I. HISTORY AND MECHANISM OF ACTION

Chloramphenicol was isolated from the soil organism *Streptomyces venezuelae*. It was released in the U.S. in 1949 and was widely used in the 1950s. Reports of aplastic anemia surfaced and the drug fell into disfavor. It was the first antibiotic that was chemically synthesized in an efficient process.

Chloramphenicol inhibits protein synthesis by reversibly binding to the 50S ribosomal subunit. Prevents attachment of the amino acid end of t-RNA to its binding site. In general it is considered to be bacteriostatic although *in vitro* evidence suggests that it is bactericidal against *H. influenzae*, *Strep. pneumoniae*, and *N. meningitidis* at therapeutic concentrations.

II. SPECTRUM

a.) active against a wide variety of gram positive and gram negative bacteria

b.) important activity versus *H. influenzae*, *Strep. pneumoniae*, and *N. meningitidis*

c.) good activity against anaerobes esp. *Bacteroides fragilis*

III. USES

Due to dangerous toxicity, chloramphenicol is not the drug of choice for any organism. It may be used as an alternative agent for the following:

a.) In combination with ampicillin it may be used for the treatment of bacterial meningitis in infants greater than 1 month old, children, and adults.

b.) Typhoid fever. Chloramphenicol is an alternate drug of choice for *Salmonella typhi*, although resistance is a significant problem in third world countries (not in U.S.).

c.) *Bacteroides fragilis* infections when other agents (clindamycin, metronidazole, or cefoxitin) have been shown to be resistant or ineffective.

IV. RESISTANCE

a.) production of an acetyltransferase that inactivates the enzyme - R-factor mediated R-factors are responsible for the widespread resistance by *Salmonella typhi* and *Shigella*. Resistance has led to epidemics in Central and South America and The Far East.

b) bacterial membrane impermeability
V. ADVERSE EFFECTS

a.) **Blood dyscrasias & Aplastic Anemia.** Most serious adverse effect is bone marrow suppression - dose related. Serious and fatal cases of aplastic anemia, hypoplastic anemia, thrombocytopenia, and granulocytopenia may occur. Irreversible aplastic anemia (usually fatal) is characterized by bone marrow aplasia or hyperplasia weeks or months after therapy. Generally associated with oral therapy (83%). Estimated rate 1:40,000.

Reversible bone marrow depression associated with peak levels ≥25 µg/ml and trough levels ≥10 µg/ml.

b.) **Gray baby syndrome.** Neonates do not have the ability to metabolize chloramphenicol to the acyl glucuronide metabolite. May be exacerbated by preexisting liver failure.

– Symptoms appear in this order: Abdominal distension with or without emesis, progressive pallid cyanosis, vasomotor collapse & irregular respiration, death. Death occurs in 40% of patients within 2 days of initial signs.

– Symptoms first appear after 3-4 days of high dose treatment. Drug concentrations are generally ≥40 µg/ml.

c.) **GI upset.** Take with food if necessary

d.) **CNS effects - headache, confusion, mild depression.** Rare optic and peripheral neuritis.

e.) **Hypersensitivity - rare.** May be Herxheimer reaction during therapy of typhoid fever caused by release of bacterial contents.

VI. DISPOSITION, METABOLISM, AND EXCRETION

a) Rapidly absorbed as free base with F= 0.75-0.9. Chloramphenicol palmitate (a non-bitter prodrug for oral suspensions) has a bioavailability of ~80%. Chloramphenicol succinate (the water soluble injectable form) has a bioavail. of ~70%. Prodrug release is variable.

b.) Therapeutic levels are 10-20 µg/ml (peak) and 5-10µg/ml trough. Half-life is 4 hours.

c.) Compound is widely distributed. Highest concentrations in liver and kidney. ~60% protein bound. CSF levels are 45-100% of serum levels.

d.) Chloramphenicol is extensively metabolized, primarily by glucuronidation. Approximately 5-15% of the drug is excreted unchanged, although urinary concentrations (~200 µg/ml) are sufficient for treatment of UTIs. Decreased clearance in severe liver disease.

VII. PRODUCTS

Chloramphenicol - Chloromycetin® capsules - 250 mg
Chloromycetin® Palmitate Oral suspension - 150 mg/5ml
Chloromycetin® Sodium Succinate Powder for Injection -100 mg/ml when reconstituted

**Dosing requirements**

Adults: 50 mg/kg/day in divided doses q 6 hr. For severe infections such as meningitis or brain abscess - 100 mg/kg/day. Note: should monitor concentrations in serum weekly, esp. in hepatic dysfunction.

