PROTEIN SYNTHESIS INHIBITORS
- CLINDAMYCIN
- MACROLIDES
- STREPTOGRAMINS

Jenna Lopez, PharmD, BCIDP
Clinical Pharmacy Specialist, Infectious Disease

Learning Objectives

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

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

Clindamycin

Clindamycin is a semisynthetic derivative of lincomycin, isolated from Streptomyces lincolnensis in 1962. It was introduced into clinical practice in 1966.

Antimicrobial Class
- Lincosamide

Mechanism of Action
- Inhibits protein synthesis by binding to the 50S subunit of the ribosome → Bacteriostatic effect
  - Binds in close proximity to macrolides and Quinupristin/Dalfopristin (Synercid®) – may cause competitive inhibition
Clindamycin

Spectrum of activity:
- Gram positive:
  - Peptococcus sp
  - Peptostreptococcus sp
  - Staphylococcal sp (including methicillin resistant strains)
    - Increasing resistance with community acquired methicillin resistant Staphylococcus aureus (CA-MRSA)
  - Streptococcus sp
- Gram negative anaerobes:
  - Actinomyces sp
  - Bacteroides sp (Only certain species)
  - Clostridium sp
  - Fusobacterium sp
  - Prevotella sp

Clindamycin

<table>
<thead>
<tr>
<th>Gram Positive Bacteria 2017-2018</th>
<th>N</th>
<th>TETRACYCLINE</th>
<th>CLOXACILLIN</th>
<th>MACROLIDES</th>
<th>CLINDAMYCIN</th>
<th>LINCOSAMIDES</th>
<th>SULFAMETOXAZOLE</th>
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Clindamycin

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<thead>
<tr>
<th>Anaerobic Organism</th>
<th>Number of Strains</th>
<th>Clindamycin</th>
<th>Macrolides</th>
<th>Lincosamides</th>
<th>Tetracycline</th>
<th>Ciprofloxacin</th>
<th>Sulfamethoxazole</th>
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Clindamycin
Clindamycin

### Mechanisms of Resistance

- **Altered target sites** – encoded by the *erm* gene, which alters 50S ribosomal binding site; confers high level resistance to macrolides, clindamycin and Synercid® (MLSb resistance)

- **Active efflux** – *mef* gene encodes for an efflux pump that pumps antibiotic out of the cell

- **Drug inactivation**

### Absorption – available IV and PO

- Rapidly and completely absorbed (90%); food has minimal effect on absorption

### Distribution

- Good serum concentrations with both IV & PO formulations
- Good tissue penetration including bone; minimal CSF penetration

### Elimination

- Clindamycin primarily metabolized by the liver (85%)
- Half-life is 2.5 to 3 hours
- Clindamycin is NOT removed during hemodialysis
**Clindamycin**

**Clinical Uses**
- **Anaerobic infections**
  - Not great for intra-abdominal anaerobes → many Bacteroides sp with high resistance
- **Skin and soft tissue infections**
  - Examples: decubitus ulcers, diabetic foot infections, cellulitis
- **Respiratory tract infections (empyema, abscess, pneumonitis, aspiration pneumonia)**

**Clinical Uses Continued**
- **Streptococcus pyogenes toxic shock syndrome**
  - Inactivates toxin
  - Used in combination with penicillin
- **Clostridium perfringens**
  - Inactivates toxin
  - Used in combination with a bactericidal agent
- **Alternative therapy**
  - PCP*, toxoplasmosis*, malaria*, bacterial vaginosis

*Not given as a single agent

**Clindamycin**

**Dosing:**
- IV: 600-900 mg IV every 8 hours
- PO: 300-450 mg PO every 6-8 hours
- No renal dose adjustments

**Adverse Effects:**
- C. difficile (0.01-10% incidence) → pseudomembranous colitis (Black Box Warning)
- Increased AST/ALT/Alk Phos/serum bilirubin → Rare, usually reversible
- Nausea/vomiting/diarrhea (3-4% incidence)
  - More prominent with oral formulation
- Allergy
Clindamycin

