefotetan (3.5 hours), and cefixime (3.7 hours)**.**

B. **Dosing guidelines** for the cephalosporins in the presence of normal renal and hepatic function

| **Antibiotic and Route of Administration** | **Adult Dosage** | **Pediatric Dosage** |
|---|---|---|
| ***1st generation*** | | |
| cefazolin (IV) | 1 - 2 grams every 8 hours | 25 - 100 mg/kg/day in 3 to 4 divided doses |
| cephalothin (IV) | 1 - 2 grams every 4 hours | 60 - 100 mg/kg/day in 4 to 6 divided doses |
| cephalexin (PO) | 250 - 500 mg every 6 hours | 25 - 50 mg/kg/day in 4 divided doses |
| cefadroxil (PO) | 500 - 1,000 mg twice daily | 30 mg/kg/day in 2 divided doses |
| ***2nd generation*** | | |
| cefuroxime (IV) | 0.75 - 1.5 g every 8 hours | 75 - 100 mg/kg/day in 3 divided doses given every 8 hours |
| cefoxitin (IV) | 2 g every 6 hours | 80 - 160 mg/kg/day in 4 to 6 divided doses |
| cefotetan (IV) | 1 to 2 grams every 12 hours | 40 - 60 mg/kg/day in 2 divided doses |
| cefuroxime (PO) | 250 - 500 mg twice daily | 125 - 250 mg twice daily |
| cefprozil (PO) | 250 - 500 mg twice daily | 15 mg/kg twice daily |
| ***3rd generation*** | | |
| cefotaxime (IV) | 1 - 2 g every 6 to 8 hours | 50 - 180 mg/kg/day in 4 divided doses |
| ceftriaxone (IV) | 1 - 2 g **every 12-24 hours** | 50 - 100 mg/kg/day divided every 12 hours (max 4 g/day) |
| ceftazidime (IV) | 1 - 2 g every 8 hours | 90 - 150 mg/kg/day in 3 divided doses |
| cefixime (PO) | 400 mg once daily | 8 mg/kg/day once daily |

| | | |
|---|---|---|
| cefpodoxime (PO) | 100 - 400 mg every 12 hours | 10 mg/kg/day divided every 12 hours |
| ceftibuten (PO) | 400 mg once daily | 9 mg/kg once daily |
| cefdinir (PO) | 300mg twice daily | 7 mg/kg twice daily |
| ***4th generation*** | | |
| cefepime (IV) | 0.5 - 2 g every 8 to 12 hours | up to 50 mg/kg every 8 hours has been used, not approved |
| ***5th generation*** | | |
| ceftaroline | 600 mg IV every 12 hours | |
| ceftolozane-tazobactam | 1.5 gm IV every 8 hours | |

## CEPHALOSPORIN PHARMACOKINETIC TABLE

| GENERIC NAME | PEAK SERUM CONC (µg/ml) | | CSF CONC (µg/ml) | ROUTE OF ELIMINATION | HALF-LIFE hrs | EFFECT OF FOOD ON PEAK CONC | SERUM PROT BIND % |
|---|---|---|---|---|---|---|---|
| 1st generation | | | | | | | |
| Cefazolin - IV | 80 | (1 g) | | Renal | 1.8 | | 80 |
| Cephalothin - IV | 30 | (1 g) | | Renal | 0.6 | | 71 |
| Cephalexin - PO | 18 | (0.5 g) | | Renal | 0.9 | None | 10 |
| Cefadroxil - PO | 16 | (0.5 g) | | Renal | 1.2 | None | 20 |
| Cephradine - PO | 10 | (0.5 g) | | Renal | 0.7 | None | 10 |
| 2nd generation | | | | | | | |
| Cefamandole - IV | 150 | (2 g) | | Renal | 0.8 | | 75 |
| Cefonicid - IV | 260 | (2 g) | | Renal | **4.5** | | 98 |
| Cefuroxime - IV | 100 | (1.5 g) | **1.1 - 17** | Renal | 1.3 | | 35 |
| Cefoxitin - IV | 150 | (2 g) | | Renal | 0.8 | | 70 |
| Cefotetan - IV | 230 | (2 g) | | Renal | **3.5** | | 90 |
| cefuroxime axetil - PO | 8 - 9 | (0.5 g) | | Renal | 1.3 | Increased | 35 |
| Cefaclor - PO | 13 | (0.5 g) | | Renal | 0.8 | **Decreased** | 25 |
| Cefprozil - PO | 10 | (0.5 g) | | Renal | 1.2 | None | 42 |
| Loracarbef - PO | 15 | (0.4 g) | | Renal | 1.1 | **Decreased** | 35 |
| 3rd generation | | | | | | | |
| Cefotaxime - IV | 130 | (2 g) | **5.6 - 44** | Renal | 1.0 | | 35 |
| Ceftriaxone - IV | 250 | (2 g) | **1.2 - 39** | **Biliary/renal** | **8.0** | | 83 - 96 |
| Ceftizoxime - IV | 130 | (2 g) | **0.5 - 29** | Renal | 1.7 | | 30 |
| Cefoperazone - IV | 250 | (2 g) | | **Hepatic** | 2.0 | | 87 - 93 |
| Ceftazidime - IV | 160 | (2 g) | **0.5 - 30** | Renal | 1.8 | | 17 |
| Cefixime - PO | 3.9 | (0.4 g) | | Renal | **3.7** | None | 67 |
| Cefpodoxime axetil - PO | 4 | (0.4 g) | | Renal | 2.2 | Increased | 40 |
| Ceftibuten - PO | 11 | (0.2 g) | | Renal | 2.5 | None | 63 |
| Cefdinir - PO | 2.87 | (0.6 g) | | Renal | 1.8 | None | 60 - 70 |
| 4th generation | | | | | | | |
| Cefepime - IV | 150 | (2 g) | yes, unknown | Renal | 2.1 | | 20 |
| cefpirome | 100 | (1 g) | **1.3 - 7.5** | Renal | 2.0 | | 10 |

## VII. CLINICAL USES

### A. First generation cephalosporins

1. Orally-administered 1st generation cephalosporins achieve lower serum concentrations than parenteral agents and should only be used for the treatment of mild to moderate skin infections or uncomplicated urinary tract infections.