Children: 50-75 mg/kg/day in divided doses q 6 hr
Neonates: 25 mg/kg once daily (birth-7 days old). After 2 weeks of life 50 mg/kg/day.
Vancomycin

I. HISTORY AND STRUCTURAL CHARACTERISTICS

Vancomycin is a complex glycopeptide antibiotic (MW=1450) that was isolated from *Streptomyces* (now *Amycolatopsis*) orientalis. The compound contains two unusual chlorinated β-hydroxytyrosine moieties as part of a seven membered peptide. It was introduced in 1956 primarily for treatment of penicillin-resistant staphylococci. The original preparation was impure (Mississippi Mud) and the early reports of hypersensitivity, nephrotoxicity and ototoxicity combined with poor oral bioavailability restricted its use. In the late 1960's methicillin resistant *Staph. aureus* appeared with increasing frequency and vancomycin use dramatically increased. In 1986, a new formulation was introduced with 95% purity and this coupled with better knowledge of therapeutic drug monitoring has greatly reduced the toxicity.

II. MECHANISM OF ACTION

**Inhibition of Transpeptidation** - Forms a complex with the D-alanyl-D-ala end of peptidoglycan precursors thereby inhibiting cell wall biosynthesis.

**Inhibition of Transglycosylation** - Binding of $^{125}$I-vancomycin is in the cell wall and the cell membrane (not the cytoplasm), so complexation must occur in either Stage II or Stage III of peptidoglycan biosynthesis. This may lead to a buildup of lipid intermediates. Lipophilic derivatives of vancomycin (teicoplanin and oritivancin) appear to primarily inhibit the transglycosylation reaction. These newer analogs may be useful in inhibiting *vanA* mutants (see below).

Vancomycin is bactericidal, but only effects multiplying organisms.
III. SPECTRUM

Vancomycin has a relatively narrow spectrum of action against gram positive bacteria

a.) *Staphylococcus aureus* and *Staphylococcus epidermidis* including methicillin-resistant and ß-lactamase producing strains. Synergistic with gentamicin.

b.) *Streptococcus pyogenes*, *Strep. pneumoniae*, and Group B streptococci.

c.) *Enterococcus* - bactericidal only at high concentrations. Synergistic with aminoglycosides

d.) Anaerobic infections including *Clostridium perfringens* and *C. difficile*, other clostridia, lactobacilli, and actinomycetes.

e.) *Listeria monocytogenes*, *Bacillus anthracis*, Corynebacteria, some strains of *Neisseria gonorrhoeae*

### TABLE 39. GRAM POSITIVE COCCI - SUSCEPTIBILITY DATA
(Regions Hospital, St. Paul, MN 1999)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Enterococcus sp. all isolates</th>
<th>Nafcillin resistant</th>
<th>Coagulase neg. Staph. pneumoniae</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ampicillin</td>
<td>91</td>
<td>474</td>
<td>689</td>
</tr>
<tr>
<td>Ampicillin/Sulbactam†</td>
<td>77</td>
<td>0</td>
<td>46</td>
</tr>
<tr>
<td>Cefazolin</td>
<td>&quot;</td>
<td>77</td>
<td>0</td>
</tr>
<tr>
<td>Ceftriaxone</td>
<td></td>
<td></td>
<td>100</td>
</tr>
<tr>
<td>Ciprofloxacin¥</td>
<td>78</td>
<td>98</td>
<td>0</td>
</tr>
<tr>
<td>Clindamycin</td>
<td>78</td>
<td>17</td>
<td>71</td>
</tr>
<tr>
<td>Erythromycin</td>
<td>62</td>
<td>0</td>
<td>36</td>
</tr>
<tr>
<td>Gentamicin† (≤500 µg/ml)</td>
<td>82</td>
<td>93</td>
<td>85</td>
</tr>
<tr>
<td>Oxacillin</td>
<td>77</td>
<td>0</td>
<td>46</td>
</tr>
<tr>
<td>Norfloxacin¥</td>
<td>100</td>
<td>&quot;</td>
<td>100</td>
</tr>
<tr>
<td>Penicillin</td>
<td>10</td>
<td>0</td>
<td>13</td>
</tr>
<tr>
<td>Streptomycin† (≤2000 µg/ml)</td>
<td>75</td>
<td></td>
<td>69</td>
</tr>
<tr>
<td>Tetracycline¥*</td>
<td>35</td>
<td>96</td>
<td>70</td>
</tr>
<tr>
<td>TMP-SMX</td>
<td>94</td>
<td>75</td>
<td>63</td>
</tr>
<tr>
<td>Vancomycin</td>
<td>93</td>
<td>&quot;</td>
<td>100</td>
</tr>
</tbody>
</table>

%S = % of susceptible strains, # = no. of strains tested

† - Combined therapy with ampicillin is necessary for bactericidal action for most serious infections. Susceptibility to gentamicin (500 µg/ml) or streptomycin (2000 µg/ml) is a screening method to predict synergy between ampicillin or vancomycin and aminoglyside combinations in blood, tissue and body fluid isolates.