Monitoring:
- LFTs (periodically)

Drug-drug interactions:
- Cyclosporine: Decreased effects of cyclosporine
- Neuromuscular Blockers: Clindamycin enhances blocking effects

Clinical pearls:
- Compliance is difficult due to 3-4 times daily dosing
- Dosing of 450 mg PO is limited due to gastrointestinal side effects with higher doses
- CA-MRSA coverage declining
  ▪ Think twice before prescribing for these infections
- No CNS penetration

Azithromycin, Clarithromycin, Erythromycin

Erythromycin is a naturally-occurring macrolide derived from Streptomyces erythreus

- Structural derivatives include azithromycin and clarithromycin:
  ▪ Broader spectrum of activity
  ▪ Improved pharmacokinetic (PK) properties – better bioavailability, better tissue penetration, prolonged half-lives
  ▪ Improved tolerability
Azithromycin, Clarithromycin, Erythromycin

Antimicrobial class:
- Macrolide

Mechanism of action:
- Bind to the 50s ribosomal subunit  
  Inhibits protein synthesis  
  Bacteriostatic effect
  - Bactericidal when present at high concentrations against susceptible organisms
  - Erythromycin and clarithromycin display time-dependent activity
  - Azithromycin is concentration-dependent

Spectrum of activity:

- Gram positive: (Clarithro> Erythro> Azithro)
  - Group A,B,C, and G Streptococcus
  - Staphylococcus aureus (MSSA)
  - Streptococcus pneumoniae (resistance increasing)
  - Streptococcus pyogenes

- Gram negative: (Azithro> Clarithro> Erythro)
  - Bordetella pertussis
  - Haemophilus influenzae (erythro has less activity)
  - Helicobacter pylori (clarithro is the most active)
  - Moraxella catarrhalis
  - Neisseria gonorrhoea
  - Neisseria meningitidis

- Atypical:
  - Chlamydia trachomatis
  - Legionella pneumophila
  - Mycoplasma pneumoniae
  - Rickettsia sp

- Mycobacterium:
  - Mycobacterium avium
  - Mycobacterium chelonae
Azithromycin, Clarithromycin, Erythromycin

Mechanisms of resistance:

- Active efflux – mef gene encodes for an efflux pump that pumps the macrolide out of the cell and away from the ribosome; confers low level resistance to macrolides
  - Most common in the United States

- Altered target sites – encoded by the erm gene which alters the macrolide binding site on the ribosome; confers high level resistance to all macrolides, clindamycin, and Synercid®

Azithromycin, Clarithromycin, Erythromycin

Absorption

- Erythromycin – variable absorption (15 to 45%); food may decrease the absorption
  - Base: destroyed by gastric acid; enteric coated
  - Esters and ester salts: more acid stable

- Clarithromycin – acid stable and well-absorbed (55%) regardless of presence of food

- Azithromycin – acid stable; bioavailability = 37% regardless of presence of food
Azithromycin, Clarithromycin, Erythromycin

Distribution
- Extensive tissue and cellular distribution – clarithromycin and azithromycin with higher tissue concentrations
- Minimal CSF penetration

Elimination
- Erythromycin is excreted in bile and metabolized by CYP450
- Clarithromycin is metabolized and also partially eliminated by the kidney (18% of parent and all metabolites)
- Half-life:
  - Azithromycin: 68 hours
  - Clarithromycin: 3-7 hours
  - Erythromycin: 1.5-2 hours

Clinical Uses
- Respiratory tract infections
  - Pharyngitis/ Tonsillitis → PCN-allergic patients
  - Sinusitis, Chronic obstructive pulmonary disease (COPD) exacerbation, Otitis Media (azithro best if *H. influenzae* suspected)
  - Community-acquired pneumonia (+/- a beta-lactam dependent on patient specific factors)
  - Pertussis
- Sexually transmitted diseases (i.e. Chlamydia)
  - Single dose azithromycin 1 gram
Azithromycin, Clarithromycin, Erythromycin