2. Treatment of skin and soft tissue infections, septic arthritis, osteomyelitis, and endocarditis due to **MSSA** and **streptococci**.

3. **Cefazolin is the drug of choice for surgical prophylaxis** against surgical site infections for many surgical procedures because of its activity against staphylococci; can usually be administered as a single preoperative dose.

4. First generation cephalosporins have coverage against a few gram-negative aerobes and can be used for the treatment of urinary tract infections (oral or intravenous) or bacteremias (intravenous) due to susceptible organisms (**PEK**).

5. First generation cephalosporins do not penetrate the central nervous system, and should **NOT** be used for meningitis.

### B. Second generation cephalosporins

1. Due to their activity against gram-positives and expanded spectrum of activity against gram-negative bacteria including *H. influenzae* and *M. catarrhalis*, oral 2nd generation agents, such as cefuroxime, are useful for the treatment of pharyngitis, tonsillitis, sinusitis, otitis media, bronchitis and mild to moderate community-acquired pneumonia.

2. Oral 2nd generation cephalosporins are also useful for the treatment of mild to moderate skin and soft tissue infections, and uncomplicated urinary tract infections due to susceptible bacteria.

3. Although cefuroxime does penetrate the central nervous system, adequate CSF bactericidal activity is not routinely achieved so that it is **no longer recommended for the treatment of meningitis**.

4. The **cephamycins, cefoxitin, cefotetan, and cefmetazole**, have activity against gram-negative aerobes and anaerobes, including ***Bacteroides fragilis,*** so they are useful for prophylaxis in abdominal surgical procedures and for the treatment of **polymicrobial infections** such as intraabdominal infections (diverticulitis, appendicitis, bowel perforation), pelvic infections (pelvic inflammatory disease), and skin and soft tissue infections in patients with diabetes.

C. **Third generation cephalosporins**

1. Due to expanded activity against gram-negative aerobes, 3rd generation cephalosporins are used for the treatment of bacteremia, pneumonia, complicated urinary tract infection, peritonitis, intraabdominal infections, skin and soft tissue infections, bone and joint infections, and meningitis (those that penetrate the CSF) caused by gram-negative bacteria (nosocomial infections). If ***Pseudomonas aeruginosa*** **is known or suspected**, **ceftazidime or cefoperazone** should be used. If anaerobes are known or suspected, metronidazole or clindamycin should be added.

2. **Ceftriaxone** is used as a single IM dose for **uncomplicated gonorrhea**.

3. **Cefotaxime and ceftriaxone** have good activity against gram-positive aerobes, and may be used for the treatment of infections due to **penicillin-resistant *Streptococcus pneumoniae*** (meningitis, pneumonia). Ceftriaxone can be used for the treatment of viridans strep endocarditis in clinically stable patients as outpatient parenteral therapy.

4. Oral third generation cephalosporins are used for the treatment of uncomplicated urinary tract infections, acute otitis media, minor soft tissue infections, and acute sinusitis.

D. **Fourth generation cephalosporins**

1. Cefepime is used for the treatment of community- and hospital-acquired pneumonia, bacteremia, uncomplicated and complicated urinary tract infections, skin and soft tissue infections, intraabdominal infections gram-negative meningitis, and empiric therapy for febrile neutropenia. **Cefepime also has antipseudomonal activity.** If anaerobes are known or suspected, metronidazole or clindamycin should be added.

**E. Fifth generation cephalosporins**

1. Ceftaroline is used for community acquired pneumonia and skin and skin structure infections. It has minimal gram negative activity: Haemophilus, Moraxella – respiratory pathogens
2. Activity against staphylococcus and streptococcus, including multidrug resistant pneumococcus and MRSA.
3. Dose adjust in renal impairment
4. Ceftolozane-tazobactam is used for intraabomdinal infections and complicated UTIs, particularly due to drug resistant gram negative rods.

## VIII. ADVERSE EFFECTS

A. Hypersensitivity - 5%

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

2. **Hypersensitivity reactions to cephalosporins occur most frequently in patients with a history of penicillin allergy. The degree of cross-reactivity is 5 to 15%,** and clinicians must consider the allergic reaction to penicillin (? IgE mediated) and the degree of cross-reactivity when deciding if a cephalosporin should be used in a patient with a history of allergy to penicillin.

   a. Immediate or accelerated hypersensitivity reactions (anaphylaxis, laryngeal edema, hives, bronchospasm) – avoid other cross-reactive β-lactams, such as cephalosporins.

   b. Delayed hypersensitivity reactions (rash, pruritus) – give other β-lactams with caution keeping in mind the degree of cross-reactivity.

3. Other skin reactions include Stevens-Johnson syndrome, erythema multiforme, toxic epidermal necrolysis, and exfoliative dermatitis.

B. Some cephalosporins have a 5-NMTT side chain (nitromethylthiotetrazole) that confers unique adverse effects.

1. **Cephalosporins with the NMTT side chain include cefamandole, cefotetan, cefmetazole, cefoperazone,** and **moxalactam**.

2. ***Hypoprothrombinemia*** with or without bleeding due to blocking of enzyme in vitamin K metabolism or reduction of vitamin K producing bacteria in the GI tract. Moxalactam also reduces platelet aggregation that significantly increased the incidence of bleeding.

3. ***Disulfiram reaction*** (ethanol intolerance).

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.