¥ – Reported only for urine isolates

¥* – For enterococci, reported only on urine isolates
IV. USES

a.) Drug of choice for methicillin-resistant Staph. aureus and S. epidermidis. Should be combined with rifampin and or gentamicin for methicillin-resistant coagulase-negative staphyloccocal endocarditis.

b.) Serious infections caused by Staph. or Strep. in patients intolerant to ß-lactams.

c.) Alternative to penicillins in treatment of endocarditis due to streptococci (Group A, B, and Strep. viridans). For enterococcal endocarditis, combine with gentamicin. May also be used as a prophylactic agent against endocarditis in combination with gentamicin.

d.) Clostridium difficile pseudomembraneous colitis (oral administration).

e.) Other miscellaneous gram positive and anaerobic infections e.g. penicillin-resistant strains of Strep. pneumoniae, Corynebacterium jeikeium, that are resistant to standard drugs.


The following are situations in which the use of vancomycin should be discouraged:

• Routine surgical prophylaxis other than in a patient who has a life-threatening allergy to beta-lactam antibiotics

• Empiric antimicrobial therapy for a febrile neutropenic patient, unless initial evidence indicates that the patient has an infection caused by gram positive organisms (e.g. at an inflamed exit site of a Hickman catheter) and the prevalence of infections caused by MRSA at the hospital is substantial.

• Treatment in response to a single blood culture positive for coagulase-negative staphylococcus, if other blood cultures taken during the same time frame are negative (i.e., if contamination of the blood culture is likely). Because contamination of blood cultures with skin flora (e.g., Staph. epidermidis) could result in inappropriate administration of vancomycin, phlebotomists and other personnel who obtain blood cultures should be trained to minimize microbial contamination of specimens.

• Continued empiric use for presumed infections in patients whose cultures are negative for beta-lactam-resistant, gram positive organisms

• Systemic or local (e.g. antibiotic lock) prophylaxis for infection or colonization of indwelling central or peripheral intravascular catheters.

• Selective decontamination of the digestive tract

• Eradication of MRSA colonization

• Primary treatment of antibiotic associated colitis due to Clostridium difficile

• Routine prophylaxis for very low-birthweight infants (i.e., infants who weigh < 1.5kg (3 lb, 4 oz)

• Routine prophylaxis for patients on continuous ambulatory peritoneal dialysis or hemodialysis.

• Treatment (chosen for dosing convenience) of infections caused by ß-lactam sensitive, gram positive organisms in patients who have renal failure.

• Use of vancomycin solution for topical application or irrigation
V. RESISTANCE

Resistance has been surprising rare. Recently, vancomycin resistant strains of *S. haemolyticus*, *Leuconostoc* sp., and enterococci (esp. *E. faecium*) have been reported. In the late 1990s resistance to enterococci increased dramatically.

**Vancomycin Resistant Enterococci (VRE)** - In enterococci, *van A, vanB, vanC*, and *vanD* mutants have been described. The *vanA* mutation complex encoding 7 new gene products produces a terminal D-ala-D-lactate instead of a D-ala-D-ala in the peptidoglycan layer. Vancomycin binds poorly to D-lactate.

**VISA = vancomycin intermediate-resistant Staph. aureus** - Scattered reports of resistant strains of methicillin-resistant *Staph. aureus* have appeared in U.S. and Nosocomial transmission has now occurred in Japan. The resistance is plasmid-mediated and if resistance spreads this could become a major clinical problem. Resistance in almost all cases is not due to the *vanA* mutation complex, although this has been accomplished in vitro.

VI. DISPOSITION AND EXCRETION.

- Poor oral absorption - patients with colitis and renal failure may accumulate drug
- Distributed primarily in extracellular fluid - only penetrates CSF when meninges are inflamed. For meningitis may give intrathecally or intraventricularly.
- Primarily eliminated by glomerular filtration. Clearance is dependent upon creatinine clearance. Some biliary excretion. May be metabolized to a small extent.

**PHARMACOKINETIC PARAMETERS OF VANCOMYCIN**

<table>
<thead>
<tr>
<th>Oral Bio-Availability</th>
<th>% Protein Binding</th>
<th>% excreted unchanged</th>
<th>Adult Half-life Normal</th>
<th>Adult Half-life Anephric</th>
<th>Desired Trough Concentration</th>
<th>Desired Peak Concentration</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-5%</td>
<td>50%</td>
<td>80-90%</td>
<td>3-8 h</td>
<td>5-35 h</td>
<td>5-10 µg/ml</td>
<td>30-40 µg/ml</td>
</tr>
</tbody>
</table>

VII. ADVERSE EFFECTS

Much of the data accumulated on the adverse reactions of vancomycin was accumulated in the late 1950s and early 1960s. Many of the events may have been caused by impurities in the preparation. The new commercial preparation by Lilly is much purer and thus some aspects of vancomycin toxicity are controversial esp. ototoxicity and nephrotoxicity.