Clinical Uses
- Uncomplicated skin infections
- *H. pylori* (Clarithro)
- *Mycobacterium avium* complex
  - Prophylaxis: Azithro
  - Treatment: Claritro and azithro

Azithromycin, Clarithromycin, Erythromycin

Dosing:
- **Azithromycin:**
  - 250-500 mg IV/PO once daily; 1000 mg PO once (Chlamydia); 1200 mg PO weekly (MAC prophylaxis)
  - No renal dose adjustments
- **Clarithromycin:**
  - CrCl ≥ 30 mL/min: 250-500 mg PO every 12 hours; 1000 mg PO once daily
  - CrCl < 30 mL/min: Decrease dose by 50%
- **Erythromycin:**
  - 250-500 mg PO every 6-12 hours
  - No renal dose adjustments

Azithromycin, Clarithromycin, Erythromycin

Adverse effects
- Gastrointestinal – up to 33%
  - Diarrhea/nausea/vomiting/abdominal pain
    - Highest incidence in erythromycin
- Increased AST/ALT
- Ototoxicity – tinnitus or deafness (reversible)
  - Dependent on serum concentration
- QT prolongation (Erythromycin > Clarithromycin > Azithromycin)
- Thrombophlebitis – IV erythro and azithro
  - Dilution of dose; slow administration
Azithromycin, Clarithromycin, Erythromycin

**Monitoring:**
- EKG (QT)
- Liver Function Tests (LFTs)
- Serum Creatinine (Scr) for clarithromycin

**Drug-drug interactions:**
- CYP 3A4 substrates (least interaction with Azithromycin)
- QT prolonging medications: Additive effect can prolong QT and possible result in Torsades
- Clarithromycin and Erythromycin
  - HMG CoA reductase inhibitors metabolized by CYP 3A4: Increased serum levels of HMG CoA reductase inhibitors
  - Clarithromycin
    - Zidovudine: Clarithromycin may decrease levels of zidovudine

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Azithromycin, Clarithromycin, Erythromycin

**Drug-drug interactions:**
- Erythromycin and clarithromycin– are inhibitors of cytochrome p450 system in the liver and may increase concentrations of:
  - Carbamazepine
  - Cisapride*      Phenytoin
  - Colchicine*     Statins (lovastatin*, simvastatin*)
  - Cyclosporine    Theophylline
  - Digoxin, Disopyramide Valproic acid
  - Ergot alkaloids* Warfarin
  - Terfenadine*, Astemizole*
  - Colchicine
  - Theophylline
  - Digoxin
  - Disopyramide
  - Ergot alkaloids
  - Terfenadine
  - Astemizole

*Contraindicated
*Contraindicated in certain circumstances

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Azithromycin, Clarithromycin, Erythromycin

**Clinical pearls:**
- Dosing of azithromycin for hospitalized patients is 500 mg IV/PO daily (NOT “z-pack” dosing i.e. 500 mg once followed by 250 mg on days 2-5)
- Erythromycin can be used for gastroparesis and/or as a laxative
  - Not used much in clinical practice as an antimicrobial agent
- Do not cover Enterobacteriaceae
Quinupristin-dalfopristin

Quinupristin/Dalfopristin (Synercid®) is the first available streptogramin, which received FDA approval in September 1999.

Developed in response to the need for antibiotics with activity against resistant gram-positive bacteria, namely vancomycin resistant Enterococcus (VRE).