2. Biliary sludging – with **ceftriaxone** therapy.

3. Nausea, vomiting.

4. **Pseudomembranous colitis (*Clostridium difficile* diarrhea)**. Some cephalosporins may cause diarrhea that is not due to *C. difficile*.

E. Precipitation of ceftriaxone with IV calcium products – avoid coadministration.

F. Other adverse effects include phlebitis; drug fever; interstitial nephritis (rare); neurotoxicity; nonconvulsive status epilepticus (cefepime, ceftazidime).

# CARBAPENEMS

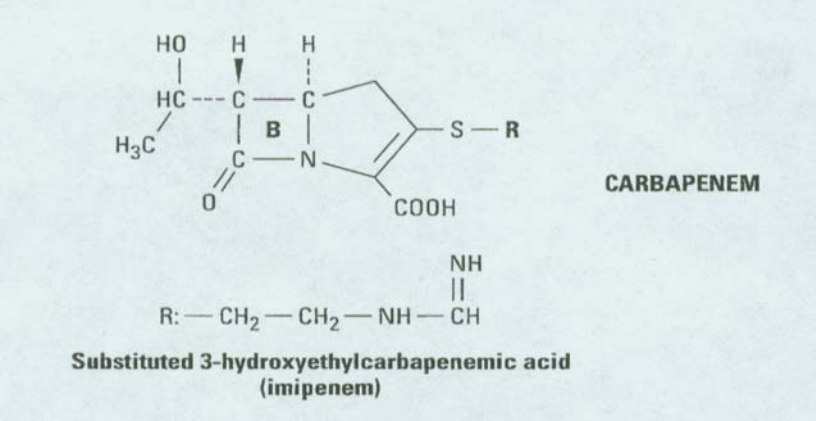
## I. INTRODUCTION

The carbapenem antibiotics, β-lactam antibiotics with a carbapenem nucleus, were initially discovered in the mid-1970s. The clinical development of the carbapenems was delayed due to chemical instability and toxicity (nephrotoxicity and neurotoxicity) associated with earlier compounds in this class. Currently, four carbapenem antibiotics are commercially available in the United States: imipenem, the first carbapenem antibiotic, received FDA approval in 1986, meropenem received FDA approval in 1996, ertapenem received FDA approval in 2001, and doripenem received FDA approval in 2007.

## II. CHEMISTRY

A. Carbapenems are β-lactam antibiotics that contain a β-lactam ring fused to a 5-membered ring, like the penicillins. However, the 5-membered ring of the carbapenems contains a carbon atom at position one (hence the name, carbapenem) instead of a sulfur atom, and the addition of a double bond.

B. All carbapenems contain a hydroxyethyl group in the *trans* configuration at position 6 as compared to an acylamino group in the *cis* configuration of the penicillins and cephalosporins. This structural difference results in increased antibacterial activity and greater stability against most β-lactamase enzymes.




B = β-lactam ring

## III. MECHANISM OF ACTION

A. Like other β-lactam antibiotics, carbapenem antibiotics display time-dependent **bactericidal** activity (except against *Enterococcus*), and cause bacterial cell death by covalently binding to PBPs that are involved in the biosynthesis of bacterial cell walls.

B. Each carbapenem displays different affinities for specific PBPs, which appear to be genus-specific. The highest binding affinity for imipenem, meropenem and doripenem is PBP-2.

C. The carbapenems are zwitterions that are relatively small, which enable them to penetrate the outer membrane of most gram-negative bacteria and gain access to the PBPs more readily than many other β-lactam antibiotics.

## IV. MECHANISMS OF RESISTANCE

A. Decreased permeability as a result of alterations to outer membrane porin proteins is an important mechanism of resistance in gram-negative bacteria, particularly *Pseudomonas aeruginosa*.

B. Hydrolysis of carbapenem antibiotics by β-lactamase or carbapenemase enzymes. However, all of the carbapenems display intrinsic resistance to nearly all β-lactamases (are very stable and not destroyed), including both plasmid- and chromosomally-mediated enzymes.

C. Alterations in PBPs that lead to decreased binding affinity of the carbapenem.

## V. SPECTRUM OF ACTIVITY

A. The carbapenems are currently the **most broad-spectrum antibiotics**, with good activity against **many gram positive AND gram-negative aerobes AND anaerobes**.

B. **Gram-positive aerobes - imipenem and doripenem exhibit good activity**; meropenem and ertapenem are generally 2 to 4 times less active than imipenem

methicillin-susceptible *Staphylococcus aureus* (**MSSA**)
penicillin-susceptible *Streptococcus pneumoniae*
Groups A, B, and C streptococci
viridans streptococci
*Enterococcus faecalis* only (most strains of *E. faecium* are resistant)

C. **Gram-negative aerobes** – the carbapenems display excellent activity against many gram-negative aerobes (**doripenem and meropenem are the best**, followed by imipenem and ertapenem); differences in susceptibility exist between the agents and are species-dependent; **carbapenems display activity against β-lactamase producing strains that display resistance to other β-lactam antibiotics**

| | |
|---|---|
| *E. coli* | *Citrobacter freundii* |
| *Klebsiella spp.* | *Enterobacter spp.* |
| *Serratia marcescens* | *Proteus spp.* |
| *Morganella morganii* | *Providencia spp.* |
| *Yersinia spp.* | *Acinetobacter spp.* (not ertapenem) |

| | |
|---|---|
| *Neisseria spp.* | *Haemophilus influenzae* |
| *Moraxella catarrhalis* | *Campylobacter jejuni* |
| *Salmonella spp.* | *Shigella spp.* |

***Pseudomonas aeruginosa*** (**NOT ertapenem**)

D. **Anaerobes** – all carbapenems display excellent activity against clinically significant gram-positive and gram-negative anaerobes including:

**Gram-positive anaerobes**

| | |
|---|---|
| *Peptostreptococcus sp.* | *Peptococcus spp.* |

*Clostridium perfringens* and *tetani*

**Gram-negative anaerobes**

| | |
|---|---|
| *Bacteroides fragilis* | *Bacteroides vulgatus* |
| *Bacteroides distasonis* | *Bacteroides thetaiotamicron* |
| *Bacteroides ovatus* | *Prevotella bivia* |
| *Fusobacterium spp*. | *Veillonella parvula* |

E. The carbapenems do **NOT** have activity against **methicillin-resistant *Staphylococcus aureus* (MRSA)**, coagulase-negative staphylococci, some enterococci, ***Clostridium difficile*, *Stenotrophomonas maltophilia***, Nocardia, and **atypical bacteria**.

