# Pharmacology/Therapeutics I Block IV lectures

2011-2012

46.  Introduction to Antibiotics & General Principles of Antimicrobial Therapy I – O'Keefe

47.  Introduction to Antibiotics & General Principles of Antimicrobial Therapy II – O'Keefe

48.  Cell Wall Inhibitors I:  Penicillins – O'Keefe

49.  Cell Wall Inhibitors II:  Cephalosporins, Carbapenems & Monobactams – Lentino

50.  Cell Wall Inhibitors III:  Vancomycin & Misc. Antibacterial Wall Agents… - Lentino

51.  Histamine Release & Antagonists – Patel (To be posted later)

52.  Treatment of Asthma   -   Patel (To be posted later)

53.  Fluoroquinolones & Metronidazole  -  Hecht  (To be posted later)

54.  Anti-Mycobacterials  -  Pachucki

55.  Protein Synthesis Inhibitors I:  Aminoglycosides  -  Pachucki

56.  Protein Synthesis Inhibitors II:  Tetracyclines & Chloramophenicol, Sulfonamides…. – Lopansri

57.  Protein Synthesis Inhibitors III:  Macrolides, Clindamycin & Streptogramins  -  Lentino

# SPECTRUM OF ACTIVITY SUMMARY CHART

Column groups: **Penicillins** (PenG, Naf, Amp, Una/Aug, Tic, Pip, Tim/Zos); **Cephalosporins** (1st, 2nd, 3rd, 4th, Anti MRSA); **Carba** (Imi, Mero, Erta, Dor); **Mono** (Aztreo); **FQs** (Cip, Levo£/Moxi); **Mac** (Ery, Cla, Azi); **AGs** (Gent, Tob, Amik); **Vanc**; **Syner, Linez, Dapto, Telav**; **Tets¶**; **Bact**; **Col**; **Clind**; **Metro**

| Organism | PenG | Naf | Amp | Una, Aug | Tic | Pip | Tim/Zos | 1st | 2nd | 3rd | 4th | Anti MRSA | Imi, Mero, Erta, Dor | Aztreo | Cip | Levo£ Moxi | Ery, Cla, Azi | Gent, Tob, Amik | Vanc | Syner, Linez, Dapto, Telav | Tets¶ | Bact | Col | Clind | Metro |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| MSSA |  | 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 |  |  |  |
| PSSP | 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 | X |  |  |  |  |  |
| Viridans Strep | X | X | X | X |  | X | X | X | X | X‡ | X | X | X |  | ?X | X | X | X | X | X |  |  |  | X |  |
| Group Strep | X | X | X | X |  | X | X | X | X | X‡ | X | X | X |  | ?X | X | X |  | X | X |  |  |  | X |  |
| *Enterococcus* | X |  | X | X |  | X | X |  |  |  |  |  | X (E. faecalis) |  |  | ?X |  | X | X | X*** (VRE) |  |  |  |  |  |
| *H. influenzae* |  |  | X§ | X | X | X | X |  | X | X | X | X | X | X | X | X | X∞ |  |  |  | X | X | X |  |  |
| *M. catarr* |  |  |  | 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 |  |  |  |  |  |  |  |  |
| *E coli* |  |  | 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 |  |  |
| *Klebsiella* |  |  | 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 |  |  |
| *Serratia* |  |  |  |  |  | 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 |  |  |
| *Pseudomonas* |  |  |  |  | X | X | X |  |  | X† | X |  | X** | X | X | X€ |  | X |  |  |  |  | X |  |  |
| ADA | X |  | X | X |  | X | X |  |  |  |  |  | X |  |  |  |  |  | X |  |  |  |  | X | ?X |
| BDA |  |  |  | X |  | X | X |  | X* |  |  |  | X |  |  |  |  |  |  |  |  |  |  | ?X | X |
| *C. difficile* |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  | X |  |  |  |  |  | X |
| *Legionella* |  |  |  |  |  |  |  |  |  |  |  |  |  |  | X | X | X |  |  |  | X |  |  |  |  |

**MSSA = Methicillin-Susceptible *Staphylococcus aureus***
**MRSA = Methicillin-Resistant *Staphylococcus aureus***
**PSSP = Penicillin-Susceptible *Streptococcus pneumoniae***
**PRSP = Penicillin-Resistant *Streptococcus pneumoniae***
**Una = Unasyn (ampicillin/sulbactam), Aug = Augmentin (amoxicillin/clavulanate)**
**Tim/Zos = Timentin (ticarcillin/clavulanate) and Zosyn (piperacillin/tazobactam)**

**ADA = Above the Diaphragm Anaerobes**
**BDA = Below the Diaphragm Anaerobes, especially *Bacteroides* spp.**

**§ β-lactamase negative strains only**    **‡ Ceftriaxone and cefotaxime only**    **† Ceftazidime and cefoperazone only**
**\* Cephamycin antibiotics including cefotetan and cefoxitin**
**\*\* Not ertapenem**    **£ Levofloxacin with better activity against gram-negatives**    **€ Not moxifloxacin**    **∞ Azithromycin and clarithromycin only**
**\*\*\*Activity versus VRE (Synercid only vs VRE faecium; telavancin only against some VRE) - a TARGET organism**
**¶ Tigecycline with expanded coverage against gram-positive aerobes, gram-negative aerobes (except *Proteus* and *Pseudomonas*) and anaerobes**

## #46 & 47 - 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.*) | *Bacteroides spp.* |
| *Propionibacteriaceae* | *Haemophilus spp.* |
| *Bacillus spp.* | *Neisseria spp.* |
| Staphylococci (esp. coagulase-negative) | Streptococci (anaerobic) |
| Streptococci | |
| **GASTROINTESTINAL TRACT** | **GENITOURINARY TRACT** |
| *Bacteroides spp.* | *Lactobacillus spp.* |
| *Clostridium spp.* | *Corynebacterium spp.* |
| Enterobacteriaceae (*E. coli, Klebsiella spp.*) | Enterobacteriaceae – especially *E.coli* |
| Streptococci (anaerobic) | Staphylococci (*S. saprophyticus*) |
| *Enterococcus spp.* | Streptococci |
| *Fusobacterium spp.* | |

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

*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 some infections where bactericidal activity may be more predictive of a favorable outcome (meningitis, endocarditis).
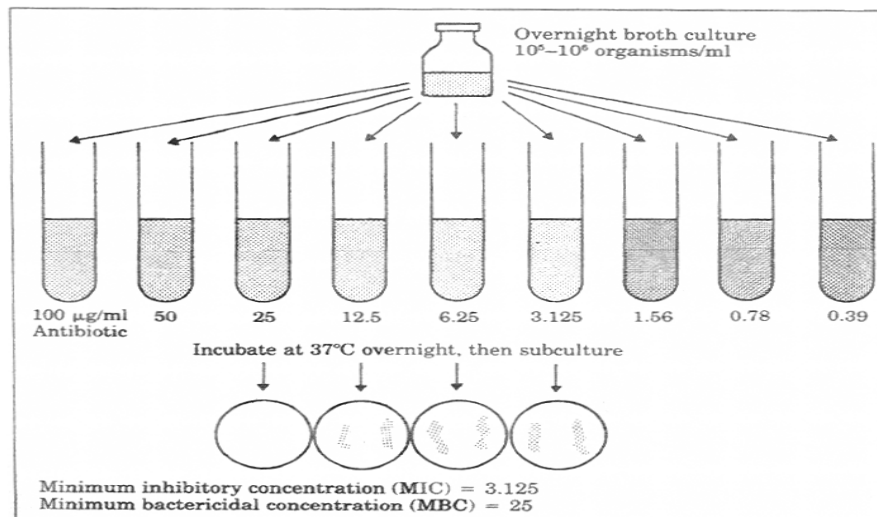


With permission from: A Practical Approach to Infectious Diseases, 4th edition, 1996, page 955

    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.
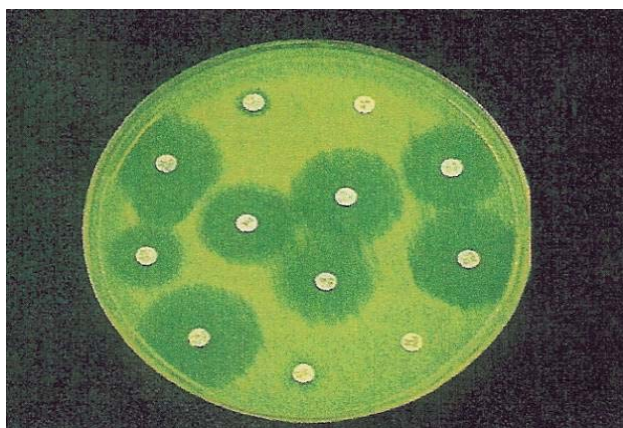


With permission from: Diagnostic Microbiology, 12th edition, 2007, page 195

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.
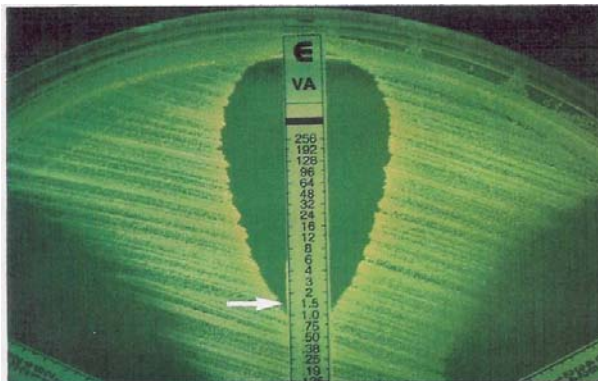
With permission from: Diagnostic Microbiology, 12<sup>th</sup> edition, 2007, page 200

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 Enterocus | 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 damaged heart valves 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.
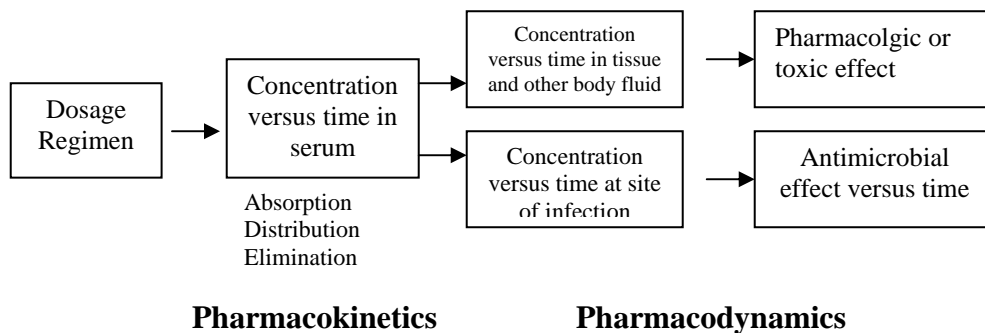
E. **Combination Therapy**
1. Combination therapy may be selected in a limited number of circumstances for the treatment of infection:
   a. To provide coverage against all organisms in a mixed, polymicrobial infection where a single antibiotic does not cover all of the infecting organisms – used to 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.

```
                              ┌──────────────────┐      ┌──────────────────┐
                              │   Concentration  │      │   Pharmacolgic or│
                              │ versus time in   │ ───▶ │   toxic effect   │
                              │ tissue and other │      │                  │
┌──────────┐   ┌────────────┐ │   body fluid     │      └──────────────────┘
│  Dosage  │   │Concentration│ └──────────────────┘
│ Regimen  │──▶│versus time  │
│          │   │ in serum    │ ┌──────────────────┐      ┌──────────────────┐
└──────────┘   └────────────┘ │   Concentration  │      │   Antimicrobial  │
                              │ versus time at   │ ───▶ │  effect versus   │
               Absorption     │  site of infection│     │      time        │
               Distribution   └──────────────────┘      └──────────────────┘
               Elimination
```

               **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
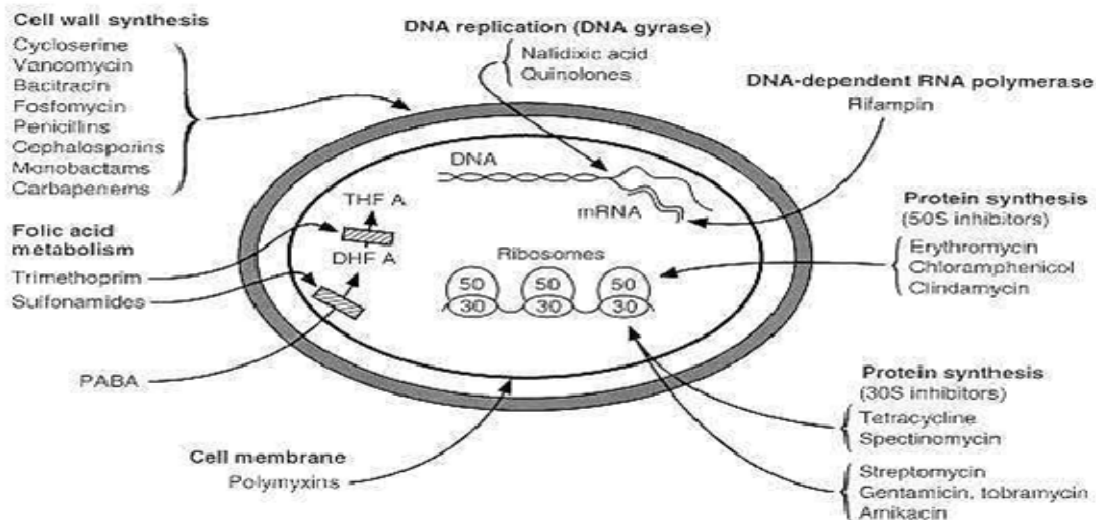
# #48 - PENICILLINS

**Date:** November 29, 2011, 8:30 – 9:20 AM

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

## Learning Objectives:

### Beta-Lactams
1.    Explain the differences in the chemical structure between the penicillins, cephalosporins, carbapenems, and monobactams.
2.    Describe the general characteristics of β-lactam antibiotics including their mechanism of action, mechanisms of resistance, pharmacodynamic properties, elimination half-life, route of elimination, and potential for cross-allergenicity.

### Penicillins
1.    Describe the differences in the spectrum of activity between the natural penicillins, the penicillinase-resistant penicillins, the aminopenicillins, the carboxypenicillins, the ureidopenicillins, and the β-lactamase inhibitor combinations with special emphasis on the specific penicillin agents that have activity against *Staphylococcus aureus*, *Pseudomonas aeruginosa*, and *Bacteroides fragilis*.  List examples of commonly used agents within each of the penicillin classes.
2.    Describe the distribution characteristics of the penicillins into the cerebrospinal fluid, urinary tract, lungs, skin/soft tissue, and bone.  List the penicillins that are not primarily eliminated by the kidneys.  List the penicillins that require dosage adjustment in renal insufficiency, and those that are removed by hemodialysis.
3.    List the penicillins that should be used with caution in patients with congestive heart failure (CHF) or renal failure due to the sodium load associated with their parenteral formulations.  List the parenteral penicillin agent that has the most mEq of sodium per gram.
4.    Discuss the main clinical uses of representative penicillins within each group of penicillins.
5.    Describe the major adverse effects associated with the penicillin antibiotics.  List the penicillins that are most likely to cause interstitial nephritis.

## 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-Clavulanate (Augmentin®)
Piperacillin-Tazobactam (Zosyn®)

**β-LACTAMS (Penicillins, Cephalosporins, Carbapenems, Monobactams)**

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

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

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

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

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

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

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

---

### #51 - PENICILLINS

**I.      INTRODUCTION**

In 1929, 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.
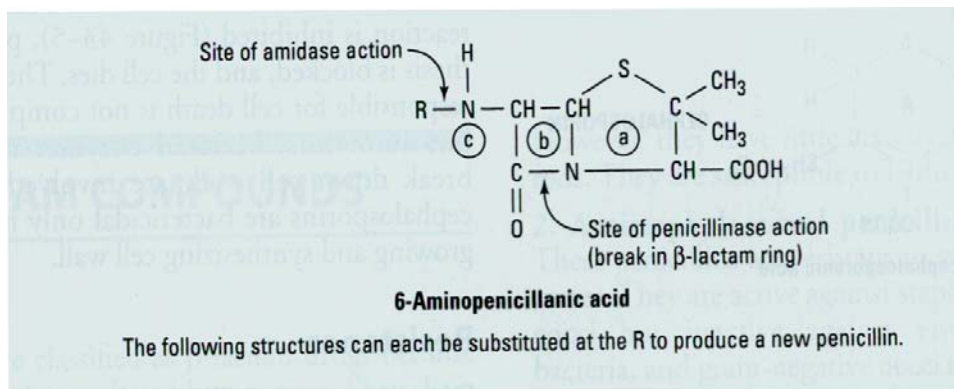
A = thiazolidine ring, B = β-lactam ring, C = acyl side chain

## 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.    **<u>Natural Penicillins</u>** - 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.*
- *Clostridium spp*. (gram-positive bacilli, "below the diaphragm"), with the exception of *C. difficile*

4.     **Other**
   - *Treponema pallidum, Actinomyces spp.*

**Penicillin G is still considered to be a <u>DRUG OF CHOICE</u> 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.     <u>**Penicillinase-Resistant Penicillins**</u>   - 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*, oxacillin, cloxacillin, and **dicloxacillin**.

   1.     **Gram-Positive**
      - **M**ethicillin **S**usceptible *Staphylococcus **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.     <u>**Aminopenicillins**</u>   - 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)
      - <u>***Better***</u> 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

<u>**Drug of Choice**</u> **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. Examples include carbenicillin and **ticarcillin**.

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*. or *Serratia 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 most broad-spectrum penicillins available without β-lactamase inhibitors. Examples include mezlocillin, azlocillin, and **piperacillin.**

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*
      - Some activity against *Bacteroides fragilis*

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 / Clavulanic Acid (Augmentin®) – PO**
  **Ampicillin / Sulbactam (Unasyn®) – IV**
  Ticarcillin / Clavulanic Acid (Timentin®) – IV
  **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 *Serratia marcescens,* **P.** *aeruginosa,* **i**ndole-positive *Proteus spp., Citrobacter spp.,* and *Enterobacter spp.* (SPICE bacteria).

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
iv.    *Extended Spectrum Penicillins* – carbenicillin available orally but with low bioavailability (30-40%); used for UTIs only

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
- Carbenicillin contains 4.7 mEq per gram
- **Ticarcillin** contains **5.2** mEq per gram (also in Timentin®)
- Piperacillin contains 1.85 mEq per gram (also in Zosyn®)

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

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

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

### Table: Pharmacokinetic Characteristics of Carboxypenicillins and Ureidopenicillins

| Drug | Sodium Content (mEq/g) | Protein Binding | Half-life (hours) | Route of Excretion | Removal by HD | Dosing Change For RI | Route of Admin |
|---|---|---|---|---|---|---|---|
| Carbenicillin | 4.7 | 50-60 | 1.1 | Renal | Yes | Yes | Oral, IM, IV |
| 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* (amoxicillin) and *Shigella* (ampicillin).