Synercid® is a combination of two semi-synthetic pristinamycin derivatives in a 30:70 w/w ratio

Quinupristin:Dalfopristin

Antimicrobial Class:
- Streptogramin

Mechanism of action:
- Each compound binds to the 50S subunit of the bacterial ribosome → Inhibits protein synthesis
  - Bactericidal against most susceptible bacteria
    - Each compound separately displays bacteriostatic activity
    - Bactericidal activity may be diminished if resistance is observed among either compound
    - Concentration dependent bactericidal activity
  - Post-antibiotic effect for gram positive bacteria
    - 2-6 hours for S. aureus
    - 8.5 hours for VSE; 0.2-3.2 hours for VRE

Spectrum of activity:
- Gram positive:
  - Corynebacterium jeikeium
  - Enterococcus faecium (does NOT cover E. faecalis)
  - Staphylococcus sp (including methicillin resistant strains)
  - Streptococcus
    - Including Streptococcus pneumoniae, pyogenes, viridans streptococcus, and group C and G streptococcus
Quinupristin-dalfopristin

Mechanism of resistance:
- Alterations in ribosomal binding sites (erm)
- Enzymatic inactivation
- Active transport out of the cell

Quinupristin-dalfopristin

Absorption
- Only available parentally

Distribution
- Penetrates into extravascular tissue, lung, skin/soft tissue;
  minimal CSF penetration

Elimination
- Both agents are excreted hepatically and biliary
  - Half-life: 0.7-1.3 hours

Quinupristin-dalfopristin

Clinical uses
- VRE bacteremia
  - Lost FDA approval for VRE in 2010 as the submitted data failed to verify clinical benefit
- Complicated skin and soft tissue infections due to methicillin susceptible Staphylococcus aureus (MSSA) or Streptococcus pyogenes
Quinupristin-dalfopristin

Clinical Uses
- Limited data in treatment of catheter-related bacteremia, infections due to MRSA, and community-acquired pneumonia

Quinupristin-dalfopristin

Dosing:
- 7.5 mg/kg IV every 8-12 hours
- No renal dose adjustments

Adverse effects:
- Arthralgias/myalgias
  - Incidence up to 47%
- Headache
- Increased bilirubin
- Nausea/vomiting/diarrhea
- Venous irritation
  - Should be administered via central line

Quinupristin-dalfopristin

Drug interactions:
- Cytochrome p450 3A4 inhibitor

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Specific Agents</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antiretrovirals</td>
<td>Didanosine, efaviren, indinavir, nelfinavir</td>
</tr>
<tr>
<td>Anti-HIV (NNRTIs and protease inhibitors)</td>
<td>Nevirapine, delavirdine, fosamprenavir, lopinavir/ritonavir</td>
</tr>
<tr>
<td>Anti-microbial</td>
<td>Moxifloxacin, azithromycin</td>
</tr>
<tr>
<td>Agents</td>
<td>Diiodohydroxyquinoline</td>
</tr>
<tr>
<td>Proton pump</td>
<td>Omeprazole, ranitidine</td>
</tr>
<tr>
<td>Inhibitors</td>
<td>Amoxicillin, metronidazole</td>
</tr>
<tr>
<td>Other</td>
<td>Methotrexate, mycophenolate</td>
</tr>
</tbody>
</table>

NNRTIs = non-nucleoside reverse transcriptase inhibitors.
Quinupristin-dalfopristin

Clinical pearls:
- Limited use in clinical practice due to arthralgias/myalgias
- Given via central line in order to prevent venous irritation that can occur with peripheral administration

Review
Which one of the following statements regarding Clindamycin is true?

A. Clindamycin is readily removed by either hemodialysis or peritoneal dialysis
B. Clindamycin is ineffective in the treatment of CNS infections
C. Clindamycin’s activity is limited to gram-positive anaerobes
D. Clindamycin has never been associated with causing C. difficile colitis

Review
Which of the following is NOT an adverse effect of the macrolide antimicrobials?

A. QTc prolongation
B. Nausea
C. Red-orange urine discoloration
D. Ototoxicity
PROTEIN SYNTHESIS INHIBITORS
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