## VI. PHARMACOLOGY – no oral agents at this time

A. **Distribution** – all carbapenems are widely distributed in various body tissues and fluids including saliva, sputum, aqueous humor, skin, soft tissue, bone, bile, endometrium, heart valves, placenta; pleural, peritoneal, and wound fluids.

1. **CSF penetration** - only low concentrations of imipenem diffuse into the CSF following IV administration, with CSF concentrations approximately 1 to 10% of concurrent serum concentrations; **meropenem penetrates into the CSF better than imipenem and ertapenem**, with CSF concentrations up to 52% of simultaneous serum concentrations in patients with inflamed meninges

B. **Elimination**

1. The major route of elimination of all of the carbapenems is urinary excretion of unchanged drug involving both glomerular filtration and tubular secretion.

a. **Imipenem** undergoes hydrolysis in the kidney by an enzyme called dihydropeptidase (DHP) to microbiologically inactive and potentially nephrotoxic metabolites. A DHP inhibitor called **cilastatin** is added to commercially-available preparations of imipenem to prevent renal metabolism and protect against potential nephrotoxicity.

2. The elimination half-life of imipenem, meropenem and doripenem is approximately 1 hour in patients with normal renal function; **the elimination half-life of ertapenem is approximately 4 hours**.

3. **All carbapenems require dosage adjustment in patients with renal dysfunction** and are removed during hemodialysis procedures so they are usually dosed after hemodialysis.

C. **Dosing** of the carbapenems in patients with normal renal function

| | **Adult Dosage** | **Pediatric Dosage** |
|---|---|---|
| IMIPENEM | 250 mg to 500 mg IV every 6 hours (usual dose 500 mg IV every 6 hours) | 15 to 25 mg/kg IV every 6 hours (not recommended) |
| MEROPENEM | 1 to 2 grams IV every 8 hours | 20 to 40 mg/kg IV every 8 hours |
| ERTAPENEM | 1 gram IV every 24 hours | |
| DORIPENEM | 500 mg IV every 8 hours | |

## VII. CLINICAL USES - are very expensive

A. The carbapenems are very broad-spectrum antibiotics that are typically used for **polymicrobial infections** where they can be used as monotherapy such as intraabdominal infections or skin and skin structure infections in diabetic patients. **Ertapenem does not have activity against *Pseudomonas aeruginosa*.**

B. Empiric therapy for **nosocomial infections** such as serious lower respiratory tract infections, septicemia, and complicated urinary tract infections, while waiting for the results of culture and susceptibility data. **Ertapenem does not have activity against *Pseudomonas aeruginosa*.** Once results of the cultures and susceptibilities are known, therapy is often changed to a less broad spectrum and less costly (and more targeted) antimicrobial agent.

C. **Infections due to resistant bacteria, especially those organisms that produce type 1 or class C β-lactamase enzymes.**

D. Febrile neutropenia – imipenem or meropenem

E. Meningitis (children) - meropenem

## VIII. ADVERSE EFFECTS

A. **Hypersensitivity** - 3%

1. Reactions include rash, fever, pruritus, urticaria, angioedema, hypotension and anaphylaxis.

2. Cross reactivity (5 to 15%) can occur in patients who have a history of hypersensitivity to penicillins, so clinicians must consider the degree of cross reactivity and reaction to penicillin before using a carbapenem in a penicillin-allergic patient.

    a. Immediate or accelerated hypersensitivity reactions (anaphylaxis, laryngeal edema, hives, bronchospasm) – avoid other cross-reactive β-lactams, such as carbapenems.

    b. Delayed hypersensitivity reactions (rash, pruritus) – give other β-lactams with caution keeping in mind the degree of cross-reactivity.

B. **Gastrointestinal**

1. Nausea, vomiting, and diarrhea have been reported in up to 5% of patients receiving carbapenems.

2. Antibiotic-associated pseudomembranous colitis (*C. difficile*).

C. **Central nervous system – direct toxic effect**

1. Insomnia, agitation, confusion, dizziness, hallucinations, and depression.

2. **Seizures** - have been reported in patients receiving imipenem (1.5%), meropenem (0.5%), ertapenem (0.5%), and doripenem (<0.5%).

    a. Historically, initial imipenem dosage recommendations were 1 gram every 6 hours without specific guidelines for dose adjustment in renal insufficiency - may have led to the initial increased incidence of seizures. Today, 500 mg every 6 hours is used with dosage adjustments in renal dysfunction, and the incidence of seizures has decreased.

    b. **Risk factors** for the development of seizures during carbapenem therapy include preexisting CNS disorders (e.g. history of seizures, brain lesions, recent head trauma), high doses (> 2 grams imipenem per day), and the presence of renal dysfunction.

D. Other adverse effects associated with carbapenems include thrombophlebitis, neutropenia, thrombocytopenia, transient LFT increases, and yeast infections.