D.      **Carboxypenicillins and Ureidopenicillins**

   1.      Due to enhanced activity against gram-negative bacteria, these agents are 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*.**

   2.      May be used as *empiric* therapy in immunocompromised patients.

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. **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, nafcillin, and carbenicillin

2. Nausea, vomiting

3. Diarrhea – especially with amoxicillin-clavulanate

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** (carbenicillin and ticarcillin because they act 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, 10$^{th}$ edition, 2007, page 732

Pharmacology and Therapeutics
November 29, 2011

Cephalosporins, Carbapenems & Monobactams
Joseph R. Lentino, M.D., Ph.D.

# CEPHALOSPORINS, CARBAPENEMS, and MONOBACTAMS

**Date:** November 29, 2011 – 9:30 am

**Suggested Reading:**
Marshall WF, Blair JE. The cephalosporins. *Mayo Clinic Proceedings* 1999;74:187-95.

Hellinger WC, Brewer NS. Carbapenems and monobactams: Imipenem, meropenem, and aztreonam. *Mayo Clinic Proceedings* 1999;74:420-34.

## Learning Objectives:

1. Describe the differences in the spectrum of activity between the four generations of cephalosporins. Describe the cephalosporins that are best for *Staphylococcus aureus*, *Pseudomonas aeruginosa*, and anaerobes (*Bacteroides fragilis*, etc.).
2. List the cephalosporins that penetrate the central nervous system and achieve therapeutic concentrations in the cerebrospinal fluid. List the cephalosporin with the longest elimination half-life, which allows for dosing every 12 or 24 hours. List the cephalosporins that do not require dosage adjustment in the presence of renal insufficiency.
3. Describe the major adverse effects associated with cephalosporins. Explain the risk of cross-reactivity between penicillins and cephalosporins and describe the situations in which a penicillin-allergic patient should and should not receive a cephalosporin. List the cephalo-sporins that contain a MTT (methylthiotetrazole) side chain and describe its clinical significance.
4. List the spectrum of activity of the carbapenems and aztreonam, with special emphasis on the agents with activity against specific organisms such as *Staphylococcus aureus*, *Pseudomonas aeruginosa*, and *Bacteroides spp*.
5. Describe the distribution of the carbapenems and aztreonam into the cerebrospinal fluid, the urinary tract, the lungs, skin/soft tissue and bone. Explain the purpose of co-formulating imipenem with cilastatin. List the carbapenems and monobactams that require dosage adjustment in renal insufficiency.
6. List the major adverse effects associated with the carbapenems and aztreonam. Describe the risk factors associated with the development of central nervous system toxicity with the carbapenems. Describe the risk of cross-reactivity between penicillins and the carbapenems or aztreonam. List the antibiotic agent that can be safely used in a patient who has a history of anaphylaxis to penicillin.
7. List the clinical uses of representative agents within each generation of cephalosporins, carbapenems, and aztreonam.

## Drugs Covered in this Lecture:
**1st Generation Cephalosporins:** Cefazolin, Cephalexin
**2nd Generation Cephalosporins:** Cefuroxime, Cefoxitin, Cefotetan, Cefprozil
**3rd Generation Cephalosporins:** Ceftriaxone, Ceftazidime, Cefpodoxime
**4th Generation Cephalosporins:** Cefepime
**Carbapenems:** Imipenem, Meropenem, Ertapenem, Doripenem
**Monobactams:** Aztreonam

Pharmacology and Therapeutics
November 29, 2011

Cephalosporins, Carbapenems, and Monobactams
Joseph R. Lentino, M.D., Ph.D.
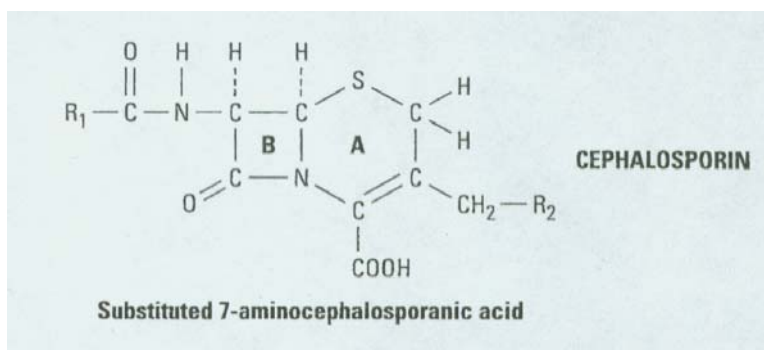
# CEPHALOSPORINS
**Original Handout written by S. Erdman, Pharm.D. presented by J. Lentino, M.D.**

## 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.

Pharmacology and Therapeutics
November 29, 2011

Cephalosporins, Carbapenems, and Monobactams
Joseph R. Lentino,M.D.,Ph.D.

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; 3$^{rd}$ and 4$^{th}$ 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).

Pharmacology and Therapeutics
November 29, 2011

Cephalosporins, Carbapenems, and Monobactams
Joseph R. Lentino, M.D., Ph.D.

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.

Pharmacology and Therapeutics
November 29, 2011

Cephalosporins, Carbapenems, and Monobactams
Joseph R. Lentino,M.D.,Ph.D.

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:

*Haemophilus influenzae*
*Moraxella catarrhalis*
*Neisseria spp.*

In addition, may be active against some strains of *Citrobacter* and *Enterobacter* 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.

Pharmacology and Therapeutics
November 29, 2011

Cephalosporins, Carbapenems, and Monobactams
Joseph R. Lentino, M.D., Ph.D.

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, Neisseria gonorrhoeae* (**even β-lactamase producing strains**)
*Neisseria meningitidis*
*Citrobacter spp., Enterobacter spp.* (less with oral agents)
*Morganella spp., Providencia spp., Serratia marcescens*
*Salmonella spp., Shigella 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)

Pharmacology and Therapeutics
November 29, 2011

Cephalosporins, Carbapenems, and Monobactams
Joseph R. Lentino, M.D., Ph.D.

**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 |

    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

Pharmacology and Therapeutics
November 29, 2011

Cephalosporins, Carbapenems, and Monobactams
Joseph R. Lentino, M.D., Ph.D.

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 |

## 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.

December 1, 2009

Cephalosporins, Carbapenems, and Monobactams
Joseph R. Lentino,M.D.,Ph.D.

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, and empiric therapy for febrile neutropenia. **Cefepime also has antipseudomonal activity.** If anaerobes are known or suspected, metronidazole or clindamycin should be added.

VIII. **ADVERSE EFFECTS**

A. Hypersensitivity - 5%

1.  Reactions include pruritus, rash (maculopapular, erythematous, or morbilloform), 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.

December 1, 2009

Cephalosporins, Carbapenems, and Monobactams
Joseph R. Lentino, M.D., Ph.D.

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 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 – especially 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).
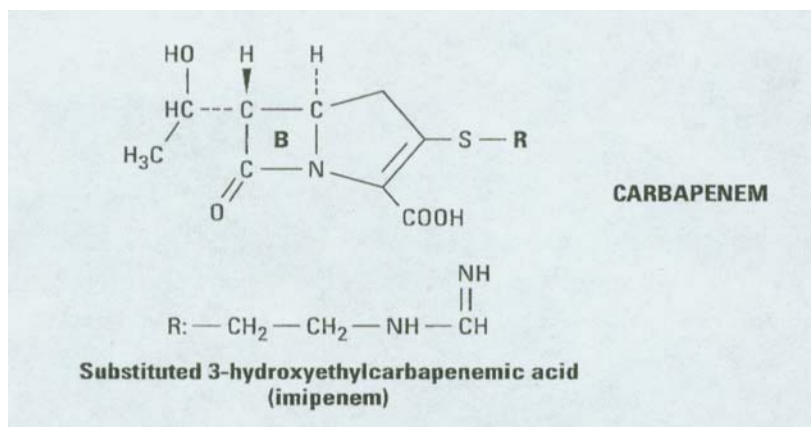
## CARBAPENEMS

### 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.



Substituted 3-hydroxyethylcarbapenemic acid
(imipenem)

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.

December 1, 2009

Cephalosporins, Carbapenems, and Monobactams
Joseph R. Lentino,M.D.,Ph.D.

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.*
*Veillonella parvula*       *Clostridium perfringens* and *tetani*

**Gram-negative anaerobes**
*Bacteroides fragilis*       *Bacteroides vulgatus*
*Bacteroides distasonis*       *Bacteroides thetaiotamicron*
*Bacteroides ovatus*       *Prevotella bivia*
*Fusobacterium spp*.

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.

December 1, 2009

Cephalosporins, Carbapenems, and Monobactams
Joseph R. Lentino,M.D.,Ph.D.

# 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
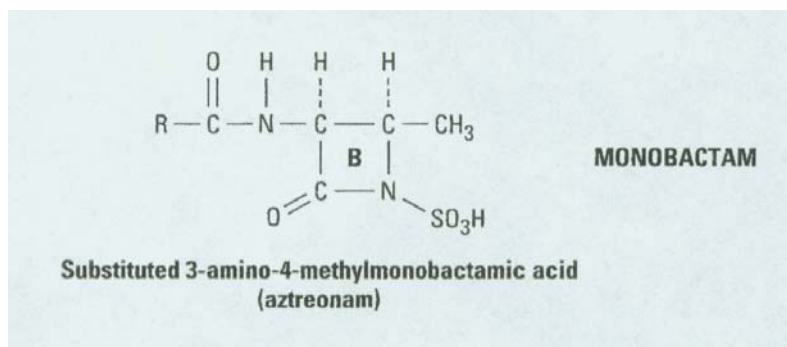
## III. MECHANISM OF ACTION

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.*

December 1, 2009

Cephalosporins, Carbapenems, and Monobactams
Joseph R. Lentino,M.D.,Ph.D.

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

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

December 1, 2009

Cephalosporins, Carbapenems, and Monobactams
Joseph R. Lentino,M.D.,Ph.D.

## 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

# VANCOMYCIN AND OTHER AGENTS WITH ACTIVITY AGAINST GRAM-POSITIVE AEROBES

**Date:**   November 29, 2011– 10:30 am

**Suggested Readings:**

Wilhelm MP, Estes L.  Vancomycin.  *Mayo Clinic Proceedings* 1999;74:928-35.

Lentino JR, Narita M, Yu,VL. New Antimicrobial agents as therapy for resistant gram-positive cocci. *Eur J Clin Microbiol Infect Dis* 2008;27:3-15

## Learning Objectives:

1.   Describe the mechanism of action of vancomycin, linezolid, and daptomycin.
2.   Describe the mechanisms by which bacteria become resistant to vancomycn, linezolid, and daptomycin.
3.   List the general spectrum of activity of vancomycin, linezolid, and daptomycin, with special emphasis on the agents that have activity against *S. aureus* (MSSA and MRSA)*,* vancomycin-resistant *Enterococcus* (VRE), and *C. difficile*.
4.   Identify the major pharmacokinetic characteristics of vancomycin, linezolid and daptomycin including bioavailability, half-life, CSF penetration, route of elimination, necessity for dosage adjustment in renal insufficiency, and removal by hemodialysis.
5.   List the major clinical uses of vancomycin, linezolid, and daptomycin.
6.   Identify the major adverse reactions associated with vancomycin, linezolid, and daptomycin.
7.   Identify the major drug interactions associated with  linezolid, and daptomycin.

## Drugs Covered in this Lecture

**Glycopeptides:**       Vancomycin

**Oxazolidinones:**      Linezolid (Zyvox[®])

**Lipopeptides:**        Daptomycin (Cubicin[®])

Final Copy Received:  11/12/09

VANCOMYCIN AND OTHER ANTIBIOTICS WITH ACTIVITY
**AGAINST GRAM-POSITIVE AEROBES**
**Original Handout written by S. Erdman, Pharm.D. presented by J. Lentino, M.D.**

I.     **INTRODUCTION**

Vancomycin has been commercially available in the United States since 1956. The original branded product underwent extensive purification over the years that led to a decrease in the incidence of adverse effects such as phlebitis and nephrotoxicity, which were commonly reported with the original compound. The clinical use of vancomycin for the treatment of infections decreased with the introduction of the antistaphylococcal penicillins (nafcillin, oxacillin, methicillin) in the 1960s and 1970s. However, the use of vancomycin has steadily increased since the 1980s due to the emergence of resistant bacteria, most notably MRSA and PRSP.

II.    **CHEMISTRY**

A.     Vancomycin is derived from *Streptomyces orientalis*, and is structurally unrelated to any other commercially available antibiotic. It is a *complex tricyclic glycopeptide*, with a molecular weight of 1500 Daltons.
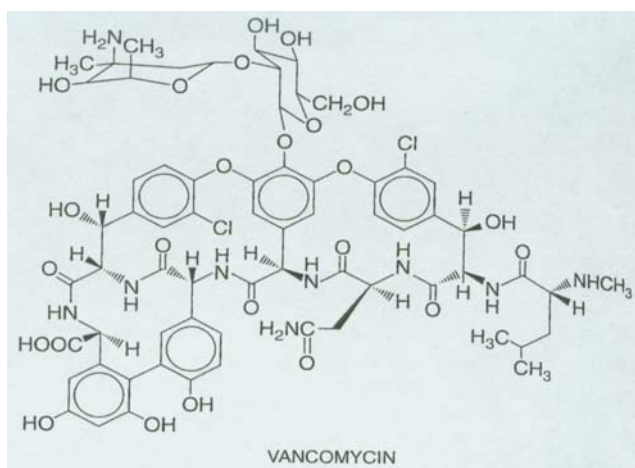


VANCOMYCIN

III.   **MECHANISM OF ACTION**

A.     Vancomycin **inhibits the synthesis of the bacterial cell wall** by blocking glycopeptide polymerization at a site different from that of the β-lactams.

B.     Vancomycin **inhibits the synthesis and assembly during the second stage** of cell wall synthesis by firmly binding to the D-alanyl-D-alanine portion of cell wall precursors. Vancomycin **prevents cross-linking and further elongation of peptidoglycan**, which weakens the cell wall making it susceptible to lysis.

Cell Wall Inhibitors III
November 29, 2011

Vancomycin and Other Gram-Positive Agents
Joseph R. Lentino,M.D.,Ph.D.

C.	Vancomycin is **bactericidal in a time-dependent manner,** except against *Enterococcus spp*. where it displays bacteriostatic activity.

IV.	**MECHANISMS OF RESISTANCE**

A.	In VRE and VRSA, resistance to vancomycin is due to **modification of the D-alanyl-D-alanine vancomycin-binding site** of the peptide side chain of the peptidoglycan precursors.  The terminal D-alanine is replaced by D-lactate, which results in the loss of a critical hydrogen bond that facilitates high-affinity binding of vancomycin to its target.  The end result is the loss of antibacterial activity.

B.	Three phenotypes of vancomycin resistance are recognized.

1.	*vanA* - most common; plasmid mediated; confers high-level, inducible resistance to both vancomycin and teicoplanin

2.	*vanB* - inducible resistance; confers low-level resistance to vancomycin but not teicoplanin

3.	*vanC* - constitutive and chromosomally mediated; confers low-level resistance to vancomycin only (species other than *E. faecalis* or *faecium*)

V.	**SPECTRUM OF ACTIVITY**

A.	Vancomycin displays activity against many **gram-positive aerobic and anaerobic bacteria**

*Staphylococcus aureus* and coagulase-negative staphylococci (**both methicillin-susceptible and methicillin-resistant strains – MSSA and MRSA**)
*Streptococcus pneumoniae* (including **penicillin-resistant strains - PRSP**)
Groups A, B, C, D, F, and G streptococci
Viridans streptococci
*Enterococcus faecalis* and *faecium* (ONLY BACTERIOSTATIC)
*Corynebacterium spp.*
*Listeria monocytogenes*
*Actinomyces*
*Clostridium spp.* (**including** *C. difficile*)

B.	In vitro studies demonstrate synergistic activity of vancomycin with gentamicin or streptomycin against *Enterococcus spp*., and with gentamicin against *Staphylococcus spp*.

C.	Gram-positive organisms that display resistance to vancomycin include select isolates of *Enterococcus faecalis* and *E. faecium*; and most isolates of *E. gallinarum*, *E. casseliflavus*, *Pediococcus spp*., and *Leuconostoc spp*.

Cell Wall Inhibitors III
November 29, 2011

Vancomycin and Other Gram-Positive Agents
Joseph R. Lentino,M.D.,Ph.D.

D.  Vancomycin is **NOT active against gram-negative aerobes or anaerobes**.

VI.  **PHARMACOLOGY**

A.  Interpatient variability exists in the pharmacokinetic characteristics of **volume of distribution and clearance of vancomycin**.
.

B.  **Absorption**

1.  Absorption of vancomycin from the gastrointestinal tract *is negligible* after oral administration.  Absorption may be enhanced in the presence of intense inflammatory colitis, and serum concentrations may accumulate after oral administration in patients with renal insufficiency.

2.  **For the treatment of systemic infections, intermittent intravenous infusion is the preferred route of administration.**

C.  **Distribution**

1.  Vancomycin is widely distributed in body tissues and fluids, including pleural fluid, synovial fluid, ascites, **adipose tissue**, and bile.  Vancomycin displays variable penetration into the CSF, even in the presence of inflamed meninges.

2.  Vancomycin takes approximately **one hour** to distribute from plasma into peripheral tissues and fluids.

3.  Interpatient variability exists in the volume of distribution:

a.  Vd adults = 0.50 to 0.65 L/kg

b.  Neonates and infants have a larger volume of distribution than adults.  Over the time span from birth to the first year of life, the volume continues to decline from an initial value of > 0.7 L/kg to the adult value of 0.5 L/kg.

c.  **Total body weight (TBW) should be used for vancomycin dosing** as it results in a more accurate approximation of the Vd.

D.  **Elimination**

1.  Intravenous vancomycin is primarily eliminated unchanged by the kidney via glomerular filtration.

Cell Wall Inhibitors III
November 29, 2011

Vancomycin and Other Gram-Positive Agents
Joseph R. Lentino,M.D.,Ph.D.

2.  In adults with normal renal function, the elimination half-life ranges between 6 and 8 hours. **The half-life progressively increases with decreases in renal function.** In patients with end-stage renal disease, the elimination half-life of vancomycin approaches **7 to 14 days**.

3.  Vancomycin is NOT appreciably removed by hemodialysis. Vancomycin may be removed by peritoneal dialysis or continuous hemofiltration.

E.  **Serum concentration monitoring**

1.  There are **no well-controlled clinical trials relating vancomycin serum concentrations to efficacy or toxicity**.

2.  Because of interpatient variability in pharmacokinetic parameters, serum concentration monitoring may be warranted in some patients (patients with renal dysfunction, changing renal function, or receiving long term therapy) to help avoid excessive serum concentrations.