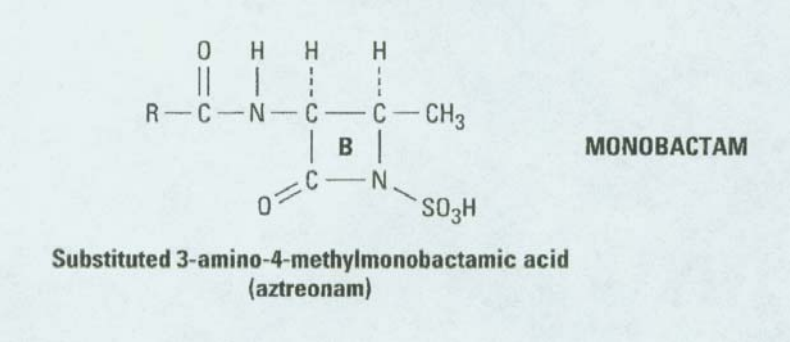
# MONOBACTAMS

## I. INTRODUCTION

Naturally occurring monobactams are produced by various bacteria found in soil, and generally have only weak antibacterial activity. Synthetic monobactams, such as aztreonam, have greater antimicrobial potency and display stability against hydrolysis by some β-lactamase enzymes. Currently, aztreonam is the only monobactam antibiotic available in the United States.

## II. CHEMISTRY

A. Aztreonam is a synthetic monocyclic, β-lactam antibiotic (monobactam). Unlike other currently available β-lactam antibiotics that are bicyclic and contain a ring fused to the β-lactam ring, aztreonam contains only a β-lactam ring with various side chains.




B = β-lactam ring

## III. MECHANISM OF ACTION

A. Like bicyclic β-lactam antibiotics, aztreonam is **bactericidal** because of its ability to bind to and inhibit PBPs and ultimately inhibit peptidoglycan synthesis, which is essential for the synthesis, assembly and maintenance of bacterial cell walls.

B. Aztreonam binds preferentially to PBP-3 in aerobic gram-negative bacilli, interfering with cell wall synthesis. Aztreonam has poor affinity for PBPs of gram-positive and anaerobic bacteria.

## IV. MECHANISMS OF RESISTANCE

A. Hydrolysis by bacterial β-lactamase enzymes - aztreonam is relatively stable against hydrolysis by some plasmid- and chromosomally-mediated β-lactamases; aztreonam is hydrolyzed by some β-lactamases produced by *Klebsiella spp.*, *Enterobacter spp.*, and *Pseudomonas aeruginosa.*

B. Alteration in outer membrane porin proteins in gram-negative bacteria leading to decreased permeability.

## V. SPECTRUM OF ACTIVITY

A. Aztreonam preferentially binds to PBP-3 in gram-negative aerobic bacteria; therefore, aztreonam **only has activity against gram-negative aerobes**.

1. **Gram-positive aerobes** - inactive

2. **Gram-negative aerobes** - aztreonam is active against a wide range of gram-negative aerobes including:

*Haemophilus influenzae*
*Citrobacter spp.*
*E. coli*
*Proteus spp.*
*Providencia spp.*
*Salmonella spp.*
***Pseudomonas aeruginosa***
*Moraxella catarrhalis*
*Enterobacter spp.*
*Klebsiella pneumoniae*
*Morganella morganii*
*Serratia marcescens*
*Shigella spp.*

3. **Anaerobes** - inactive

## VI. PHARMACOLOGY – only available IV

A. **Distribution** - Aztreonam is widely distributed into body tissues and fluids including skeletal muscle, adipose tissue, skin, bone, gallbladder, liver, lungs, prostatic tissue, endometrium, sputum, bronchial secretions, aqueous humor, bile, pleural fluid, peritoneal fluid, and synovial fluid. **Aztreonam DOES penetrate into the CSF, especially in the presence of inflamed meninges.**

B. **Elimination** - Aztreonam is excreted principally in the urine as unchanged drug. The half- life of aztreonam is 1.3 to 2.2 hours in patients with normal renal function. Doses need to be adjusted in patients with renal insufficiency, and aztreonam is removed during hemodialysis.

C. **Dosing** in normal renal function

Adults: 0.5 to 2 grams IV every 8 hours
Pediatric: 30 to 50 mg/kg IV every 8 hours

## VII. CLINICAL USES

A. Aztreonam can only be used for the treatment of **infections caused by gram-negative aerobes** such as complicated and uncomplicated urinary tract infections, lower respiratory tract infections, meningitis, bacteremia, skin and skin structure infections, intraabdominal infections, and gynecologic infections caused by susceptible gram-negative aerobes. If anaerobes are known or suspected, metronidazole or clindamycin should be added.

B. **Aztreonam is especially useful for the treatment of gram-negative infections in patients with a history of a severe penicillin allergy.**

## VIII. ADVERSE EFFECTS

A. **Hypersensitivity** - rash, pruritus, urticaria, angioedema, anaphylaxis (rare). Studies in rabbits and humans suggest that antibodies directed against penicillin show negligible cross-reactivity with aztreonam. **Because of a low to negligible incidence of cross-reactivity, aztreonam can be used in a patient with a history of penicillin allergy.**

B. **Gastrointestinal** - diarrhea, nausea, vomiting in 1 to 2% of patients

C. Other: neutropenia, thrombocytopenia, eosinophilia, transient LFT increases, phlebitis, drug fever

# AMINOGLYCOSIDES

## Drugs covered: gentamicin, tobramycin, amikacin, streptomycin

**Date: September 8, 2017**

**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 (gentamicin, tobramycin, 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 gentamicin, 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) |

# 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.

Gram Positive Antibiotics

| Drug | SE/AEs | Spectrum | Indications | Misc |
|---|---|---|---|---|
| **Vancomycin IV/PO** | Nephrotoxic<br>Red man syndr<br>Ototoxic<br>Cytopenias<br>phlebitis | GPO- MRSA, PRSP, corynebacter, bacillus, listeria, action, clostridium | Rx-resistant MRSA, endocaraditis<br>C diff colitis<br>Strep meningitis | Not vs GNRs<br>Minimal gi absorption |
| **Dalbavancin IV** | N, D, pruritus<br>Anaphylaxis<br>Skin rxn<br>Increased ALT | MRSA, PRSP | Acute bacterial SSTI | Long T1/2, 9-12 d |
| **Linezolid IV/PO** | SSRI intrxn<br>Thrombocytopenia<br>GI, h/a<br>Neuropathy<br>Lactic acidosis | MRSA, Strep, VRE, GPOs, atypicals, Baccilus, listeria, | Serious infections by resistant GPOs | Follow platelets<br>Not active vs GNRs |
| **Daptomycin IV** | Myositis<br>GI, h/a<br>Rash<br>Eosinophilic pneumonia | GPOs, MRSA, VRE | Bacteremia, endocarditis | Inactivated by surfactant<br>Follow CKs<br>Interacts with HMG CoA reductase inh → myopathy |

## 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

Protein and TH4 synthesis inhibitors, and UTI drugs

| Drug | SE/AEs | Spectrum | Indications | Misc |
|---|---|---|---|---|
| **Tetracycline IV/PO**<br>**Doxycycline IV/PO** | GI, photosensi, hepatotoxic<br>Discolor teeth<br>Fanconi syndrome if outdated | Rickettsia<br>Chlamydia<br>Mycoplasma<br>Spirochetes<br>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<br>+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<br>Gray Baby | GPC, GNRs, anaerobies | Infant Meningitis w/ pcn allergy<br>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, 8th Edition.

## 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

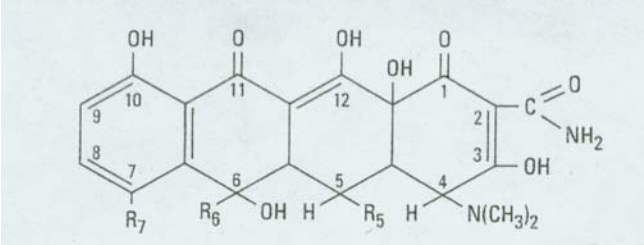
# TETRACYCLINES and GLYCYLCYCLINES

## 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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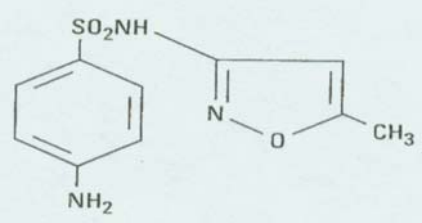
# TRIMETHOPRIM-SULFAMETHOXAZOLE (SULFONAMIDES)

## 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.

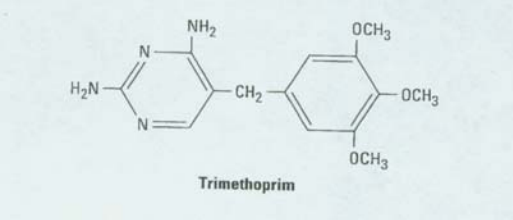
## II. CHEMISTRY

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

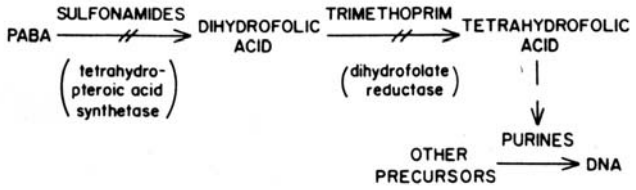



**FIG. 3.** Action of sulfonamides and trimethoprim on the metabolic pathway of bacterial folic acid synthesis.

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)<br>**Prophylaxis:** one DS tablet daily |

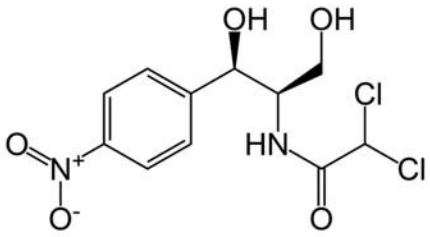
# Chloramphenicol

## 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.

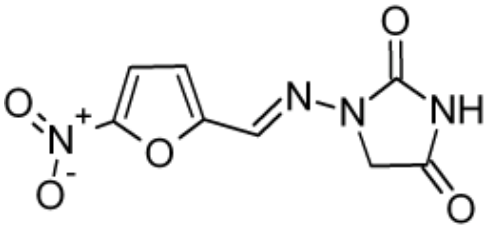
## Urinary Tract Agents (Nitrofurantoin and Methenamine)

## I. Introduction

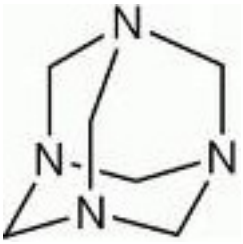
Nitrofurantoin is a weak acid and s amember of a group of synthetic nitrofuran compounds. Along with Methenamine, these two agents are used almost exclusively for treatment or prophylaxis of urinary tract infections.

## 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.

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

# Protein Synthesis Inhibitors

## Marcrolides, Ketolides, Streptogramins & Lincosamides

At the conclusion of the lecture, the audience should be able to meet the following objectives regarding protein synthesis inhibitors:

1. Identify the mechanism of action
2. Compare and contrast the appropriate clinical uses between each antibiotic
3. Describe the most common side effects associated with each medication
4. Categorize their spectrum of activity