3.  "Target" peak concentrations = 30 to 40 μg/ml
    "Target" trough concentrations = 5 to 15 μg/ml (some clinicians target higher trough concentrations in the treatment of meningitis, endocarditis, and osteomyelitis)

4.  **Peak concentrations** should be obtained <u>one hour after the end of infusion</u>; trough concentrations just prior to the dose.

F.  **Dosing of vancomycin**

1.  The differences in the pharmacokinetic parameters for vancomycin must be considered when determining a vancomycin dose for each patient. Factors that should be considered include the patient's volume status, renal function, age, gender, weight, concomitant drug therapy, and infection being treated, etc.

2.  Several vancomycin-dosing nomograms are available to assist with dosing based on a patient's age, weight, and renal function.

3.  Adults with normal renal function:
    10 to 15 mg/kg (typically 1 to 1.5 grams) every 12 hours

    Adults with impaired renal function:
    10 to 15 mg/kg (typically 1 to 1.5 grams) with interval based on renal function (every 18, 24, 36, 48 hours)

    Dosing Interval Depends on Renal Function:

    <u>CrCl (ml/min)</u>        <u>Initial Dosing Interval</u>

Cell Wall Inhibitors III
November 29, 2011

Vancomycin and Other Gram-Positive Agents
Joseph R. Lentino,M.D.,Ph.D.

| >70 | Every 12 hours |
| 40 - 69 | Every 24 hours |
| 25 - 39 | Every 48 hours |
| < 25 | Every 72 hours or longer |

Neonates and children: 10 to 15 mg/kg every 6 to 24 hours based on gestational age or renal function

**\*\*TBW should be used for dosing – maximum initial dose should be 2000 to 2500 mg in obese patients (> 150 to 200 kg)**

VII. **CLINICAL USES**

A. Infections due to **methicillin-resistant staphylococci** including bacteremia, pneumonia, empyema, endocarditis, peritonitis, osteomyelitis, and skin and soft tissue infections. Intraventricular vancomycin has been used for the treatment of meningitis.

B. **Serious gram-positive infections in patients allergic to β-lactam antibiotics**.

C. Infections caused by **multiply resistant** gram-positive organisms such as *Corynebacterium jeikeium* or *Streptococcus pneumoniae (PRSP)*.

D. Perioperative prophylaxis to reduce the risk of infection in patients undergoing cardiac, neurosurgical, orthopedic, or vascular surgical procedures where the incidence of MRSA is high.

E. **Oral vancomycin for the treatment of moderate to severe *Clostridium difficile* colitis (125 mg PO Q 6 hours)**

VIII. **ADVERSE EFFECTS** - overall incidence of adverse effects decreased with the purification of branded vancomycin; however, generic products now available

A. **Red-Man Syndrome (Red Neck Syndrome)**

1. Characterized by flushing, pruritus, and a maculopapular or erythematous rash on the face, neck, chest, and upper extremities. The reaction may also be accompanied by hypotension.

2. Usually begins within 5 to 15 minutes of the start of the vancomycin infusion, and resolves spontaneously over several hours after the discontinuation of the infusion. The reaction has also been rarely reported after oral and intraperitoneal administration.

3. Related to the **rate of vancomycin infusion** (faster than 15mg per minute); rapid infusion causes the release of histamine and other vasodilating substances.

Cell Wall Inhibitors III
November 29, 2011

Vancomycin and Other Gram-Positive Agents
Joseph R. Lentino, M.D., Ph.D.

4.  To minimize or prevent this reaction, **vancomycin doses of 1 gram should be infused over at least one hour (larger doses should be administered over 90 to 120 minutes)**. Other measures to alleviate this reaction include further lengthening of the infusion (over 2 or 3 hours) and premedication with antihistamines or corticosteroids.

B.  **Nephrotoxicity and Ototoxicity**

1.  Occurs rarely with vancomycin monotherapy ($< 5\%$); may be seen in patients receiving concomitant ototoxins and nephrotoxins (10 to 15%).

2.  Risk factors include the presence of underlying renal insufficiency, the use of prolonged therapy or high doses, ? high serum vancomycin concentrations, and concomitant use of other ototoxins or nephrotoxins.

3.  Correlations between serum vancomycin concentrations and toxicity remain to be clarified.

4.  Nephrotoxicity is manifested by transient increases in BUN or serum creatinine, and occasionally the presence of granular casts in the urine. The occurrence of nephrotoxicity is usually transient and reversible.

5.  Vancomycin may cause damage to the auditory branch of the 8th cranial nerve. Tinnitus and high-frequency hearing loss may precede the onset of deafness, and necessitates the discontinuation of therapy. Hearing loss is permanent.

C.  **Dermatologic**

1.  Hypersensitivity skin reactions occur in <5% of patients who receive vancomycin. Reactions include exfoliative dermatitis, linear IgA bullous dermatosis, macular rashes, vasculitis, and Stevens-Johnson.

D.  **Hematologic** - neutropenia, thrombocytopenia, and rarely eosinophilia; especially with prolonged therapy

E.  **Other** - thrombophlebitis, muscle spasms in the back and neck; cardiovascular collapse (rapid infusion); drug fever, interstitial nephritis (rare).

Cell Wall Inhibitors III
November 29, 2011

Vancomycin and Other Gram-Positive Agents
Joseph R. Lentino,M.D.,Ph.D.

II.    **OXAZOLIDINONES**

    A.    **LINEZOLID (Zyvox®)** – IV and PO

        1.    **Introduction** – Oxazolidinones are a synthetic group of antibacterials, first developed by Dupont in 1978.  Manipulations of the original oxazolidinones led to the development of linezolid, the first and only oxazolidinone available in the US.  Linezolid was approved by the FDA on April 18, 2000, and was developed in response to the need for antibiotics with activity against resistant gram-positive organisms, namely MRSA, VISA (GISA), and VRE.

        2.    **Chemistry** – Linezolid is a semisynthetic oxazolidinone antibiotic.
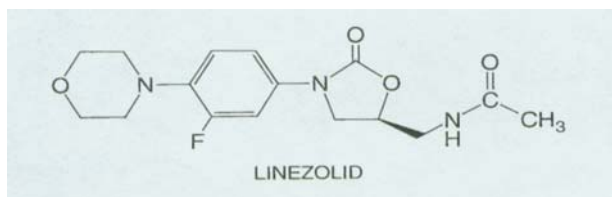


LINEZOLID

        **3.**    **Mechanism of Action** – Linezolid binds to the 50S ribosomal subunit near the surface interface of the 30S subunit – producing inhibition of the 70S initiation complex for protein synthesis (ultimately, **inhibits protein synthesis**).  This mechanism of action (and site of binding) is unique, making cross-resistance with other protein synthesis inhibitors unlikely.  For the most part, linezolid is **bacteriostatic**.

        4.    **Mechanism of Resistance** – alteration of the ribosomal subunit target site; has *rarely* emerged during therapy in *Enterococcus* and *S. aureus*

        5.    **Spectrum of Activity:**

            a.    **Gram-positive organisms**

- *Staphylococcus aureus* and CNS (**MS and MR and GI**)
- *Streptococcus pneumoniae* (including **PRSP**)
- Group Streptococci (A, B)
- Viridans Streptococci
- ***Enterococcus faecium*  AND *faecalis*** (including **VRE** )
- Others – *Listeria monocytogenes, Clostridium (*not *C difficile), Bacillus, Peptostreptococcus, P. acnes*

Cell Wall Inhibitors III
November 29, 2011

Vancomycin and Other Gram-Positive Agents
Joseph R. Lentino, M.D., Ph.D.

        b.        **Gram-negative organisms** – relatively inactive against *Neisseria, Moraxella, Haemophilus* and Enterobacteriaceae

        c.        **Atypical organisms** – some in vitro activity against *Mycoplasma pneumoniae, Chlamydophila* and *Legionella* (not used clinically)

6.      **Pharmacology**

        a.        **Time-dependent bactericidal activity** – Time above the MIC is the major predictor of efficacy

        b.        **Significant PAE** exists for gram-positive organisms: 3 to 4 hours for *S. aureus* and *S. pneumoniae*, 0.8 hours for *Enterococcus*

        c.        **Absorption** – **Linezolid is rapidly and completely absorbed after oral administration with an oral bioavailability of 100%;** food slightly decreases the rate but not extent of absorption

        d.        **Distribution** – readily distributes into well-perfused tissues; limited data suggest that linezolid penetrates into CSF (30% of simultaneous serum concentrations); protein binding = 31%

        e.        **Elimination** – linezolid is eliminated by both renal and non-renal routes (65%); primarily metabolized by oxidation; half-life ranges from 4 .4 to 5.4 hours; is removed by hemodialysis and does NOT require dosage adjustment in the presence of renal insufficiency

7.      **Clinical Uses and Dosing (very expensive: $75 to $140 per day)** – use reserved for management of serious or complicated infections caused by resistant organisms, especially for infections **where vancomycin cannot be used**; good oral absorption provides convenient option for "stepdown" therapy

        a.        Treatment of **infections (bacteremia) due to vancomycin-resistant** *Enterococcus spp* - 600 mg IV or PO every 12 hours

        b.        **Complicated skin and skin structure infections caused by MSSA or** *S. pyogenes* - 600 mg IV or PO every 12 hours; 400 mg PO every 12 hours for uncomplicated infection

        c.        **Community-acquired pneumonia due to PSSP, MSSA**– 600 mg IV or PO every 12 hours

        d.        **Nosocomial pneumonia due to MSSA, MRSA and PSSP**– 600 mg IV or PO every 12 hours

Cell Wall Inhibitors III
November 29, 2011

Vancomycin and Other Gram-Positive Agents
Joseph R. Lentino,M.D.,Ph.D.

    e.    **Other uses**: serious infections due to MRSA or VRE (including endocarditis, meningitis and osteomyelitis); catheter-related bacteremias

8.    **Drug Interactions** – linezolid is a very **weak inhibitor of monoamine oxidase ⇒ potential for drug interactions** although no evidence of MAO inhibition emerged during clinical trials; linezolid has the potential for interaction with adrenergic and serotonergic agents – a reversible enhancement of the pressor response to agents such as dopamine or epinephrine and a **risk of serotonin syndrome** (e.g., hyperpyrexia, cognitive dysfunction, diarrhea, restlessness, clonus) **in patients receiving concomitant serotonergic agents** (SSRIs such as fluoxetine, sertraline, citalopram, escitalopram, etc); full significance yet to be determined

9.    **Adverse Effects**

    a.    **Gastrointestinal** – nausea, diarrhea (6 to 8%), lactic acidosis

    b.    **CNS** – Headache (6.5%), peripheral neuropathy

    c.    **Thrombocytopenia and anemia (2 to 4 %)** – most often seen with treatment > 2 weeks; platelet counts and red blood cell counts return to normal upon discontinuation of therapy

6.    **Availability**

    a.    IV Injection – 2 mg/ml

    b.    Oral Tablets – 400 mg, 600 mg

    c.    Oral Suspension – 100mg/5 ml

III.    **LIPOPEPTIDES**

A.    **DAPTOMYCIN (Cubicin®)** – IV only

1.    **Introduction** – Daptomycin is a cyclic lipopeptide antibiotic that has been in clinical development for over 15 years. Clinical development of daptomycin was halted in the early 1990s after several reports of treatment failure for endocarditis as well as safety concerns of myopathy during treatment. However, with the increasing need for antibiotics with activity against resistant gram-positive bacteria, daptomycin was reevaluated in the late 1990s for its potential usefulness in the treatment of these infections. PD evaluation of daptomycin led to different dosing strategies that appear to maximize efficacy while decreasing the incidence of myopathy.

Daptomycin has been commercially available in the US since September 2003.

2. **Chemistry** – Daptomycin is a cyclic lipopeptide antibacterial agent derived from the fermentation of *Streptomyces roseosporus*. It is also a very large compound, with a molecular weight of 1620 Daltons.



*Figure 43–8.* Structure of daptomycin.
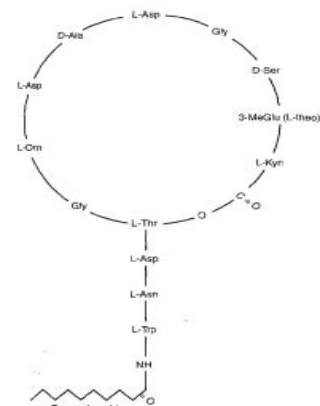
3. **Mechanism of Action** – Daptomycin binds to bacterial membranes and causes rapid depolarization of the membrane potential. This loss of membrane potential leads to inhibition of protein, DNA, and RNA synthesis, resulting in bacterial cell death. Daptomycin exhibits **rapid, concentration-dependent bactericidal activity.**

4. **Mechanism of Resistance** – Resistance to daptomycin has been rarely reported in VRE and MRSA due to altered cell membrane binding through loss of a membrane protein.

5. **Spectrum of Activity:**

   a. **Gram-positive organisms** – excellent activity

      - *Staphylococcus aureus* and CNS (**MS, MR, GI, GR, LR**)
      - *Streptococcus pneumoniae* (including **PRSP** - cidal)
      - Group Streptococci (A, B)
      - ***Enterococcus faecium*** **AND** *faecalis* (including **VRE** – static)
      - *Corynebacterium jeikeium*

   b. **Gram-negative organisms** – is inactive against *Neisseria, Moraxella, Haemophilus* and Enterobacteriaceae

6. **Pharmacology**

   a. **Rapid, concentration-dependent bactericidal activity**

Cell Wall Inhibitors III
November 29, 2011

Vancomycin and Other Gram-Positive Agents
Joseph R. Lentino,M.D.,Ph.D.

       b.      **Distribution** – daptomycin distributes fairly well into tissues and is highly protein bound to serum albumin (90 to 93%)

       e.      **Elimination** – daptomycin is excreted primarily by the kidney, with 78% of the dose being recovered in the urine; half-life ranges from 7.7 to 8.3 hours in healthy volunteers and is prolonged in patients with renal insufficiency; **dosage adjustments of daptomycin are required in the presence of renal insufficiency**

**7.**      **Clinical Uses and Dosing (very expensive: \$165/day for adults)** –use is reserved for the management of serious or complicated infections caused by resistant gram-positive organisms where vancomycin and/or linezolid cannot be used

       a.      **Complicated skin and skin structure infections caused by susceptible gram-positive bacteria (MSSA, MRSA, *S. pyogenes, etc*)** – 4 mg/kg IV once daily

       b.      *Staphylococcus aureus* bacteremia and endocarditis – 6 mg/kg once daily

       c.      **Other uses**: serious infections due to MRSA or VRE (including endocarditis, meningitis and osteomyelitis); catheter-related bacteremias

       d.      **Daptomycin should NOT be used for the treatment of pneumonia since the compound is inactivated by pulmonary surfactant.**

8.      **Drug Interactions** – HMG-CoA reductase inhibitors (statins) – may lead to increased incidence of myopathy

9.      **Adverse Effects**

       a.      **Gastrointestinal** – nausea, diarrhea (5%)
       b.      **Headache** – 5.4%
       c.      **Injection site reactions – 5.8%**
       d.      **Rash – 4.3%**
       e.      **Myopathy and CPK elevation – 0.9 to 1.5%**

10.     **Availability**
       a.      IV Injection – 500mg vial

## #54 - ANTIMYCOBACTERIALS

**Date:** December 1, 2011 – 2:00 PM

**Reading Assignment: Basic & Clinical Pharmacology, B.G. Katzung, 11<sup>th</sup> Edition.** Chapter 47

## LEARNING OBJECTIVES:

1.      To be able to list first line antituberculosis agents.

2.      To be able to list major toxicities of first line anti-mycobacterial agents.

3.      To be able to list the treatment principals which should be followed when treating patients with *M. tuberculosis*.

4.      To be able to discuss all the therapeutic indications of rifampin.

5.      To be able to discuss the mechanism of primary and secondary resistance in *M. tuberculosis* infections.

6.      To be able to list the major determinant of outcome of treatment for tuberculosis and list ways to improve this determinant.


## LIST OF DRUGS COVERED IN LECTURE

Isoniazid, Isonicotinic Acid Hydrazide, INH
Rifampin, Rifampicin
Ethambutol
Pyrazinamide
Streptomycin
Rifapentine
Rifabutin

#54 – **ANTIMYCOBACTERIALS**

I.      Tuberculosis pathogenesis and impact on treatment

- Cavitary pulmonary disease is spread by coughing. Contacts inhale the organism when sharing air with ill patients. Following inhalation of *M. tuberculosis,* patient walls off the infection.
- The organism stays viable but latent and the contact develops delayed hypersensitivity to PPD. A positive PPD means a person is infected with *M. tuberculosis* and has latent infection. Latent infection is treated differently than active infection or disease.
- Patients may reactivate their latent infection at a future date. At that time they develop symptoms and most frequently have cavitary pulmonary disease.
- Cavitary pulmonary tuberculosis is a chronic infection. The organism divides slowly so symptoms of weight loss, night sweats, fever and cough develop and persist over months.
- Pathologically caseating granulomas are seen in the lungs
- There are high numbers of organisms in cavities from M. tuberculosis infection.
- Resistance to the antimicrobials develops if only one anti-TB drug is used for active disease.
- Long doubling times, presence of organisms intracellular and extracellular and ready development of antimicrobial resistance necessitate treatment with multiple drugs given for at least 6 months.
- Patients who do not take meds relapse. The most important determinant of outcome is adherence.

II.     Goals of Therapy
        Eradicate the infection caused by *M. tuberculosis*
        Monitor adequacy of therapy with:
- Loss of fever, weight gain, feeling of well being
- Microbiology-Sputum specimens smear negative for  afb, or quantitatively less organisms seen on smear
- cultures show no growth of afb
- CXR clears the infiltrate, lags behind clinical cure

II.     Aspects of Bacterial Resistance in Tuberculosis & Rationale for Multiple Drug Treatment Regimens

A.      Primary resistance
        1.An untreated patient acquires a wild type strain which is resistant to TB
        2. Wild strains of *Mycobacterium tuberculosis* have intrinsic resistance to the antituberculous drugs.
        3. One organism in $10^6$ is resistant to INH..

B.      Secondary resistance
        1.      Develops in patients who have been treated.

2. Taking only one drug or taking meds erratically can lead to secondary resistance because:
   a. Cavitary lesions contain $10^7 - 10^9$ organism
   b. In a population of M. TB 1 organism in $10^6$ may mutate by chance and become reisistant to antib-tb drug
   c. If only one anti-tb med is taken then all sensitive organisms will be killed but $10^1$-$10^3$ resistant organisms will survive and grow

C.  Cross resistance
    1. Cross resistance- presence of resistance to one drug is accompanied by resistance to another between i.e. viomycin and capreomycin
    2. Some INH resistant mutants are also resistant to ethionamide

D.  Multi-drug resistance
    1. MDR TB- resistant to both INH and rifampin
    2. More common in HIV infected patients
    3. Associated with nosocomial transmission and a high mortality in HIV infected patients

E.  Extensive Drug Resistant (XDR)  TB
    1. Resistant to all of the following:
          Both INH and Rifampin,
          Resistant to any fluoroquinolone and
          Resistant to at least one of the 3 injectable second-line drugs-
          Streptomycin, Capreomycin, kanamycin, amikacin

F.  Principles of Treatment for Tuberculosis
    1.  Multiple drugs which organisms are susceptible
    2.  Drugs must be taken regularly
    3.  Drug therapy must continue for a sufficient periods of time- safest, most effective therapy in the shortest time

E.  Rationale for multiple drug Rx is based on principles of resistance

    1. In a cavitary lesion, there $10^7$ - $10^9$ organisms.
    2. There will be 1 in $10^6$ organisms that are intrinsically resistant to the drug. If you treat with one drug a population of approximately 10 to 1,000 organisms will survive that are resistant. If you treat with 2 drugs the chance that 1 organism will be resistant to both is $10^6$ x $10^6$ =$10^{12}$, 1 in $10^{12}$. But there are only $10^9$ organisms, so none will be resistant when treating with several drugs.

## III.  ISONIAZID, ISONICOTINIC ACID HYDRAZIDE, INH

A.  Clinical use - never alone for active infection

1.      First line drug for active pulmonary TB- ideal agent
2.      Treatment for latent infection

B.      Mechanism of action
1.  Isoniazid is a prodrug
2.  active form inhibits the synthesis of mycolic acid in the mycobacterial cell wall
3.  drug must be activated by catalase peroxidase which is regulated by the *katG* gene
4.  Bactericidal on actively replicating organisms
5.  Bacteriostatic on "resting organisms"
6.  Active against *M. kansasii*
7.  Active against intracellular and extracellular organisms
8.  Not active against non-tuberculous Mycobacteria

C.      Resistance
1.  Many mutations in *katG* gene result in inactivation of catalase-peroxidase
2.  Mutation in regulatory region of inhA gene which is involved in mycolic acid synthesis
      a.Also results in resistance to ethionamide (cross resistance)

C.      Pharmacokinetics

1.      Dose - oral route 5-8 mg/kg/day usual dose 300 mg.
2.      Renal failure patients 5 mg/kg/day 3 x week
3.      Reduce dosage by half in severe hepatic insufficiency
4.      Metabolism - acetylation in liver by N-acetyltransferase
      a. Non-acetylate INH is excreted in urine
      b. Rate of acetylation in humans is genetically controlled-
- rapid or slow acetylators
- Slow acetylators 6 hours after a 4mg/kg dose plasma INH level more than 0.8 µg/ml and
- Rapid acetylators  INH level less than 0.2 µg/ml
- Acetylator status has no effect on the outcome of daily therapy because the plasma levels are maintained well above inhibitory concentrations

5.      Distribution wide including CSF, CSF levels 20% plasma levels but may equal plasma in meningeal inflammation.
6.  No doseage adjustment necessary for renal insufficiency

D.      Toxicity

1.      Hepatotoxicity-  Asymptomatic elevation of transaminases seen within the first month of therapy in 10-20% of reciepients

a.Rate of clinical symptomatic hepatitis patients given INH alone 0.6%

   b. Occurs after weeks to months of therapy

   c.  Hepatotoxicity correlated with age older more likely to occur

   d.  Increased in alcoholics, preexisting liver damage, pregnant women, women up to 3 months post-partum, in combination with acetaminophen, patients receiving other hepatotoxic drugs such as rifampin, patients with active Hepatitis B,

2. Neurotoxicity

   a. Peripheral neuritis more frequent in slow acetylators who have higher plasma levels of unaltered drug

   b. Use pyridoxine to prevent neuritis

3.   Hypersensitivity reaction- fever, maculopapular rash
        lupus like syndrome,  positive ANA,

E.      Drug Interactions - Dilantin toxicity,
   1. INH and rifampin increases occurrence of hepatitis
   2.  Decreases itraconazole
   3.  Decreases levodopa

IV.   <u>RIFAMPIN, RIFAMPICIN</u> - semisynthetic derivative of a complex macrocyclic antibiotic rifamycin B produced by *Streptomyces mediterranei*.

   A.    Clinical use

      1.      First line drug for TB
      2.      Gram positive organisms, <u>*Staph aureus*</u>

   B.    *N. meningitidis*, prophylaxis meningococcal meningitis

      1.      Cannot be used alone in therapy as an antibacterial agent because of rapid development of resistance.

   C.    Mechanisms of action and resistance

      1.      Inhibits DNA dependent RNA polymerase
      2.   *rpoB* gene produces RNA polymerase ß subunit
      3.   *rpoB* mutations lead to rifampin resistance
            a.  Frequency $10^8$
            b.  RNA polymerase can no longer bind the drug
      4.  Bactericidal to all population of organisms

   D.    Pharmacokinetics

      1.      Dose 9 mg/kg/day, 600 mg/day oral

2.     Metabolized in the liver
3.     Meningococcal meningitis chemoprophylaxis 600 mg BID x 2 days
4.     Distribution penetrates well into most tissues, CSF levels 0.5 µg normal meninges, 4-8 x increase inflamed meninges

E.    Toxicity

1.     Most common- GI upset
2.     Hepatotoxicity enhanced with use of other hepatotoxic drugs including INH
3.     Red discoloration urine, tears, pleural fluid- permanent discoloration of soft contacts
4.     Acute renal failure, interstitial nephritis
5.     Influenza syndrome- more common with intermittent dosing
6.     Thrombocytopenia
7.     Cholestatic jaundice

F.    Drug interactions

1.     Induces hepatic microsomal enzymes reacts with 100 drugs2.
2.     Accelerates clearance of: methadone, coumadin derivatives, glucocorticoids, estrogen, oral hypoglycemic agents, digitoxin, anti-arrhythmic agents (quinidine, verapamil, mexiletine), theophylline anticonvulsants, ketoconazole, cyclosporin, protease inhibitors, and non-nucleoside reverse transcriptase inhibitors
3.     Impairs effectiveness of oral contraceptives.
4.     should not be used with protease inhibitors and non-nucleoside reverse transcriptase inhibitors because it induces metabolism of the drugs

V.    <u>RIFABUTIN</u>

Clinical use

1.     Second line drug for TB
2.     Recommended agent for patients co-infected with HIV & TB

Drug interactions

1.     Reduces levels of many drugs including protease inhibitors and Non-nucleoside reverse transcriptase inhibitors **BUT REDUCES THESE DRUGS LESS THAN RIFAMPIN**
3.     Dapsone
4.     Ketoconazole
5.     Birth control pills

VI.    <u>RIFAPENTINE</u>

A.      Clinical use- may be given weekly in the combination phase of directly observed therapy regimens

Mechanism of action and resistance- cross resistance with rifampin
        -bactericidal

C.      Pharmacokinetics

        1.      Dose 600 mg once or twice a week

VII.    ETHAMBUTOL - active only against mycobacteria

A.      Clinical use - first line tuberculosis therapy
        a.   Used to inhibit the development of resistance to other agents

B.      Mechanism of action

        1.      inhibits synthesis mycobacterial arabinosyl transferase encoded by *embB*
        2.       Effects biosynthesis within cell wall
        3.       Bacteriostatic

C.      Pharmacokinetics

        1.      Dose 15 mg/kg/day as maintenance - may treat for first several months at 25 mg/kg/day as 1 dose, oral
        2.      Reduce dose in renal failure
        3.      Distributed throughout the body. Cerebrospinal levels low even in inflamed meninges.

D.      Toxicity

        1.      Ocular - retrobulbar neuritis- symptoms: blurred vision, central scotomata, red-green color blindness, dose related, < 1%
        2.      Don't use in children who are too young for assessment of visual acuity and color blindness
        3.      Peripheral neuropathy less common

VII.    PYRAZINAMIDE

A.      Clinical use

        1.      Antituberculous therapy first line for initial therapy

B.      Mechanism of action and resistance

1.      Bactericidal
2.      Mutation in gene *pncA* encoding pyrazinamidase
3.      Results in loss of pyrazinamidase
        Which converts drug  to active form of pyrazinoic acid

C.      Pharmacokinetics

1.      Dose 15-25 mg/kg/day in 1 dose
2.      Best avoided in renal failure because metabolic products excreted largely
        in urine
3.      Distribution good, CSF in tuberculous meningitis

D.      Toxicity

1.      Hepatitis, worse in patients with preexisting liver disease
2.      Skin rash and gastrointestinal intolerance
3.      Arthralgia, increased serum uric acid levels, but acute gout is uncommon

E.      Drug interactions

1.      Cyclosporine
2.      Ethionamide
3.      Rifampin
4.      Zidovudine

IX.    <u>STREPTOMYCIN</u> - used as an antituberculous agent, first line agent bactericidal for
        extracellular organisms

A.      Clinical use: second  line antituberculous agent

B.      Mechanism of action and resistance

1.      Bactericidal
2.      Inhibits protein synthesis by binding to ribosome
3.      Resistance mutational changes ribosomal binding protein or ribosomal
binding site
4.      *rpsL* gene 16-S ribosomal RNA gene
5.      Isolates resistant to streptomycin are **not** cross resistant to amikacin,
kanamycin or capreomycin

C.      Pharmacokinetics

1.    Intramuscular dose 15 mg/kg, 0.75 - 1.0 gm/day for 60-90 days, then 1.0 gm 2-3 times/week
2.    15 mg/kg gives serum peak levels of 40 µg/ml.  Most strains of *M.TB* inhibited by 8.0 µg/ml
3.    Excretion renal- use in reduced dose in renal failure
4.    Enters CSF only in the presence of meningeal inflammation

D.    Toxicity

1.    Ototoxicity
2.    Nephrotoxicity
3.    Both toxicities related to cumulative dose and peak serum concentrations
4.    Total cumulative dose > 120 g should not be given unless there are no other options
5.    Toxicities more common in persons older than 60
6.    Pain and tenderness at injection site

X.    TREATMENT REGIMENS

A.    Multiple drugs taken regularly over time for active disease,
1.   should be given by Directly Observed Therapy
2.   Many variations on the following:
    a. Initial phase: standard four drug regimens (INH, RIF, PZA, EMB), for 2 months
    b. Continuation phase: additional 4 months or (7 months for some patients)
3.   MAJOR DETERMINANT OF OUTCOME IS ADHERENCE
    a.   Ways to foster adherence include:
        • Clinic hours and locations to suit needs of patient
        • Give DOT (Directly Observed Therapy) in clinic, home, workplace \
        • Incentive enablers such as food, carfare, baby-sitting, small gifts

    b. Other determinant of outcome is presence of a drug resistance infection

B.    Treatment of Latent Infection

1.    single drug isoniazid for 6 months or 9 months:
    a single drug may be administered  because the number of organisms in the body is low.

XI.   Alternative second line drugs for tuberculosis
        Ethionamide, Capreomycin, Cycloserine,  PAS (aminosalicylic acid).
        Fluroquionolones, linezolid, aminoglycosides specifically amikacin and
        kanamycin.


XII    Dapsone

        A.  Clinical use
            i.  Leprosy

        B.  Mechanism of action and resistance
                1.  Bacteriostatic
                2.  Resistance
                        a.   Both secondary and primary

        C.  Pharmacology
                1.  Distributed throughout the body
                2.  Reduce dose in renal failure
                3.  Dose 25mg/week, increase 25 mg weekly until 100mg/d

        D.  Toxicity
                1.  Minor hemolysis in patients with G6PD deficiency
                2.  Anorexia, nausea, vomiting
                3.  Hematuria, fever, pruritis
                4.  Sulfone syndrome
                5.  Erythema nodosum leprosum

XIII   Clofazamine

        A.  Clinical use -leprosy, multidrug resistant TB, *M. avium intracellulare*
            infections

        B.   Mechanism of action
                1. Weakly bactericidal

        C.  Pharmacokinetics
                1.Dose 100-300 mg/day
                2. Widely distributed

        E.  Toxicity
                1.  GI intolerance
                2.  Skin pigmentation

XIV      Drugs used for Mycobacterium avium-intracellular infections
         A. clarithromycin, ethambutol , rifabutin

XV     <u>LIST OF DRUGS COVERED IN LECTURE</u>

Isoniazid, Isonicotinic Acid Hydrazide, INH
Rifampin, Rifampicin
Ethambutol
Pyrazinamide
Streptomycin
Rifapentine
Rifabutin
       Dapsone
       Clofazamine

**#55 – AMINOGLYCOSIDES**
**Drugs covered**
**Amikacin, tobramycin, gentamycin, streptomycin**

I.    **INTRODUCTION**

Aminoglycoside antibiotics have been in clinical use since their initial discovery in the 1940s.  Streptomycin was the first aminoglycoside discovered from a soil actinomycete named *Streptomyces griseus*.  Other aminoglycosides were then discovered during the 1950s and 1960s, with gentamicin, tobramycin, and amikacin being the most commonly used parenteral aminoglycosides in the United States.  Gentamicin is derived from species of the actinomycete *Micromonospora*, tobramycin is derived from *Streptomyces tenebrarius*, and amikacin is a semisynthetic derivative of kanamycin.

II.    **CHEMISTRY**

A.    The aminoglycosides consist of 2 or more amino sugars linked to an aminocyclitol ring by glycosidic bonds, hence the name ***aminoglycosides***.

B.    The six-membered aminocyclitol ring of the aminoglycosides is either streptidine (streptomycin) or 2-deoxystreptamine (gentamicin, tobramycin, netilmicin, amikacin, kanamycin, and neomycin).

C.    The aminoglycosides are **polar compounds** that are **polycationic, highly soluble in water (distribute primarily into extracellular fluid compartment; renally eliminated),** and **incapable of crossing lipid-containing cellular membranes** (**poor oral absorption; poor penetration through meninges**).
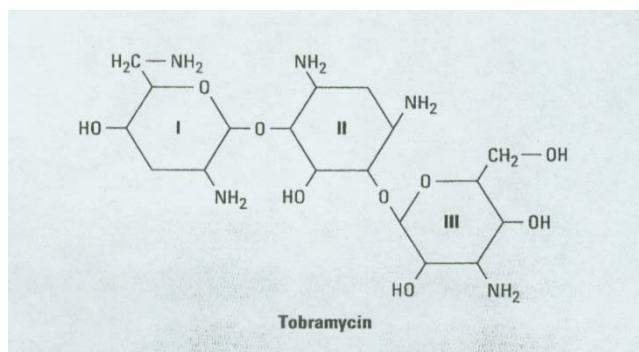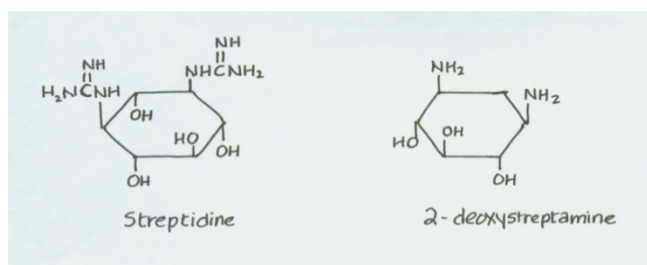
III.    **MECHANISM OF ACTION**

A.      The mechanism of action of the aminoglycosides is multifactorial, but ultimately involves the 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 two energy dependent mechanism.
    a.    Initial slow energy dependent phase (EDP-I) which transport drug into cytosol
    b.    Rapid energy dependent phase (EDP-II)   represents binding to the ribosomes.
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)

C.      Aminoglycoside antibiotics are **rapidly bactericidal in a concentration-dependent manner**, except against *Enterococcus spp.*

IV.    **MECHANISMS OF RESISTANCE**

A.      **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.

B.      **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.     A large number of 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.

C.      **Alteration in ribosomal binding sites**

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

V. **SPECTRUM OF ACTIVITY**

A. The aminoglycosides demonstrate **concentration-dependent bactericidal** activity against aerobic gram-positive and gram-negative bacteria, where the Peak:MIC ratio correlates best with clinical efficacy for infections due to gram-negative aerobes (Peak:MIC ratio of 10 to 20:1 is optimal).

B. **Gram-positive aerobes**: (*NEVER USED ALONE, are used with cell-wall active agents to provide synergy; LOW DOSES*) – **primarily gentamicin**

   Most strains of *S. aureus* and coagulase-negative staphylococci
   Viridans streptococci
   *Enterococcus spp.* (gentamicin or streptomycin)

C. **Gram-negative aerobes**: are <u>very active</u> against gram-negative aerobes; *often used with cell-wall active agents to provide synergy* – **primarily gentamicin, tobramycin and amikacin A>T>G (NOT streptomycin);** *HIGHER DOSES*

   | | |
   |---|---|
   | *Acinetobacter spp.* | *Proteus spp.* |
   | *Citrobacter spp.* | *Providencia spp.* |
   | *E. coli* | ***Pseudomonas aeruginosa*** |
   | *Enterobacter spp.* | *Salmonella spp.* |
   | *Klebsiella spp.* | *Serratia marcescens* |
   | *Morganella morganii* | *Shigella spp.* |

   Gentamicin and streptomycin are active against *Brucella* and *Yersinia*.

D. **Anaerobes** - aminoglycosides are INACTIVE.

E. **Mycobacteria**

   1. **Streptomycin** is active against *Mycobacterium tuberculosis*, *M. bovis*, *M. marinum*, and some strains of *M. kansasii* and *M. avium-intracellulare*.

   2. Amikacin has some activity against *M. chelonae, M. fortuitum, M. kansasii*, and *M. marinum*.

F. **Post-Antibiotic Effect (PAE)**

   1. Aminoglycosides display a post-antibiotic effect for most gram- negative bacteria, as well as *S. aureus*.

2. PAE is the persistent suppression of bacterial growth after the concentrations of the antibiotic have fallen below the minimum inhibitory concentration (MIC) for the bacteria.

3. The PAE exists for a finite period of time; usually 2 to 4 hours for gram-negative bacteria.

G. **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 (gent-amicin, tobramycin or amikacin)

VI. **PHARMACOLOGY**

A. Aminoglycosides are **highly polar cations**, which accounts for their lack of absorption after oral administration, their pattern of distribution throughout the body, and their elimination in the urine as unchanged drug. Interpatient variability exists in the pharmacokinetic parameters of **volume of distribution** and **clearance,** which influence dosing of aminoglycosides.

B. **Absorption**

1. Aminoglycosides are very poorly absorbed from the gastrointestinal tract.
2. Aminoglycosides are well absorbed after IM administration, Rarely used.
3. Intermittent intravenous infusion is the preferred route of administration, with the aminoglycoside dose infused over 30 to 60 minutes.