# 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

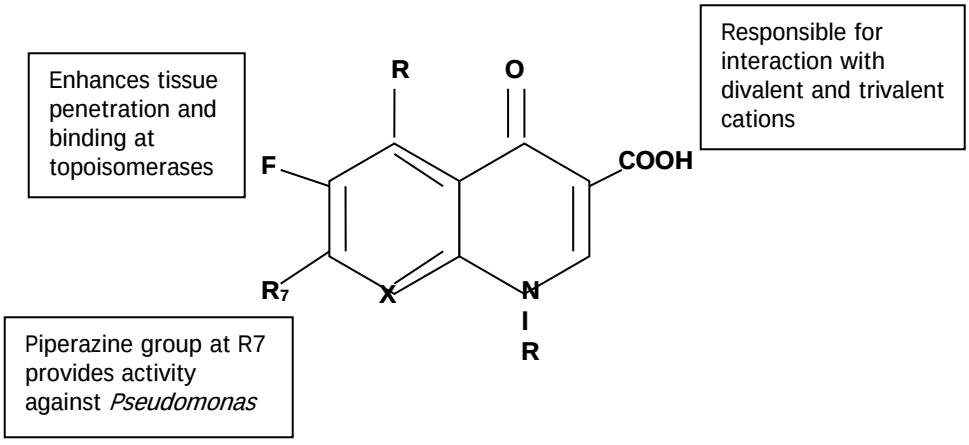
# FLUOROQUINOLONES

## 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 | | | |

# METRONIDAZOLE (Flagyl®) – IV, PO, topical

Chapter 53: Antiprotozoal Drugs. In: Katzung, BG, ed. *Basic and Clinical Pharmacology*, 11th edition, McGraw-Hill, New York, NY, 2007.

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

Lofmark S, Edlund C, Nord CE. Metronidazole Is Still the Drug of Choice for Treatment of Anaerobic Infections. Clinical Infectious Diseases 2010;50:S16-23.

## Learning Objectives:

1. Describe the mechanism of action and mechanisms of resistance of metronidazole.
2. List the spectrum of activity of metronidazole, with special emphasis on their activity against anaerobes and *Clostridium difficile.*
3. List the major clinical uses of metronidazole.
4. List the major adverse effects associated with metronidazole therapy.
5. List the major drug interactions associated with metronidazole therapy.

## Drugs Covered in this Lecture:

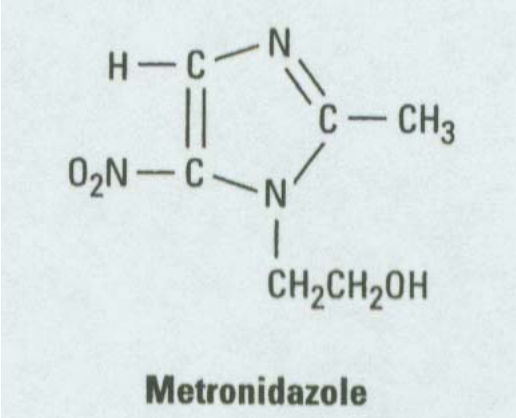
Metronidazole

## I. INTRODUCTION

Metronidazole is a synthetic nitroimidazole antibiotic originally recognized to display potent activity against certain protozoa including *Trichomonas, Giardia*, and *Entamoeba*. Studies conducted over a decade later revealed that metronidazole had extremely useful clinical activity against a wide variety of gram-positive and gram-negative anaerobic pathogens. Metronidazole is now considered one of the most useful agents in the treatment of anaerobic and polymicrobial infections in the US.

## II. CHEMISTRY

A. Metronidazole was derived from azomycin by chemical synthesis and biological testing. Its chemical name is 1-(β-hydroxyethyl)-2-methyl-5-nitroimidazole.




With permission from: Katzung's Basic and Clinical Pharmacology, 10th edition, 2007, page 857

## III. MECHANISM OF ACTION

A. Metronidazole is a prodrug that is activated by a reductive process. Its selective toxicity towards anaerobic and microaerophilic bacteria is due to the presence of electron transport components such as ferredoxins within these bacteria. Ferredoxins are small Fe-S proteins that donate electrons to metronidazole to form a highly reactive nitro radical anion.

B. These short-lived activated metabolites damage bacterial DNA (inhibit nucleic acid synthesis), and subsequently cause cell death – metronidazole is rapidly bactericidal in a concentration-dependent manner.

C. Metronidazole is catalytically recycled when loss of the electron from the active metabolite regenerates the parent compound.

D. Increased levels of oxygen inhibit metronidazole-induced cytotoxicity since oxygen competes with metronidazole for generated electrons.

## IV. MECHANISM OF RESISTANCE

A. Clinical resistance to metronidazole is well documented for *Trichomonas, Giardia*, and a variety of anaerobic bacteria, but is **relatively uncommon**.

1. **Altered growth requirements** – organism grows in higher local oxygen concentrations causing decreased activation of metronidazole and futile recycling of the active drug

2. **Altered levels of ferredoxin** – reduced transcription of the ferredoxin gene

## V. SPECTRUM OF ACTIVITY

A. Metronidazole is extremely active against a wide variety of anaerobic protozoal parasites and anaerobic bacteria**. It is the antianaerobic agent most reliably active against *Bacteroides fragilis.***

B. **Gram-negative anaerobes** – highly active against cocci and bacilli

***Bacteroides fragilis***
*Bacteroides **d**istasonis, **o**vatus, **t**hetaiotamicron, bivius*
*Fusobacterium*
*Prevotella spp.*
*Helicobacter pylori* (an obligate anaerobe)

C. **Gram-positive anaerobes** – active against cocci (variably) and sporulating bacilli

*Clostridium spp.* **(including *Clostridium difficile)***

C. **Other organisms**

*Trichomonas vaginalis*
*Entamoeba histolytica*
*Giardia lamblia*
*Gardnerella vaginalis*

E. Metronidazole is **inactive** against all common aerobic and facultatively anaerobic bacteria.

## VI. PHARMACOLOGY

### A. Absorption

1. Metronidazole is rapidly and almost completely absorbed after oral administration, achieving peak concentrations within 0.25 to 3 hours after administration.