C. **Distribution**

1. Aminoglycosides are **distributed primarily in the extracellular fluid compartment,** and are widely distributed into body fluids including ascites, pericardial, peritoneal, pleural, and synovial fluids as well as into the urinary tract.

2.      Aminoglycosides **distribute poorly into cerebrospinal fluid** (even in the presence of inflamed meninges), ocular tissue, bile, **sputum,** and **adipose tissue**

D.    **Elimination**

1.      85 to 95% of an administered aminoglycoside dose is eliminated unchanged by the kidney via glomerular filtration, resulting in high urinary concentrations.

2.      In adults with normal renal function, the elimination half-life of the aminoglycosides is 2.5 to 4 hours. Decreases in renal function directly influence the elimination of the aminoglycosides, causing a prolongation of the half-life.

3.      Hemodialysis removes 30 to 50% of aminoglycoside present in the bloodstream, requiring supplemental dosing. Peritoneal dialysis only removes 25% of serum concentrations over 48 to 72 hours

E.    **Dosing of aminoglycosides -** Factors that should be considered include renal function, age, gender, weight, infection being treated, severity of infection, etc.

1.     **Lean body weight** should be used for aminoglycoside dosing, with an adjusted dosing weight used for obese patients (> 130% of LBW). The lean body weight in kg for males and females can be calculated using the Devine method:

LBW males = 50 kg + {2.3 kg x (inches greater than 60)}
LBW females = 45.5 kg + {2.3 kg x (inches greater than 60)}

2.  **Standard or Traditional Dosing** – Smaller doses (1 to 2.5 mg/kg/dose) given 2 to 3 times daily with the dosing interval changed based on the patient's renal function. This is not widely used now. Once-daily dosing has become the preferred method.

2.     **Once-Daily Aminoglycoside Dosing (Extended Interval Dosing)**

Dosing method based on the principles of concentration-dependent bactericidal activity and the post-antibiotic effect. Larger doses (5 to 7 mg/kg/dose) are given every 24 hours to obtain high peak concentrations (better bacterial killing) and undetectable trough concentrations (less toxicity, rely on PAE).

Gent/Tobra:  5 to **7** mg/kg as a **single daily dose** (use LBW or ABW)
Amikacin:  15 to 25 mg/kg as a **single daily dose** (use LBW or ABW)

In patients with renal insufficiency the dosing interval is prolonged based on the creatinine clearance of the patient.

    F.     Serum concentration monitoring

        1.     Serum concentration monitoring is necessary in all patients.

        2.     Serum concentrations are checked at the $2^{nd}$ or $3^{rd}$ dose. Trough draw

right before the dose is administered and peak one hour after infusion.

| *ONCE DAILY DOSING* | Peak (μg/ml) | Trough (μg/ml) |
|---|---|---|
| Gentamicin, Tobramycin | 10-15 | < 1 |
| Amikacin | 30-40 | < 4 |

## VII.   CLINICAL USES – aminoglycosides are RARELY USED ALONE

    A.     **Amikacin, gentamicin, and tobramycin** are used for the treatment of serious **infections due to gram-negative bacteria** such as septicemia, bone and joint infections, skin and soft tissue infections, respiratory tract infections, intraabdominal infections, and complicated urinary tract infections.

    B.     **Gentamicin or streptomycin** may be used with appropriate cell wall active agents (ampicillin, vancomycin, etc) for the treatment of serious infections (endocarditis) due to **enterococci, viridans streptococci, or staphylococci**.

    C.     Streptomycin or amikacin is used in conjunction with other antituberculous medications in the treatment of nontuberculous infections.

    D.     neomycin topical or oral

## VIII.   ADVERSE EFFECTS

    A.     **Nephrotoxicity**

        1.     Manifested as nonoliguric azotemia secondary to proximal tubular damage, leading to an increase in BUN and serum creatinine. Reversible if the aminoglycoside dose is adjusted or the drug is discontinued early enough.

        2.     The relative nephrotoxicity- tobramycin appears to be less nephrotoxic than gentamicin, and streptomycin is the least nephrotoxic.

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.).

B.     **Ototoxicity - auditory and vestibular**

1.     Due to eighth cranial nerve damage. Vestibular symptoms include dizziness, nystagmus, vertigo and ataxia. Auditory symptoms include tinnitus, ringing in the ears, and varying degrees of hearing impairment; patients lose high frequency hearing first.

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

3.     Vestibular toxicity is more common with streptomycin, gentamicin, or tobramycin. Auditory toxicity is more common with amikacin, neomycin, or gentamicin.

4.     The risk factors for the development of ototoxicity include prolonged high trough concentrations, prolonged therapy > 2 weeks, the presence of renal insufficiency, advanced age, and the concomitant use of other ototoxic drugs(vancomycin, loop diuretics).

C.     Other rare adverse effects of the aminoglycosides include neuromuscular blockade (neomycin), hypersensitivity, and sterile abscess formation with IM injection.

## #55 - AMINOGLYCOSIDES

**Date:** December 2, 2011 - 8:30 am

### Learning Objectives:

1.      Describe the mechanism of action of the aminoglycosides.
2.      Describe the mechanisms by which bacteria become resistant to the
        aminoglycosides.
3.      List the spectrum of activity of the aminoglycoside antibiotics.
4.      List the major clinical uses of the aminoglycosides.
5..     Identify the major adverse reactions that may occur during aminoglycoside
        therapy.

### Drugs Covered in This Lecture:

Gentamicin, Tobramycin, Amikacin, Streptomycin

## #60 –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, 6th Edition. Chapter 25 Tetracyclines and Choramphenicol and Chapter 34. Urinary Tract Agents: Nitrofurantoin and Methenamine.

## Learning Objectives:

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

## Prototypical Drugs:

**Tetracyclines**: Tetracycline, Doxycycline, Minocycline

**Glycylcyclines:** Tigecycline (Tygacil®)

**Sulfonamides:** Sulfadiazine, Sulfisoxazole, Trimethoprim-Sulfamethoxazole

**Chloramphenicol**

**Urinary Tract Agents** Nitrofurantoin, Methenamine

## TETRACYCLINES and GLYCYLCYCLINES

I.  **INTRODUCTION**

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

II.  **CHEMISTRY**

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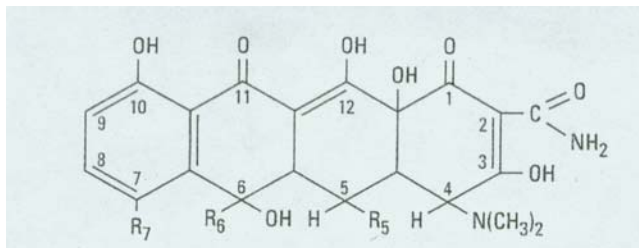


III.  **MECHANISM OF ACTION:**

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

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

IV.  **MECHANISMS OF RESISTANCE**

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

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

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

3. Enzymatic inactivation of the tetracycline.

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

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

V. **SPECTRUM OF ACTIVITY**

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

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

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

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

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

3. **Anaerobes**

Gram-positive: *Actinomyces, Proprionibacterium spp.*

4. **Miscellaneous organisms**

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

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

1.     **Gram-Positive Aerobes**

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

2.     **Gram-Negative Aerobes**

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

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

3.     **Anaerobes**

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

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

4.     **Miscellaneous organisms**

*Pasteurella multocida* and *Mycobacterium fortuitum, chelonae, abscessus*

VI.    **PHARMACOLOGY**

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

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

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

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

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

B.      **Distribution**

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

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

C.      **Elimination**

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

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

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

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

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

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

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

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

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

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

4.   *Brucellosis, bartonellosis* (doxycycline)

5.   Acne (minocycline)

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

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

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

1.   Complicated skin and skin structure infections

2.   Complicated intra-abdominal infections

## VIII.   **ADVERSE EFFECTS**

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

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

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

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

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

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

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

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

IX. **DOSING**

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

-------------------------------------------------------------------------------------------------------------
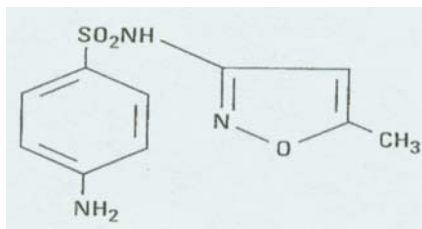
## TRIMETHOPRIM-SULFAMETHOXAZOLE (SULFONAMIDES)

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.
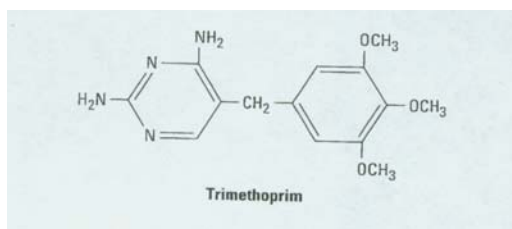
II.     **CHEMISTRY**

   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
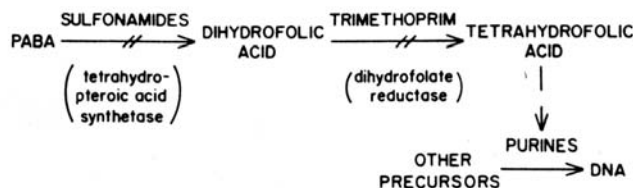          reductase to prevent the reduction of dihydrofolate to tetrahydrofolate



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

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

IV. **MECHANISMS OF RESISTANCE**

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

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

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

V. **SPECTRUM OF ACTIVITY**

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

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

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

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

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

VI. **PHARMACOLOGY**

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

B. Absorption

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

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

C. Distribution

1. TMP-SMX concentrates in most tissues, including the CSF in the presence of inflamed meninges. CSF concentrations are 30 to 50% and 20%, respectively, of concomitant plasma concentrations.

2. Concentrates well into saliva, breast milk, urine, uninflamed prostatic tissue, seminal fluid, inflamed lung tissue, and bile.

D. Elimination

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

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

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

VII. **CLINICAL USES**

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

B. **Acute or chronic bacterial prostatitis**

C. Acute bacterial exacerbations of chronic bronchitis (ABECB)

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

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

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

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

H. *Stenotrophomonas maltophilia* **infections**

I. Listeria meningitis if patient is allergic to penicillins

J. Toxoplasmosis – sulfadiazine (with pyrimethamine)

VIII. **ADVERSE EFFECTS**

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

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

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

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

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

IX.   **DRUG INTERACTIONS**

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

X.   **DOSING**

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

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

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

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

### Chloramphenicol

I.   **Introduction**

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

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

## II. Chemistry
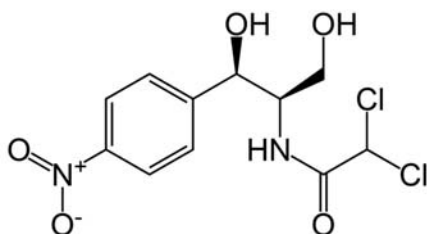


## III. Mechanism of action

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

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

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

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

  **B.** Spirochetes

  **C.** Rickettsiae

**D.** Chlamydiae

**E.** Mycoplasmas

**V.    Pharmacology**

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

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

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

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

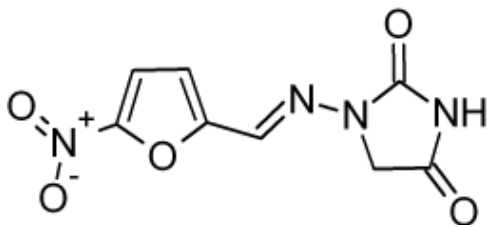    **E.** Reduces tacrolimus blood concentrations.

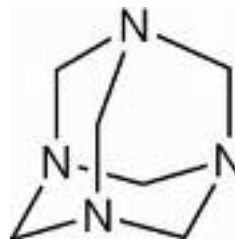**Urinary Tract Agents (Nitrofurantoin and Methenamine)**

## 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 μg/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.

## #59 - Protein Synthesis Inhibitors III

**Date:** December 5, 2011 – 10:30 am

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

## Learning Objectives:

1. Describe the mechanisms of action and mechanisms of resistance of clindamycin, macrolides and streptogramins
2. List the spectrum of activity of clindamycin, macrolides and streptogramins
3. Describe the pharmacokinetic characteristics of clindamycin, macrolides and streptogramins
4. List the major clinical uses of clindamycin, macrolides and streptogramins
5. List the major adverse effects associated with clindamycin, macrolides and streptogramins.
6. List the major drug interactions associated with clindamycin, macrolides and streptogramins.

## Prototypical Drugs:

**Lincosamides:** Clindamycin

**Macrolides:** **Erythromycin, clarithromycin, azithromycin**

**Ketolides:** Telithromycin

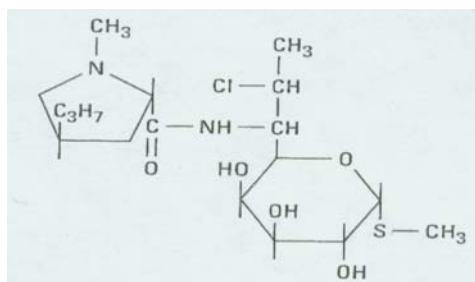**Streptogramins:** Quinupristin-dalfopristin (Synercid®)

## CLINDAMYCIN (Cleocin®) – IV and PO
### Original Handout written by S. Erdman, Pharm.D. presented by J. Lentino, M.D.

## I.   INTRODUCTION

Clindamycin is a 7-deoxy, 7-chloro-derivative of the antibiotic lincomycin, a lincosamide antibiotic first isolated from *Streptomyces lincolnesis* in 1962.  Clindamycin was introduced into clinical practice in 1966, and replaced the use of lincomycin due to its broader spectrum of antimicrobial activity and better oral absorption.

## II.   CHEMISTRY

a.   Clindamycin is a derivative of the amino acid *trans*-L-4-n-propylhygrinic acid, attached to a sulfur-containing derivative of an octose.



## III.   MECHANISM OF ACTION

A.     Clindamycin inhibits protein synthesis by exclusively binding (reversibly) to the 50S ribosomal subunit.

B.     Although clindamycin, the macrolides, the streptogramins, and chloramphenicol are not structurally related, they all act at sites within close proximity on the 50S ribosome and may competitively inhibit the action of each other.

C.     Clindamycin is **primarily bacteriostatic**, but can display **time-dependent bactericidal** activity depending on the infecting bacteria, inoculum of bacteria, and concentration of antibiotic at the site of infection.

## IV.   MECHANISM OF RESISTANCE

A.     Alteration of the ribosomal binding site – ribosomal methylation by *erm*-encoded enzymes; cross-resistance with macrolides and streptogramins occur in the presence of this enzyme ($MLS_b$ resistance)

B.     Clindamycin is NOT a substrate for macrolide efflux pumps, and strains that are resistant to macrolides by this mechanism remain susceptible to clindamycin.

Pharmacology and Therapeutics
December 5, 2011

Protein Synthesis Inhibitors III: Macrolides, Clindamycin, etc.
Joseph R. Lentino, M.D., Ph.D.

V.   **SPECTRUM OF ACTIVITY**

A.   **Gram-Positive Aerobes** – clindamycin is active against most gram-positive aerobes

*Staphylococcus aureus* (**MSSA** and **CA-MRSA**)
*Streptococcus pneumoniae* (PSSP)
*Streptococcus pyogenes* and other Group streptococci
Viridans streptococcus

B.   **Anaerobes** – clindamycin is active against many gram-positive and gram-negative anaerobes, but is primarily useful for anaerobes *above the diaphragm*

| *Gram-positive anaerobes* | *Gram-negative anaerobes* |
| --- | --- |
| *Peptostreptococcus spp.* | *Bacteroides spp.* (resistance emerging) |
| *Clostridium spp.* (**not** *C. difficile*) | *Prevotella spp.* |
| *Actinomyces* | *Fusobacterium* |
| *Propionibacterium* | |

C.   **Other Atypical Bacteria**:

*Pneumocystis carinii/jiroveci*
*Toxoplasmosis gondii*
*Plasmodium falciparum* and *vivax* (malaria)

VI.   **PHARMACOLOGY**

A.   **Absorption** – clindamycin is rapidly and almost completely absorbed after oral administration; bioavailability approaches 90%; food has minimal effect on the absorption of clindamycin

B.   **Distribution**

1.   Good serum concentrations are achieved by the oral, intramuscular or intravenous route.

2.   Clindamycin penetrates into most body tissues and fluids including sputum, bile, pleural fluid and **bone.**

3.   Clindamycin does NOT penetrate the CSF, even in the presence of inflamed meninges.

C.   **Metabolism/Elimination**

Pharmacology and Therapeutics
December 5, 2011

Protein Synthesis Inhibitors III: Macrolides, Clindamycin, etc.
Joseph R. Lentino, M.D., Ph.D.

1. Clindamycin is primarily metabolized by the liver (85%) to metabolites with varying antimicrobial activity, which are eliminated in the urine.
2. Enterohepatic circulation of clindamycin and its metabolites can lead to prolonged antimicrobial presence in the stool.

3. Half-life is 2.5 to 3 hours, which is prolonged in the presence of liver dysfunction.

4. Clindamycin is NOT removed by hemodialysis or peritoneal dialysis.

## VII. CLINICAL USES

A. **Infections due to anaerobes** (including *B. fragilis)* **OUTSIDE THE CNS** – **pulmonary infections**, intraabdominal infections, pelvic infections, **diabetic foot infections**, decubitus ulcers.

B. Alternative to penicillin in the treatment of infections due to *C. perfringens.*

C. Treatment of skin and soft tissue infections due to staphylococcus and streptococci, including **CA-MRSA**.

D. **Alternative agent for the treatment of infections due to gram-positive aerobes in patients allergic to penicillin** (cellulitis, septic arthritis, osteomyelitis).

E. Alternative for the treatment of encephalitis due to *Toxoplasmosis gondii* in AIDS patients (with pyrimethamine).

F. Alternative for the treatment of *Pneumocystis carini/ iroveci* pneumonia in AIDS patients allergic to sulfonamides (with primaquine).

G. Treatment of bacterial vaginosis (vaginal cream).

## VIII. ADVERSE EFFECTS

A. **Gastrointestinal**

1. Nausea, vomiting, diarrhea – 3 to 4%

2. *Clostridium difficile* **colitis (pseudomembranous colitis or antibiotic-associated diarrhea)**

a. Incidence 0.01 to 10% - clindamycin is **one of the worst inducers**

b. Caused by toxin produced by *C. difficile*

c. Ranges from mild and self-limiting to life-threatening

Pharmacology and Therapeutics
December 5, 2011

Protein Synthesis Inhibitors III: Macrolides, Clindamycin, etc.
Joseph R. Lentino, M.D., Ph.D.

d. Can occur with oral, intravenous, or topical

3. Other – abdominal distention, metallic taste

B. **Hepatotoxicity** – elevation in transaminases

C. **Hypersensitivity** – rash, drug fever, eosinophilia

D. **Other** – neutropenia, thrombocytopenia (rare)

IX. **DOSAGE AND ADMINISTRATION**

A. **Oral** – available as 75mg, 150mg and 300mg capsules; 75mg per 5ml oral solution

1. *Adult dose* = 150 mg to 450 mg PO every 6 hours (dose depends on the severity of infection)

*Pediatric dose* = 8 to 25 mg/kg/day in 3 to 4 divided doses

B. **Parenteral –** higher doses for more severe infections

1. *Adult dose* = 300 mg to 900 mg IV every 8 hours (dose depends on the severity of infection – up to 1200 mg every 6 hours for *Toxoplasmosis* encephalitis)

2. *Pediatric dose* = 15 to 40 mg/kg/day in 3 to 4 divided doses

## THE MACROLIDES

## I. INTRODUCTION

The macrolides currently available for use in the United States include erythromycin, clarithromycin, and azithromycin. Erythromycin is a naturally occurring macrolide that has been in clinical use for over 40 years - it is acid labile, has a relatively narrow spectrum of activity, is poorly tolerated when administered orally, and has a short elimination half-life. Both clarithromycin and azithromycin are semisynthetic derivatives of erythromycin that were approved in 1991, with structural modifications to improve tissue penetration, enhance the spectrum of activity, improve tolerability, and improve pharmacologic characteristics (less acid labile, longer elimination half-lives).

## II. CHEMISTRY

Pharmacology and Therapeutics
December 5, 2011

Protein Synthesis Inhibitors III: Macrolides, Clindamycin, etc.
Joseph R. Lentino, M.D., Ph.D.

A.    **Erythromycin** is a natural macrolide derived from *Streptomyces erythreus* that contains a 14-membered macrocyclic lactone ring.

B.    **Clarithromycin** is a semisynthetic macrolide structurally derived from erythromycin. Clarithromycin is also a 14-membered ring, synthesized by substituting a methoxy group for the C-6 hydroxyl group of erythromycin. This structural change improved oral bioavailability (by increasing acid stability), provided enhanced antibacterial potency, enhanced tissue penetration, and prolonged the elimination half-life.

C.    **Azithromycin** is also a semisynthetic derivative of erythromycin in which an amino group is inserted into the erythromycin ring at position 9a. Azithromycin is a **15**-membered ring, and is technically considered an *azalide*. These structural changes improved oral bioavailability (by increasing acid stability), improved antibacterial potency (especially against gram-negative aerobes like *H. influenzae*), enhanced tissue penetration, and prolonged the elimination half-life.



Erythromycin ($R_1 = CH_3$, $R_2 = H$)
Clarithromycin ($R_1$, $R_2 = CH_3$)

## III.    MECHANISM OF ACTION

A.    Macrolide antibiotics interfere with microbial protein synthesis (translocation steps) at the ribosomal level. The macrolides reversibly bind to the **50S ribosomal subunit** to induce dissociation of peptidyl transfer RNA from the ribosome during the elongation phase so that **protein synthesis is suppressed and bacterial growth is inhibited**.

B.    Macrolides typically display **bacteriostatic** activity; however, they may display bactericidal activity when present at high concentrations against very susceptible organisms (*S. pneumoniae*, *S. pyogenes*).

Pharmacology and Therapeutics
December 5, 2011

Protein Synthesis Inhibitors III: Macrolides, Clindamycin, etc.
Joseph R. Lentino, M.D., Ph.D.

## IV.   MECHANISMS OF RESISTANCE

A.   **Active efflux** – *mef* gene encodes for an efflux pump, which pumps the macrolide out of the cell; usually **confers low-level resistance to the macrolides (macrolide therapy may still be used in some cases);** accounts for the majority (70 to 80%) of macrolide-resistant *S. pneumoniae* in the US.

B.   **Alteration in the binding site** – methylation of the macrolide 50S binding site coded for by the *erm* gene (erythromycin ribosomal methylase), which leads to low affinity binding of the macrolides; **confers high-level resistance to all macrolides and other antibiotics that bind to the 50S ribosome** (such as clindamycin and Synercid®); accounts for the majority of macrolide-resistant *S. pneumoniae* in Europe.

C.   **Cross-resistance is usually observed among the macrolides.**

## V.   SPECTRUM OF ACTIVITY

A.   The macrolides are primarily bacteriostatic, but may display bactericidal activity under certain circumstances or against specific organisms.  They typically display **time- dependent activity**, however in some situations; azithromycin may display concentration-dependent activity.

B.   **Gram-positive aerobes** (C > E > A)

- Methicillin–susceptible *S. aureus* (MSSA – marginal activity)
- Group and viridans streptococci
- *S. pneumoniae* (active against PSSP; poor activity against PISP and PRSP; covers ~ 70% of strains)
- *Bacillus spp, Corynebacterium spp.*

C.  **Gram-negative aerobes** (A > C > E) – **NOT the Enterobacteriaceae**

- *Haemophilus influenzae* (not erythromycin)
- *Moraxella catarrhalis*
- *Neisseria spp*.

D.   **Other Organisms** (Azithro and Clarithro are better for *Legionella* and *Mycoplasma*)

- ***Legionella pneumophila***
- *Mycoplasma pneumoniae* and *hominis*
- *Chlamydophila pneumoniae* and *Chlamydia trachomatis*
- *Treponema pallidum* (Syphilis)
- *Campylobacter jejuni*

- *Borrelia burgdorferi* (Lyme disease)
- *Bordetella pertussis, Brucella, Pasteurella, Ureaplasma, Actinomyces*
- ***Mycobacterium avium complex*** (Azithro and Clarithro)
- Other atypical mycobacteria - Clarithromycin

E.  **Anaerobes** – activity against anaerobes "above the diaphragm"

**VI.  PHARMACOLOGY –erythromycin and azithromycin are available PO and IV; see Pharmacokinetic Table on page 5**

A.  **Absorption**

1.  *Erythromycin* – variable absorption (F = 15 to 45%) depending on the formulation; food decreases the absorption of all preparations except the estolate form

    a.  **Erythromycin base** is acid labile and subject to destruction by gastric acid; various preparations of erythromycin base are available with an acid-resistant coating (enteric coated) to delay destruction until it reaches the small bowel where it is absorbed.

    b.  **Erythromycin esters and ester salts (stearate, estolate, ethyl succinate)** – are more acid stable and better absorbed

2.  *Clarithromycin* – is acid stable and well absorbed from the GI tract (**regardless of the presence of food**); oral bioavailability is 52 to 55% with peak concentrations occurring at 3 hours

3.  *Azithromycin* – is acid stable; oral bioavailability approaches 37% with peak concentrations occurring at 2 to 3 hours; food does not affect the absorption of the tablets or suspension

B.  **Distribution**

1.  All 3 macrolides extensively distribute into ___tissues___ (**except for the CSF**) and ___cells___ (including macrophages and neutrophils). Both clarithromycin and azithromycin achieve substantially higher tissue concentrations in relationship to serum concentrations; achieve minimal serum concentrations that they may be ineffective for bacteremia). Both clarithromycin and azithromycin achieve higher intracellular concentrations.

C.  **Elimination**

1.  *Erythromycin*

a.    Excreted primarily in the bile with some demethylation in the liver by **CYP450 enzymes**; 2 to 15% of a dose is excreted in the urine

b.    Half-life is 1.4 hours, but may be prolonged up to 5 hours in patients with renal failure (but **NO dosage adjustment is necessary**)

2.    *Clarithromycin*

a.    Extensively metabolized in the liver by the **CYP450 enzymes** (8 metabolites, with one active metabolite); 18% of the parent drug and all of its metabolites are excreted in the urine

b.    Normal elimination half-life is 3 to 7 hours, which is markedly prolonged in the presence of renal insufficiency so that **dosage adjustment is necessary in patients with a CrCl < 30 ml/min**

3.    *Azithromycin*

a.    Biliary excretion, predominantly as unchanged drug into the feces

b.    Elimination half-life = **68 hours** due to extensive tissue sequestration and binding (tissue half-life estimated at 4 days)

4.    **NONE of the macrolides are removed during hemodialysis or peritoneal dialysis**

| Drug and Preparation | Dosage | F (%) | Cmax (mg/L) | Vd (L/kg) | Elimination Half-life (hours) | Route of Elimination |
|---|---|---|---|---|---|---|
| **Erythromycin** | 500mg BID to QID | 15-45 | 3.0 | 0.64 | 1.4 - 2 | Biliary and hepatic |
| **Clarithromycin** | 500mg BID | 50 | **2.4-3.5** | 3.2-3.8 | 3 - 7 | Renal and hepatic |
| **Azithromycin** | | | | | 68 | Biliary |
| Suspension | 10mg/kg | 37 | **0.38** | | | |
| Tablet | 500mg QD | 34 | **0.34** | 23-31 | | |
| Intravenous | 500mg QD | 100 | **3.63** | **33** | | |

F = bioavailability

**VII. CLINICAL USES – useful in penicillin-allergic patients**

    A.    **Respiratory Tract Infections**

        1.    *Pharyngitis, Tonsillitis, Otitis Media, Sinusitis* – alternative in penicillin-allergic patients

        2.    *Acute Exacerbations of Chronic Bronchitis* – azithromycin and clarithromycin are best if *H. influenzae* is suspected

        3.    *Community Acquired Pneumonia* - especially for ***atypical coverage***; **monotherapy in outpatients or combined with a β-lactam (e.g., ceftriaxone) in inpatients**

        4.    *Other* – Pertussis, *C. diphtheriae*

    B.    **Uncomplicated Skin and Soft Tissue Infections**

    C.    **Sexually Transmitted Diseases**

        **1.**    **A single 1-gram dose of azithromycin** is effective for the treatment of **nongonococcal urethritis** or **cervicitis** due to ***Chlamydia trachomatis***

    D.    ***Mycobacterium avium* Complex Infections (MAC)** – clarithromycin (500 to 1000 mg every 12 hours) as part of a primary combination regimen for treatment; azithromycin alone for prophylaxis (1200 mg weekly)

    E.    **Other**: *Campylobacter jejuni* infections, *Helicobacter pylori* (in combination)

    F.    **Macrolides are alternative antibiotics for the treatment of the following infections in penicillin-allergic patients:**

        2.    Group A streptococcal upper respiratory infections
        3.    Prophylaxis of bacterial endocarditis
        4.    Syphilis and gonorrhea
        5.    Superficial minor staphylococci infection
        6.    Rheumatic fever prophylaxis

**VIII. ADVERSE REACTIONS**

    A.    **Gastrointestinal -** epigastric distress, abdominal pain, nausea, vomiting, and diarrhea **– most common (in up to 33% of patients)** with oral administration of **erythromycin** (may also occur with IV)**;** less common with clarithromycin and azithromycin (10%)

    B.    **Cholestatic hepatitis** (rare) - most often seen in adult patients who receive > 1 to 2 weeks of erythromycin estolate therapy

Pharmacology and Therapeutics
December 5, 2011

Protein Synthesis Inhibitors III: Macrolides, Clindamycin, etc.
Joseph R. Lentino, M.D., Ph.D.

C.   **Thrombophlebitis and Infusion Site Irritation** (intravenous erythromycin and azithromycin) - erythromycin lactobionate or gluceptate can cause thrombophlebitis, which can be partially avoided by diluting the dose in at least 250 ml of intravenous fluid and infusing slowly over 60 minutes into a large vein

D.   **Allergic reactions** (rash, fever, eosinophilia)

E.   **Ototoxicity** - rare; has been reported in patients with renal insufficiency who are receiving high intravenous doses of erythromycin (≥4 gm/day)

F.   **QT prolongation** – erythromycin and clarithromycin

## IX.   DRUG INTERACTIONS

A.   Both **erythromycin** and **clarithromycin** are *inhibitors of the cytochrome P450* (3A4 and 2C9) enzyme system.  Concomitant administration may **increase the serum concentrations of the following drugs (and potentially lead to toxicity):**

- **Theophylline**
- *Carbamazepine*
- **Valproate**
- **Cyclosporine**
- **Digoxin**
- Disopyramide
- **Phenytoin**
- Terfenadine and Astemizole
- Cisapride
- **Warfarin**
- Ergot alkaloids

B.   **Azithromycin does NOT inhibit the cytochrome P450 enzyme system**, and therefore is **NOT associated with the drug-drug interactions** listed above.

# X.   DOSING IN PEDIATRICS AND ADULTS

| Agent | Route of Administration | Standard Adult Dose | Pediatric Dosing |
|---|---|---|---|
| **Erythromycin** | Oral | 250-500 mg TID to QID | 30-50 mg/kg/day, divided into 3 to 4 daily doses |
| **Erythromycin lactobionate** | Intravenous | 250-1000 mg every 6 hours | |
| **Clarithromycin** | Oral | 250-500 mg BID (1000 mg XL QD) | 15 mg/kg/day, divided in 2 daily doses |

Pharmacology and Therapeutics
December 5, 2011

Protein Synthesis Inhibitors III: Macrolides, Clindamycin, etc.
Joseph R. Lentino, M.D., Ph.D.

| | | | |
|---|---|---|---|
| **Azithromycin** | Oral | 500 mg x 1, then 250 mg QD for 4 days (Z-Pak) 500mg QD x 3 days (Tri-Pak) | 10 mg/kg/day |
| **Azithromycin** | Intravenous | 500 mg QD | |

Pharmacology and Therapeutics
December 5, 2011

Protein Synthesis Inhibitors III: Macrolides, Clindamycin, etc.
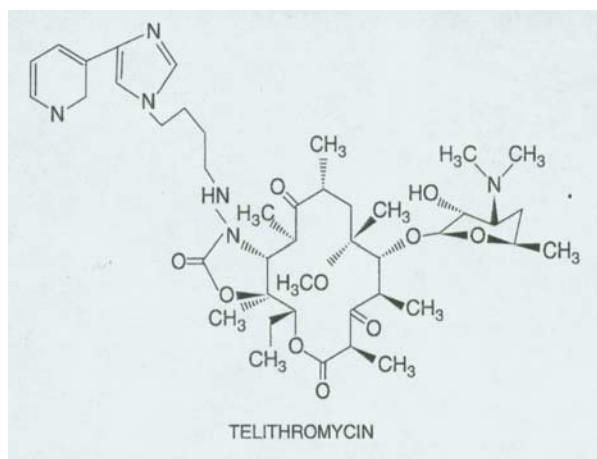Joseph R. Lentino, M.D., Ph.D.

## THE KETOLIDES

I.     **INTRODUCTION**

The ketolides are structural derivatives of macrolides that have been recently developed to provide activity against macrolide-resistant *S. pneumoniae*. However, the structural modifications provide only limited activity against *H. influenzae.* Telithromycin (Ketek[®]) is currently the only FDA-approved ketolide antibiotic and is only available orally.

II.    **CHEMISTRY**

   A.     The ketolides are structurally related to the macrolide antibiotics. Telithromycin is derived from clarithromycin, and is also a 14-membered macrocyclic ring, that contains a ketone at position 3, a methyl group at position 6, and a carbamate extension at position 11-12. These structural changes improve acid stability, increase antibacterial potency, and provide activity against macrolide-resistant bacteria.



TELITHROMYCIN

III.   **MECHANISM OF ACTION**

   A.     The ketolides are inhibitors of bacterial protein synthesis like the macrolides, and also bind to the 50S ribosomal subunit. However, telithromycin binds to 2 different sites (domain II and V) on the ribosome, and binds 10 times more tightly than the macrolides to domain II, which provides activity against macrolide-resistant strains.

IV.    **SPECTRUM OF ACTIVITY**

   A.     The ketolides are protein synthesis inhibitors that are generally **bacteriostatic**; but may display **concentration-dependent bactericidal activity** against some organisms.

       1.     The spectrum of activity of telithromycin is similar to that of the new macrolides (Azithro and Clarithro) with exceptions noted below:

Pharmacology and Therapeutics
December 5, 2011

Protein Synthesis Inhibitors III: Macrolides, Clindamycin, etc.
Joseph R. Lentino, M.D., Ph.D.

- **Gram-positive aerobes**
  Macrolide-resistant *S. pneumoniae*

- **Gram-negative aerobes**
  *H. influenzae, Moraxella catarrhalis* (potentially <u>*less*</u> active)

- **Other Organisms**
  *Borrelia burgdorferi* (10 times more active than macrolides)
  Has not been adequately studied against Mycobacteria or atypicals

## V.    PHARMACOLOGY – only available orally

A.    **Absorption** – the bioavailability of telithromycin is 57%, peak concentrations occur within 1 to 2 hours and are NOT affected by food

B.    **Distribution** – penetrates tissue well; protein binding is 60 to 70%

C.    **Elimination** – telithromycin is metabolized by the **cytochrome P450** system and then eliminated in the feces (75%); elimination half-life = 10 hours; **NO dosage adjustments are necessary in the presence of renal insufficiency**

## VI.    ADVERSE EFFECTS

A.    **Gastrointestinal – diarrhea**, nausea, vomiting, **hepatotoxicity\***

B.    **QTc interval prolongation**

C.    **Decreased visual acuity and blurred vision\***

## VII.    DRUG INTERACTIONS

A.    **Inhibitor of cytochrome P450 3A4** – watch for **drug interactions** with agents eliminated by this enzyme system

## VIII.    CLINICAL USES AND DOSING –**only currently approved for the treatment of mild-moderate community-acquired pneumonia due to adverse effect profile (risk outweighs benefit in treatment of sinusitis or bronchitis)**
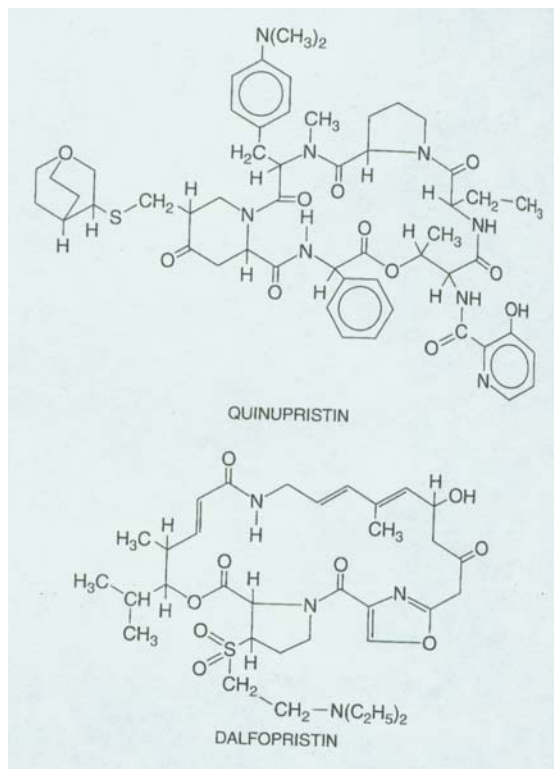
A.    Community Acquired Pneumonia – **800mg PO QD for 7 to 10 days**

Pharmacology and Therapeutics
December 5, 2011

Protein Synthesis Inhibitors III: Macrolides, Clindamycin, etc.
Joseph R. Lentino, M.D., Ph.D.