2. Food does not affect the absorption of metronidazole, but may delay the Tmax.

3. **Serum concentrations are similar after equivalent intravenous and oral doses**. Rectal absorption is adequate but delayed, and vaginal absorption is minimal.

B. **Distribution**

1. Metronidazole is well distributed into body tissues and fluids, including vaginal secretions, seminal fluids, saliva, and breast milk. Repeated dosing results in some accumulation of the drug.

1. **Metronidazole DOES penetrate into the CSF and brain tissue** achieving 50 to 100% of simultaneous serum concentrations in the CSF depending on the degree of meningeal inflammation.

C. **Metabolism/Elimination**

1. Metronidazole is metabolized by the liver to several active metabolites. Metabolism accounts for over 50% of the systemic clearance of metronidazole.

2. Metronidazole and its metabolites are primarily excreted in the urine; only 10% is recovered as unchanged drug in the urine; 6-15% of a dose is excreted in the feces.

2. The elimination half-life in normal renal and hepatic function is 6 to 8 hours for the parent drug, and 12 to 15 hours for some metabolites. The half-life is prolonged in the presence of renal or hepatic dysfunction, so that dosage adjustments are required.

3. Metronidazole is removed during hemodialysis.

VII. **CLINICAL USES, DOSAGES, AND ADMINISTRATION** – available orally as 250mg and 500 mg tablets; 500 mg for parenteral use; intravaginal gel

A. **Infections due to anaerobes** (including serious infections) such as skin and soft tissue infections, bone and joint infections, intraabdominal and pelvic infections or abscesses, **brain abscesses**, diabetic foot infections, etc. Many serious anaerobic infections are polymicrobial, and additional agents are necessary for coverage of other causative organisms (aerobes).

1. *Oral*: 250 mg to 500 mg every 6 to 8 hours

2. *Parenteral*: typical adult dose is 500 mg every 6 hours; maximum dose is 4 grams daily

B. **Pseudomembranous colitis due to *Clostridium difficile* – DRUG OF CHOICE**

1. **Oral metronidazole is the drug of choice for mild to moderate *C. difficile* colitis**
2. *Oral **or** parenteral therapy may be used:* 250 mg to 500 mg every 6 to 12 hours

C. **Bacterial vaginosis** due to **G*ardnerella vaginalis*** – oral (500 mg twice daily for 7 days) or intravaginal therapy (5 g twice daily for 5 days)

D. ***Trichomonas vaginalis*** – 2 grams orally as a single dose; 500 mg PO twice daily for 5 days; 250 mg PO every 8 hours for 7 days

E. **Amebiasis** (intestinal or extraintestinal) – 750 mg PO or IV every 8 hours for 10 days

F. **Other: *H. pylori* (in combination with other medications** 250 mg to 500 mg PO every 8 hours*);* Crohn's diseases (intestinal bacterial overgrowth); acne rosacea; gingivitis

## VIII. ADVERSE EFFECTS

A. **MOST COMMON** = **Gastrointestinal** – nausea, diarrhea, anorexia, metallic taste**,** stomatitis, pancreatitis

B. **Central nervous system** – most serious; rare unless large doses are utilized or therapy is prolonged

1. **peripheral neuropathy (**with prolonged therapy**), s**eizures, encephalopathy, cerebellar dysfunction

2. Use with caution in patient with CNS disorders

3. If neurologic symptoms develop, the drug should be discontinued immediately

C. Other: reversible neutropenia, dark brown urine, local vaginal reactions

D. **Mutagenicity and Carcinogenicity**

1. **Metronidazole may be teratogenic – should be avoided during the first trimester and during breastfeeding**

## IX. DRUG INTERACTIONS

| Drug | Interaction |
|---|---|
| **Warfarin** | **Increased anticoagulant effect** |
| **Alcohol** | **Disulfiram reaction** |
| Phenytoin | Increased phenytoin concentrations |
| Lithium | Increased lithium concentrations |
| Phenobarbital | Decreased metronidazole concentrations |
| Rifampin | Decreased metronidazole concentrations |

A 70 year old female with a past medical history of hypertension presents to the Emergency Department with fever to 103F, nausea, vomiting and altered mental status and neck stiffness. She just returned from a 2 week vacation in Mexico, where she ate local made cheeses and other dairy products. A lumbar puncture performed reveals 500 wbc/hpf with neutrophilic predominance. As the admitting house officer, which of the following infections and appropriate therapy would you be concerned with and would start while awaiting diagnosis confirmed by cultures.

A. Neisseria - ampicillin
B. Neisseria – 2nd generation cephalosporin
C. Group B strep - ampicillin
D. Listeria - ampicillin
E. Listeria – 3rd generation cephalopsporin

A 59 year old male on hemodialysis presents with fever, chills, and rigors starting after dialysis earlier that day. He has no known drug allergies. On physical exam he is febrile to 102.8 and diaphoretic (sweating profusely) with heart rate of 118 beats per minute. Blood cultures reveal Gram positive cocci in clusters, pairs, and chains and you suspect some drug resistance since he has had several courses of antibiotic therapy in the past six months for blood stream infections. Which of the following drugs might be used to treat Vancomycin resistant enterococcus (VRE) bacteremia?

A. Ampicillin-sulbactam IV
B. Ceftriaxone IV (3rd generation cephalosporin)
C. Tigecycline IV
D. Vancomycin IV
E. Daptomycin IV

A 33 yo male with no past medical history or known drug allergies presents with penile discharge and sore of 3 days duration. He admits to unprotected sexual contact with a new partner. Laboratory testing reveals a diagnosis of syphilis. He is allergic to penicillin so is given this drug instead with the following side effect profile.

A. Aminoglycoside -ototoxicity, renal impairment
B. Nitrofurantoin – renal impairment
C. Doxycycline – photosensitivity
D. Daptomycin – nephrotoxicity
E. Imipenem - nephrotoxicity