B.      **Acute Bacterial Sinusitis – 800mg PO QD for 5 days**

C.      **Acute Exacerbations of Chronic Bronchitis – 800mg PO QD for 5 days**

# I.      STREPTOGRAMINS

A.      **QUINUPRISTIN / DALFOPRISTIN (Synercid®)** – IV only

1.      **Introduction** – Synercid® is the first injectable streptogramin available in the US, approved by the FDA in September 1999. Synercid® was developed in response to the need for antibiotics with activity against resistant gram-positive organisms, namely VRE.

2.      **Chemistry** – Synercid® is a combination of 2 semisynthetic pristinamycin derivatives in a 30:70 w/w ratio (quinupristin: dalfopristin).



3.      **Mechanism of Action** – Quinupristin and dalfopristin act individually on the 50S ribosomal subunit to inhibit early and late stages of bacterial protein

Pharmacology and Therapeutics
December 5, 2011

Protein Synthesis Inhibitors III: Macrolides, Clindamycin, etc.
Joseph R. Lentino, M.D., Ph.D.

synthesis; each agent alone is **bacteriostatic**, but the combination produces an additive or synergistic effect (sometimes bactericidal)

4. **Mechanism of Resistance** – alteration of ribosomal binding site (most common – encoded by *erm* gene); enzymatic inactivation

5. **Spectrum of Activity:**

   a. **Gram-positive organisms**
   - *Staphylococcus aureus* and CNS (**MS and MR**)
   - *Streptococcus pneumoniae* (including **PRSP**)
   - Group Streptococci (A, B)
   - Viridans Streptococci
   - *Enterococcus faecium* **ONLY** – including **VRE (however, NOT ACTIVE vs.** *E. faecalis***)**
   - Others – *Listeria monocytogenes, Clostridium* (not *C. difficile*), *Peptostreptococcus*

   b. **Gram-negative aerobes** – has limited activity against *Neisseria* and *Moraxella;* not active against Enterobacteriaceae

   c. **Atypical organisms** – *Mycoplasma pneumoniae, Legionella* (*in vitro* activity, not used clinically)

6. **Pharmacology**

   a. **Time-dependent bactericidal activity** (when bactericidal)

   b. **Significant PAE** exists for gram-positive organisms: 2 to 8 hours for *S. aureus*, 8.5 hours for vancomycin-sensitive *E. faecium*, 0.2 to 3.2 hours for vancomycin-resistant *E. faecium*

   c. **Absorption** – only available parenterally

   d. **Distribution** – penetrates into extravascular tissue, lung, bile, gallbladder, skin and soft tissue; minimal penetration into CSF; protein binding is 55 to 78% for quinupristin and 11 to 25% for dalfopristin

   e. **Elimination** – both agents are converted to active metabolites, which are eliminated by hepatic clearance or biliary elimination; urinary elimination accounts for only 15-18 %; half-life ranges 0.6 to 1 hour for quinupristin and 0.3 to 0.4 hours for dalfopristin; dosage adjustments **unnecessary** in patients with renal insufficiency, but **suggested** in patients with hepatic insufficiency

Pharmacology and Therapeutics
December 5, 2011

Protein Synthesis Inhibitors III: Macrolides, Clindamycin, etc.
Joseph R. Lentino, M.D., Ph.D.

7. **Clinical Uses and Dosing (very expensive - $350 per day for a 70-kg person)** – Synercid is used for the treatment of vancomycin-resistant *Enterococcus faecium* **(VREF) bacteremia** (7.5 mg/kg every 8 hours); complicated skin and skin structure infections caused by MSSA or *S. pyogenes*\* (7.5 mg/kg every 12 hours); catheter-related bacteremia (5 to 7.5 mg/kg every 8 hours); other uses include infections due to MRSA and community-acquired pneumonia (when vancomycin, linezolid, and daptomycin cannot be used)

8. **Drug Interactions** - *Cytochrome P450 3A4 inhibitor* $\Rightarrow$ potential for drug interactions by enhancing serum concentrations of drugs eliminated by this pathway; limited clinical data available

   a. Antihistamines – astemizole, terfenadine
   b. Antiretrovirals – delavirdine, nevirapine, indinavir, ritonavir
   c. Antineoplastics – paclitaxel, docetaxel
   d. Benzodiazepines – midazolam, diazepam
   e. Calcium channel blockers – dihydropyridines, nondihydropyridines
   f. **Lipid-lowering agents - HMG-CoA reductase inhibitors**
   g. GI motility agents – cisapride
   h. **Immunosuppressive agents – cyclosporine, tacrolimus**
   i. Steroids – methylprednisolone
   j. Other – **carbamazepine**, quinidine, lidocaine

9. **Adverse Effects**

   a. **Venous irritation** – significantly greater than comparators (66% vs. 33%); especially with peripheral administration

   b. **Gastrointestinal** – nausea, vomiting, diarrhea

   c. **Myalgias, arthralgias** – 2%

   d. **Rash –** 2.5%

## Protein Synthesis Inhibitors  III

**Date:**  December 6, 2011 – 10:30 am

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

## Learning Objectives:

1.      Describe the mechanisms of action and mechanisms of resistance of  clindamycin,
        macrolides and streptogramins
2.      List the spectrum of activity of clindamycin, macrolides and streptogramins
3.      Describe the pharmacokinetic characteristics of clindamycin, macrolides and
        streptogramins
4.      List the major clinical uses of clindamycin, macrolides and streptogramins
5.      List the major adverse effects associated with clindamycin, macrolides and
        streptogramins.
6.      List the major drug interactions associated with clindamycin, macrolides and
        streptogramins.

## Prototypical Drugs:

**Lincosamides:**       Clindamycin

**Macrolides:**          **Erythromycin, clarithromycin, azithromycin**

**Ketolides:**          Telithromycin

**Streptogramins:**     Quinupristin-dalfopristin (Synercid®)

Pharmacology and Therapeutics
December 6, 2011

Protein Synthesis Inhibitors III: Macrolides, Clindamycin, etc.
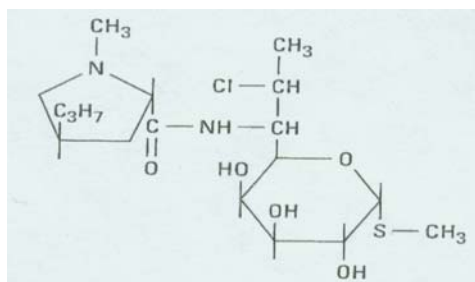Joseph R. Lentino, M.D., Ph.D.

## CLINDAMYCIN (Cleocin®) – IV and PO
### Original Handout written by S. Erdman, Pharm.D. presented by J. Lentino, M.D.

## I.  INTRODUCTION

Clindamycin is a 7-deoxy, 7-chloro-derivative of the antibiotic lincomycin, a lincosamide antibiotic first isolated from *Streptomyces lincolnesis* in 1962.  Clindamycin was introduced into clinical practice in 1966, and replaced the use of lincomycin due to its broader spectrum of antimicrobial activity and better oral absorption.

## II.  CHEMISTRY

a.  Clindamycin is a derivative of the amino acid *trans*-L-4-n-propylhygrinic acid, attached to a sulfur-containing derivative of an octose.



## III.  MECHANISM OF ACTION

A.  Clindamycin inhibits protein synthesis by exclusively binding (reversibly) to the 50S ribosomal subunit.

B.  Although clindamycin, the macrolides, the streptogramins, and chloramphenicol are not structurally related, they all act at sites within close proximity on the 50S ribosome and may competitively inhibit the action of each other.

C.  Clindamycin is **primarily bacteriostatic**, but can display **time-dependent bactericidal** activity depending on the infecting bacteria, inoculum of bacteria, and concentration of antibiotic at the site of infection.

## IV.  MECHANISM OF RESISTANCE

A.  Alteration of the ribosomal binding site – ribosomal methylation by *erm*-encoded enzymes; cross-resistance with macrolides and streptogramins occur in the presence of this enzyme (MLS$_b$ resistance)

B.  Clindamycin is NOT a substrate for macrolide efflux pumps, and strains that are resistant to macrolides by this mechanism remain susceptible to clindamycin.

V.    **SPECTRUM OF ACTIVITY**

A.    **Gram-Positive Aerobes** – clindamycin is active against most gram-positive aerobes

*Staphylococcus aureus* (**MSSA** and **CA-MRSA**)
*Streptococcus pneumoniae* (PSSP)
*Streptococcus pyogenes* and other Group streptococci
Viridans streptococcus

B.    **Anaerobes** – clindamycin is active against many gram-positive and gram-negative anaerobes, but is primarily useful for anaerobes *above the diaphragm*

| *Gram-positive anaerobes* | *Gram-negative anaerobes* |
| --- | --- |
| *Peptostreptococcus spp.* | *Bacteroides spp.* (resistance emerging) |
| *Clostridium spp.* (**not *C. difficile***) | *Prevotella spp.* |
| *Actinomyces* | *Fusobacterium* |
| *Propionibacterium* | |

C.    **Other Atypical Bacteria**:

*Pneumocystis carinii/jiroveci*
*Toxoplasmosis gondii*
*Plasmodium falciparum* and *vivax* (malaria)

VI.    **PHARMACOLOGY**

A.    **Absorption** – clindamycin is rapidly and almost completely absorbed after oral administration; bioavailability approaches 90%; food has minimal effect on the absorption of clindamycin

B.    **Distribution**

1.    Good serum concentrations are achieved by the oral, intramuscular or intravenous route.

2.    Clindamycin penetrates into most body tissues and fluids including sputum, bile, pleural fluid and **bone.**

3.    Clindamycin does NOT penetrate the CSF, even in the presence of inflamed meninges.

C.    **Metabolism/Elimination**

1.   Clindamycin is primarily metabolized by the liver (85%) to metabolites with varying antimicrobial activity, which are eliminated in the urine.
2.   Enterohepatic circulation of clindamycin and its metabolites can lead to prolonged antimicrobial presence in the stool.

3.   Half-life is 2.5 to 3 hours, which is prolonged in the presence of liver dysfunction.

4.   Clindamycin is NOT removed by hemodialysis or peritoneal dialysis.

## VII.   CLINICAL USES

A.   **Infections due to anaerobes** (including *B. fragilis)* **OUTSIDE THE CNS** – **pulmonary infections**, intraabdominal infections, pelvic infections, **diabetic foot infections**, decubitus ulcers.

B.   Alternative to penicillin in the treatment of infections due to *C. perfringens.*

C.   Treatment of skin and soft tissue infections due to staphylococcus and streptococci, including **CA-MRSA**.

D.   **Alternative agent for the treatment of infections due to gram-positive aerobes in patients allergic to penicillin** (cellulitis, septic arthritis, osteomyelitis).

E.   Alternative for the treatment of encephalitis due to *Toxoplasmosis gondii* in AIDS patients (with pyrimethamine).

F.   Alternative for the treatment of *Pneumocystis carini/   iroveci* pneumonia in AIDS patients allergic to sulfonamides (with primaquine).

G.   Treatment of bacterial vaginosis (vaginal cream).

## VIII.   ADVERSE EFFECTS

A.   **Gastrointestinal**

1.   Nausea, vomiting, diarrhea – 3 to 4%

2.   *Clostridium difficile* **colitis (pseudomembranous colitis or antibiotic-associated diarrhea)**

a.   Incidence 0.01 to 10% - clindamycin is **one of the worst inducers**

b.   Caused by toxin produced by *C. difficile*

c.   Ranges from mild and self-limiting to life-threatening

Pharmacology and Therapeutics
December 6, 2011

Protein Synthesis Inhibitors III: Macrolides, Clindamycin, etc.
Joseph R. Lentino, M.D., Ph.D.

        d.      Can occur with oral, intravenous, or topical

    3.      Other – abdominal distention, metallic taste

B.    **Hepatotoxicity** – elevation in transaminases

C.    **Hypersensitivity** – rash, drug fever, eosinophilia

D.    **Other** – neutropenia, thrombocytopenia (rare)

IX.    **DOSAGE AND ADMINISTRATION**

A.    **Oral** – available as 75mg, 150mg and 300mg capsules; 75mg per 5ml oral solution

    1.    *Adult dose* = 150 mg to 450 mg PO every 6 hours (dose depends on the severity of infection)

        *Pediatric dose* = 8 to 25 mg/kg/day in 3 to 4 divided doses

B.    **Parenteral –** higher doses for more severe infections

    1.    *Adult dose* = 300 mg to 900 mg IV every 8 hours (dose depends on the severity of infection – up to 1200 mg every 6 hours for *Toxoplasmosis* encephalitis)

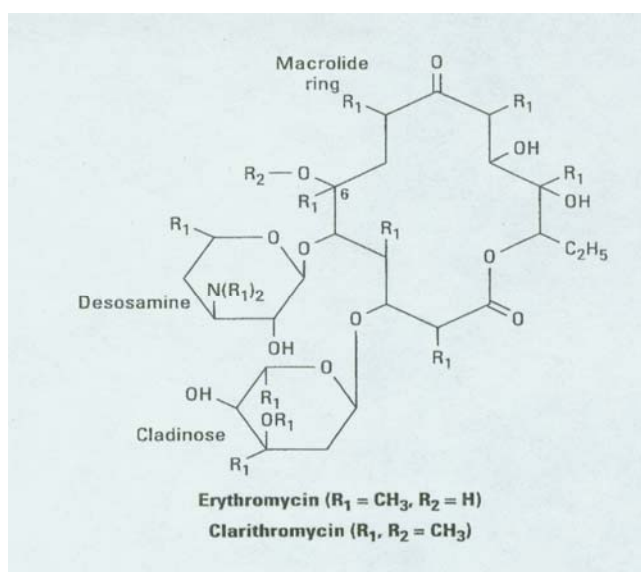    2.    *Pediatric dose* = 15 to 40 mg/kg/day in 3 to 4 divided doses

<div align="center">

**THE MACROLIDES**

</div>

I.    **INTRODUCTION**

The macrolides currently available for use in the United States include erythromycin, clarithromycin, and azithromycin.  Erythromycin is a naturally occurring macrolide that has been in clinical use for over 40 years - it is acid labile, has a relatively narrow spectrum of activity, is poorly tolerated when administered orally, and has a short elimination half-life.   Both clarithromycin and azithromycin are semisynthetic derivatives of erythromycin that were approved in 1991, with structural modifications to improve tissue penetration, enhance the spectrum of activity, improve tolerability, and improve pharmacologic characteristics (less acid labile, longer elimination half-lives).

II.    **CHEMISTRY**

A.    **Erythromycin** is a natural macrolide derived from *Streptomyces erythreus* that contains a 14-membered macrocyclic lactone ring.

B.    **Clarithromycin** is a semisynthetic macrolide structurally derived from erythromycin. Clarithromycin is also a 14-membered ring, synthesized by substituting a methoxy group for the C-6 hydroxyl group of erythromycin. This structural change improved oral bioavailability (by increasing acid stability), provided enhanced antibacterial potency, enhanced tissue penetration, and prolonged the elimination half-life.

C.    **Azithromycin** is also a semisynthetic derivative of erythromycin in which an amino group is inserted into the erythromycin ring at position 9a. Azithromycin is a **15**-membered ring, and is technically considered an *azalide*. These structural changes improved oral bioavailability (by increasing acid stability), improved antibacterial potency (especially against gram-negative aerobes like *H. influenzae*), enhanced tissue penetration, and prolonged the elimination half-life.



Erythromycin ($R_1 = CH_3$, $R_2 = H$)
Clarithromycin ($R_1$, $R_2 = CH_3$)

## III.    MECHANISM OF ACTION

A.    Macrolide antibiotics interfere with microbial protein synthesis (translocation steps) at the ribosomal level. The macrolides reversibly bind to the **50S ribosomal subunit** to induce dissociation of peptidyl transfer RNA from the ribosome during the elongation phase so that **protein synthesis is suppressed and bacterial growth is inhibited**.

B.    Macrolides typically display **bacteriostatic** activity; however, they may display bactericidal activity when present at high concentrations against very susceptible organisms (*S. pneumoniae*, *S. pyogenes*).

Pharmacology and Therapeutics
December 6, 2011

Protein Synthesis Inhibitors III: Macrolides, Clindamycin, etc.
Joseph R. Lentino, M.D., Ph.D.

## IV. MECHANISMS OF RESISTANCE

A. **Active efflux** – *mef* gene encodes for an efflux pump, which pumps the macrolide out of the cell; usually **confers low-level resistance to the macrolides (macrolide therapy may still be used in some cases);** accounts for the majority (70 to 80%) of macrolide-resistant *S. pneumoniae* in the US.

B. **Alteration in the binding site** – methylation of the macrolide 50S binding site coded for by the *erm* gene (erythromycin ribosomal methylase), which leads to low affinity binding of the macrolides; **confers high-level resistance to all macrolides and other antibiotics that bind to the 50S ribosome** (such as clindamycin and Synercid®); accounts for the majority of macrolide-resistant *S. pneumoniae* in Europe.

C. **Cross-resistance is usually observed among the macrolides.**

## V. SPECTRUM OF ACTIVITY

A. The macrolides are primarily bacteriostatic, but may display bactericidal activity under certain circumstances or against specific organisms. They typically display **time- dependent activity**, however in some situations; azithromycin may display concentration-dependent activity.

B. **Gram-positive aerobes** (C > E > A)

- Methicillin–susceptible *S. aureus* (MSSA – marginal activity)
- Group and viridans streptococci
- *S. pneumoniae* (active against PSSP; poor activity against PISP and PRSP; covers ~ 70% of strains)
- *Bacillus spp, Corynebacterium spp.*

C. **Gram-negative aerobes** (A > C > E) – **NOT the Enterobacteriaceae**

- *Haemophilus influenzae* (not erythromycin)
- *Moraxella catarrhalis*
- *Neisseria spp*.

D. **Other Organisms** (Azithro and Clarithro are better for *Legionella* and *Mycoplasma*)

- ***Legionella pneumophila***
- *Mycoplasma pneumoniae* and *hominis*
- *Chlamydophila pneumoniae* and *Chlamydia trachomatis*
- *Treponema pallidum* (Syphilis)
- *Campylobacter jejuni*

Pharmacology and Therapeutics
December 6, 2011

Protein Synthesis Inhibitors III: Macrolides, Clindamycin, etc.
Joseph R. Lentino, M.D., Ph.D.

- *Borrelia burgdorferi* (Lyme disease)
- *Bordetella pertussis, Brucella, Pasteurella, Ureaplasma, Actinomyces*
- ***Mycobacterium avium complex*** (Azithro and Clarithro)
- Other atypical mycobacteria - Clarithromycin

E.    **Anaerobes** – activity against anaerobes "above the diaphragm"

VI.    **PHARMACOLOGY –erythromycin and azithromycin are available PO and IV; see Pharmacokinetic Table on page 5**

A.    **Absorption**

1.    *Erythromycin* – variable absorption (F = 15 to 45%) depending on the formulation; food decreases the absorption of all preparations except the estolate form

a.    **Erythromycin base** is acid labile and subject to destruction by gastric acid; various preparations of erythromycin base are available with an acid-resistant coating (enteric coated) to delay destruction until it reaches the small bowel where it is absorbed.

b.    **Erythromycin esters and ester salts (stearate, estolate, ethyl succinate)** – are more acid stable and better absorbed

2.    *Clarithromycin* – is acid stable and well absorbed from the GI tract (**regardless of the presence of food**); oral bioavailability is 52 to 55% with peak concentrations occurring at 3 hours

3.    *Azithromycin* – is acid stable; oral bioavailability approaches 37% with peak concentrations occurring at 2 to 3 hours; food does not affect the absorption of the tablets or suspension

B.    **Distribution**

1.    All 3 macrolides extensively distribute into ***tissues*** (**except for the CSF**) and ***cells*** (including macrophages and neutrophils).  Both clarithromycin and azithromycin achieve substantially higher tissue concentrations in relationship to serum concentrations; achieve minimal serum concentrations that they may be ineffective for bacteremia).  Both clarithromycin and azithromycin achieve higher intracellular concentrations.

C.    **Elimination**

1.    *Erythromycin*

Pharmacology and Therapeutics
December 6, 2011

Protein Synthesis Inhibitors III: Macrolides, Clindamycin, etc.
Joseph R. Lentino, M.D., Ph.D.

a. Excreted primarily in the bile with some demethylation in the liver by **CYP450 enzymes**; 2 to 15% of a dose is excreted in the urine

b. Half-life is 1.4 hours, but may be prolonged up to 5 hours in patients with renal failure (but **NO dosage adjustment is necessary**)

2. *Clarithromycin*

a. Extensively metabolized in the liver by the **CYP450 enzymes** (8 metabolites, with one active metabolite); 18% of the parent drug and all of its metabolites are excreted in the urine

b. Normal elimination half-life is 3 to 7 hours, which is markedly prolonged in the presence of renal insufficiency so that **dosage adjustment is necessary in patients with a CrCl < 30 ml/min**

3. *Azithromycin*

a. Biliary excretion, predominantly as unchanged drug into the feces

b. Elimination half-life = **68 hours** due to extensive tissue sequestration and binding (tissue half-life estimated at 4 days)

4. **NONE of the macrolides are removed during hemodialysis or peritoneal dialysis**

| Drug and Preparation | Dosage | F (%) | Cmax (mg/L) | Vd (L/kg) | Elimination Half-life (hours) | Route of Elimination |
|---|---|---|---|---|---|---|
| **Erythromycin** | 500mg BID to QID | 15-45 | 3.0 | 0.64 | 1.4 - 2 | Biliary and hepatic |
| **Clarithromycin** | 500mg BID | 50 | **2.4-3.5** | 3.2-3.8 | 3 - 7 | Renal and hepatic |
| **Azithromycin** | | | | | 68 | Biliary |
| Suspension | 10mg/kg | 37 | **0.38** | | | |
| Tablet | 500mg QD | 34 | **0.34** | 23-31 | | |
| Intravenous | 500mg QD | 100 | **3.63** | **33** | | |

F = bioavailability

Pharmacology and Therapeutics
December 6, 2011

Protein Synthesis Inhibitors III: Macrolides, Clindamycin, etc.
Joseph R. Lentino, M.D., Ph.D.

**VII.    CLINICAL USES – useful in penicillin-allergic patients**

A.    **Respiratory Tract Infections**

1.    *Pharyngitis, Tonsillitis, Otitis Media, Sinusitis* – alternative in penicillin-allergic patients

2.    *Acute Exacerbations of Chronic Bronchitis* – azithromycin and clarithromycin are best if *H. influenzae* is suspected

3.    *Community Acquired Pneumonia* - especially for ***atypical coverage***; **monotherapy in outpatients or combined with a β-lactam (e.g., ceftriaxone) in inpatients**

4.    *Other* – Pertussis, *C. diphtheriae*

B.    **Uncomplicated Skin and Soft Tissue Infections**

C.    **Sexually Transmitted Diseases**

1.    **A single 1-gram dose of azithromycin** is effective for the treatment of **nongonococcal urethritis** or **cervicitis** due to ***Chlamydia trachomatis***

D.    ***Mycobacterium avium* Complex Infections (MAC)** – clarithromycin (500 to 1000 mg every 12 hours) as part of a primary combination regimen for treatment; azithromycin alone for prophylaxis (1200 mg weekly)

E.    **Other**: *Campylobacter jejuni* infections, *Helicobacter pylori* (in combination)

F.    **Macrolides are alternative antibiotics for the treatment of the following infections in penicillin-allergic patients:**

2.    Group A streptococcal upper respiratory infections
3.    Prophylaxis of bacterial endocarditis
4.    Syphilis and gonorrhea
5.    Superficial minor staphylococci infection
6.    Rheumatic fever prophylaxis

**VIII.  ADVERSE REACTIONS**

A**.**    **Gastrointestinal -** epigastric distress, abdominal pain, nausea, vomiting, and diarrhea **– most common (in up to 33% of patients)** with oral administration of **erythromycin** (may also occur with IV)**;** less common with clarithromycin and azithromycin (10%)

B.    **Cholestatic hepatitis** (rare) - most often seen in adult patients who receive > 1 to 2 weeks of erythromycin estolate therapy

Pharmacology and Therapeutics
December 6, 2011

Protein Synthesis Inhibitors III: Macrolides, Clindamycin, etc.
Joseph R. Lentino, M.D., Ph.D.

C. **Thrombophlebitis and Infusion Site Irritation** (intravenous erythromycin and azithromycin) - erythromycin lactobionate or gluceptate can cause thrombophlebitis, which can be partially avoided by diluting the dose in at least 250 ml of intravenous fluid and infusing slowly over 60 minutes into a large vein

D. **Allergic reactions** (rash, fever, eosinophilia)

E. **Ototoxicity** - rare; has been reported in patients with renal insufficiency who are receiving high intravenous doses of erythromycin (≥4 gm/day)

F. **QT prolongation** – erythromycin and clarithromycin

## IX. DRUG INTERACTIONS

A. Both **erythromycin** and **clarithromycin** are *inhibitors of the cytochrome P450* (3A4 and 2C9) enzyme system. Concomitant administration may **increase the serum concentrations of the following drugs (and potentially lead to toxicity):**

- **Theophylline**
- *Carbamazepine*
- **Valproate**
- **Cyclosporine**
- **Digoxin**
- Disopyramide
- **Phenytoin**
- Terfenadine and Astemizole
- Cisapride
- **Warfarin**
- Ergot alkaloids

B. **Azithromycin does NOT inhibit the cytochrome P450 enzyme system**, and therefore is **NOT associated with the drug-drug interactions** listed above.

# X. DOSING IN PEDIATRICS AND ADULTS

| Agent | Route of Administration | Standard Adult Dose | Pediatric Dosing |
|---|---|---|---|
| **Erythromycin** | Oral | 250-500 mg TID to QID | 30-50 mg/kg/day, divided into 3 to 4 daily doses |
| **Erythromycin lactobionate** | Intravenous | 250-1000 mg every 6 hours | |
| **Clarithromycin** | Oral | 250-500 mg BID (1000 mg XL QD) | 15 mg/kg/day, divided in 2 daily doses |

Pharmacology and Therapeutics
December 6, 2011

Protein Synthesis Inhibitors III: Macrolides, Clindamycin, etc.
Joseph R. Lentino, M.D., Ph.D.

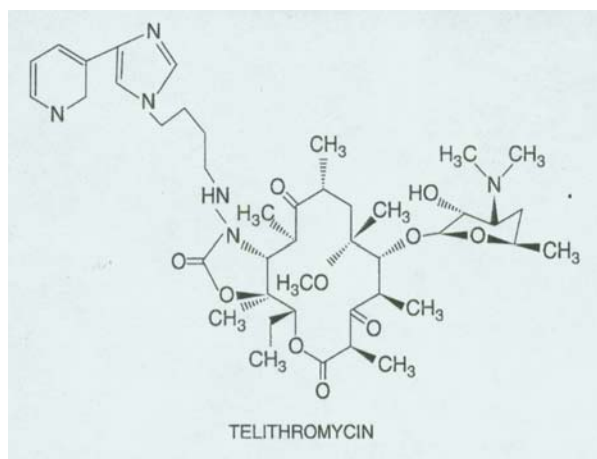| | | | |
|---|---|---|---|
| **Azithromycin** | Oral | 500 mg x 1, then 250 mg QD for 4 days (Z-Pak) 500mg QD x 3 days (Tri-Pak) | 10 mg/kg/day |
| **Azithromycin** | Intravenous | 500 mg QD | |

**THE KETOLIDES**

## I.    INTRODUCTION

The ketolides are structural derivatives of macrolides that have been recently developed to provide activity against macrolide-resistant *S. pneumoniae*.  However, the structural modifications provide only limited activity against *H. influenzae.* Telithromycin (Ketek[®]) is currently the only FDA-approved ketolide antibiotic and is only available orally.

## II.    CHEMISTRY

A.    The ketolides are structurally related to the macrolide antibiotics.  Telithromycin is derived from clarithromycin, and is also a 14-membered macrocyclic ring, that contains a ketone at position 3, a methyl group at position 6, and a carbamate extension at position 11-12.  These structural changes improve acid stability, increase antibacterial potency, and provide activity against macrolide-resistant bacteria.



TELITHROMYCIN

## III.    MECHANISM OF ACTION

A.    The ketolides are inhibitors of bacterial protein synthesis like the macrolides, and also bind to the 50S ribosomal subunit.  However, telithromycin binds to 2 different sites (domain II and V) on the ribosome, and binds 10 times more tightly than the macrolides to domain II, which provides activity against macrolide-resistant strains.

## IV.    SPECTRUM OF ACTIVITY

A.    The ketolides are protein synthesis inhibitors that are generally **bacteriostatic**; but may display **concentration-dependent bactericidal activity** against some organisms.

1.    The spectrum of activity of telithromycin is similar to that of the new macrolides (Azithro and Clarithro) with exceptions noted below:

Pharmacology and Therapeutics
December 6, 2011

Protein Synthesis Inhibitors III: Macrolides, Clindamycin, etc.
Joseph R. Lentino, M.D., Ph.D.

- **Gram-positive aerobes**
  Macrolide-resistant *S. pneumoniae*

- **Gram-negative aerobes**
  *H. influenzae, Moraxella catarrhalis* (potentially <u>less</u> active)

- **Other Organisms**
  *Borrelia burgdorferi* (10 times more active than macrolides)
  Has not been adequately studied against Mycobacteria or atypicals

# V.   PHARMACOLOGY – only available orally

A.   **Absorption** – the bioavailability of telithromycin is 57%, peak concentrations occur within 1 to 2 hours and are NOT affected by food

B.   **Distribution** – penetrates tissue well; protein binding is 60 to 70%

C.   **Elimination** – telithromycin is metabolized by the **cytochrome P450** system and then eliminated in the feces (75%); elimination half-life = 10 hours; **NO dosage adjustments are necessary in the presence of renal insufficiency**

## VI.   ADVERSE EFFECTS

A.   **Gastrointestinal – diarrhea**, nausea, vomiting, **hepatotoxicity***

B.   **QTc interval prolongation**

C.   **Decreased visual acuity and blurred vision***

## VII.   DRUG INTERACTIONS

A.   **Inhibitor of cytochrome P450 3A4** – watch for **drug interactions** with agents eliminated by this enzyme system

VIII.   CLINICAL USES AND DOSING –**only currently approved for the treatment of mild-moderate community-acquired pneumonia due to adverse effect profile (risk outweighs benefit in treatment of sinusitis or bronchitis)**
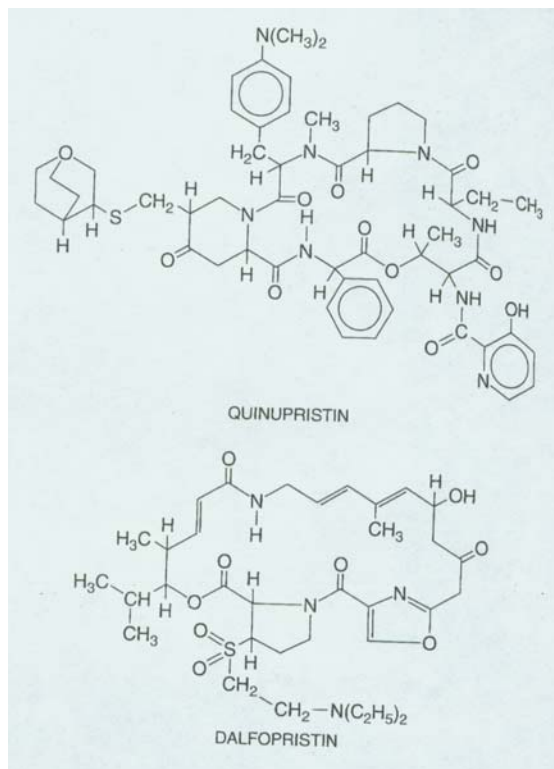
A.   Community Acquired Pneumonia – **800mg PO QD for 7 to 10 days**

Pharmacology and Therapeutics
December 6, 2011

Protein Synthesis Inhibitors III: Macrolides, Clindamycin, etc.
Joseph R. Lentino, M.D., Ph.D.

B.    **Acute Bacterial Sinusitis – 800mg PO QD for 5 days**


C.    **Acute Exacerbations of Chronic Bronchitis – 800mg PO QD for 5 days**


# I.    STREPTOGRAMINS

A.    **QUINUPRISTIN / DALFOPRISTIN (Synercid®)** – IV only

1.    **Introduction** – Synercid® is the first injectable streptogramin available in the US, approved by the FDA in September 1999. Synercid® was developed in response to the need for antibiotics with activity against resistant gram-positive organisms, namely VRE.

2.    **Chemistry** – Synercid® is a combination of 2 semisynthetic pristinamycin derivatives in a 30:70 w/w ratio (quinupristin: dalfopristin).



QUINUPRISTIN

DALFOPRISTIN

3.    **Mechanism of Action** – Quinupristin and dalfopristin act individually on the 50S ribosomal subunit to inhibit early and late stages of bacterial protein

Pharmacology and Therapeutics
December 6, 2011

Protein Synthesis Inhibitors III: Macrolides, Clindamycin, etc.
Joseph R. Lentino, M.D., Ph.D.

synthesis; each agent alone is **bacteriostatic**, but the combination produces an additive or synergistic effect (sometimes bactericidal)

4.  **Mechanism of Resistance** – alteration of ribosomal binding site (most common – encoded by *erm* gene); enzymatic inactivation

5.  **Spectrum of Activity:**

    a.  **Gram-positive organisms**
        - *Staphylococcus aureus* and CNS (**MS and MR**)
        - *Streptococcus pneumoniae* (including **PRSP**)
        - Group Streptococci (A, B)
        - Viridans Streptococci
        - *Enterococcus faecium* **ONLY** – including **VRE (however, NOT ACTIVE vs. *E. faecalis*)**
        - Others – *Listeria monocytogenes, Clostridium* (not *C. difficile*), *Peptostreptococcus*

    b.  **Gram-negative aerobes** – has limited activity against *Neisseria* and *Moraxella;* not active against Enterobacteriaceae

    c.  **Atypical organisms** – *Mycoplasma pneumoniae, Legionella* (*in vitro* activity, not used clinically)

6.  **Pharmacology**

    a.  **Time-dependent bactericidal activity** (when bactericidal)

    b.  **Significant PAE** exists for gram-positive organisms: 2 to 8 hours for *S. aureus*, 8.5 hours for vancomycin-sensitive *E. faecium*, 0.2 to 3.2 hours for vancomycin-resistant *E. faecium*

    c.  **Absorption** – only available parenterally

    d.  **Distribution** – penetrates into extravascular tissue, lung, bile, gallbladder, skin and soft tissue; minimal penetration into CSF; protein binding is 55 to 78% for quinupristin and 11 to 25% for dalfopristin

    e.  **Elimination** – both agents are converted to active metabolites, which are eliminated by hepatic clearance or biliary elimination; urinary elimination accounts for only 15-18 %; half-life ranges 0.6 to 1 hour for quinupristin and 0.3 to 0.4 hours for dalfopristin; dosage adjustments **unnecessary** in patients with renal insufficiency, but **suggested** in patients with hepatic insufficiency

Pharmacology and Therapeutics
December 6, 2011

Protein Synthesis Inhibitors III: Macrolides, Clindamycin, etc.
Joseph R. Lentino, M.D., Ph.D.

7. **Clinical Uses and Dosing (very expensive - $350 per day for a 70-kg person)** – Synercid is used for the treatment of vancomycin-resistant *Enterococcus faecium* **(VREF) bacteremia** (7.5 mg/kg every 8 hours); complicated skin and skin structure infections caused by MSSA or *S. pyogenes*\* (7.5 mg/kg every 12 hours); catheter-related bacteremia (5 to 7.5 mg/kg every 8 hours); other uses include infections due to MRSA and community-acquired pneumonia  (when vancomycin, linezolid, and daptomycin cannot be used)

8. **Drug Interactions** - *Cytochrome P450 3A4 inhibitor* $\Rightarrow$ potential for drug interactions by enhancing serum concentrations of drugs eliminated by this pathway; limited clinical data available

   a. Antihistamines – astemizole, terfenadine
   b. Antiretrovirals – delavirdine, nevirapine, indinavir, ritonavir
   c. Antineoplastics – paclitaxel, docetaxel
   d. Benzodiazepines – midazolam, diazepam
   e. Calcium channel blockers – dihydropyridines, nondihydropyridines
   f. **Lipid-lowering agents - HMG-CoA reductase inhibitors**
   g. GI motility agents – cisapride
   h. **Immunosuppressive agents – cyclosporine, tacrolimus**
   i. Steroids – methylprednisolone
   j. Other – **carbamazepine**, quinidine, lidocaine

9. **Adverse Effects**

   a. **Venous irritation** – significantly greater than comparators (66% vs. 33%); especially with peripheral administration

   b. **Gastrointestinal** – nausea, vomiting, diarrhea

   c. **Myalgias, arthralgias** – 2%

   d. **Rash –** 2.5%