a.) Hypersensitivity reactions - maculopapular rash - incidence 3%.

b.) Phlebitis - common, up to 13% incidence.

c.) *Red man or red neck syndrome* - reaction appears to occur with rapid infusion of large doses. Reaction begin in 10 min. after infusion and resolves in 1-20 min. 25-50% of patients exhibit hypotension. May be partially prevented by prior administration of antihistamines. Avoid by infusing over 1 hr. Seems to be very rare in patients.

d.) Pain and spasms - Throbbing pain in neck with rapid infusion has also been reported frequently. May be accompanied by muscle spasms in chest and back.

e.) Ototoxicity - incidence is low (≤1%) and is probably related to co-administration of aminoglycosides or in patients with renal dysfunction.
f.) Nephrotoxicity - Controversial. In animal studies, vancomycin was not nephrotoxic alone. However it has been shown to increase the nephrotoxicity of aminoglycosides both in animals and humans. Incidence of nephrotoxicity of vancomycin combined with gentamicin as high as 35%. Usually reversible.

g.) Reversible neutropenia -2%. Usually with long term use e.g. osteomyelitis

VIII. PRODUCTS

Vancomycin powder for injection - Vancocin® (Lilly) 500mg, 1, 5, and 10g - stable for 14 days after reconstitution in 5% dextrose or 0.9% NaCl at 5°C.
Note: Lilly Blue label is 93% pure. Generic products are only 85% pure.

Dosing: Adults: 500 mg IV q 6 h (infuse over 1 hr) or 1g q 12h in patients with normal renal function

For patients with altered renal function, use nomogram (see table below) or individualize dosing according to 2 or 3 compartment pharmacokinetic model.

<table>
<thead>
<tr>
<th>Creatinine Clearance (ml/min)</th>
<th>Dose (mg/24 hr)</th>
</tr>
</thead>
<tbody>
<tr>
<td>100</td>
<td>1545</td>
</tr>
<tr>
<td>90</td>
<td>1390</td>
</tr>
<tr>
<td>80</td>
<td>1235</td>
</tr>
<tr>
<td>70</td>
<td>1080</td>
</tr>
<tr>
<td>60</td>
<td>925</td>
</tr>
<tr>
<td>50</td>
<td>770</td>
</tr>
<tr>
<td>40</td>
<td>620</td>
</tr>
<tr>
<td>30</td>
<td>465</td>
</tr>
<tr>
<td>20</td>
<td>310</td>
</tr>
<tr>
<td>10</td>
<td>155</td>
</tr>
</tbody>
</table>

Children: 10 mg/kg q 6 h

Infants and neonates: Initial dose 15 mg/kg, then 10 mg/kg q 12 hrs for first week of life and q 8 hrs up to 1 month old.

Prevention of endocarditis in high risk penicillin allergic patients:

1 g IV infused over 1 hr + 1.5 mg/kg gentamicin IV or IM, 1 hour prior to procedure.

For C. difficile pseudomembraneous colitis:

Vancomycin oral - Vancocin® Pulvules (Lilly) - 125 and 250 mg. Powder for oral solution - 1g. Adult dose: 0.5-2 g/day in 3 or 4 divided doses for 7 -10 days. Lower doses (125 mg t.i.d. or q.i.d.) may be as effective as the 500mg regimen. Children: 40 mg/kg/day.
Quinupristin/Dalfopristin
(Synercid®)

I. BACKGROUND

Synercid® is a semisynthetic IV antibiotic belonging to the streptogramin class. The streptogramin class of antibiotics consists of combinations of two chemically unrelated compounds that exhibit in vitro synergistic antimicrobial activity. Synercid® is a 30/70 mixture of quinupristin and dalfopristin. The antimicrobial activity of quinupristin/dalfopristin is similar to that of pristinamycin, a naturally-occurring oral streptogramin antibiotic (from Streptomyces pristinaespiralis) in use in Europe. Approved Sept. 1999 in U.S.

II. MECHANISM OF ACTION

• Inhibit protein biosynthesis.
• Quinupristin/dalfopristin bind sequentially to different sites on the 50S subunit of the 70S bacterial ribosome.
• The binding of dalfopristin alters the conformation of the ribosome such that there is a 5- to 10-fold decrease in the dissociation constant (increase in the affinity constant) for quinupristin. As a result, a very stable quinupristin-ribosome-dalfopristin ternary complex is formed and a constriction of the exit channel of the ribosome occurs, thereby preventing the newly synthesized peptide chains from being extruded from the ribosome of that complex, thus leading to cell death.
• Individually, quinupristin and dalfopristin are bacteriostatic, whereas the combination is synergistic and usually bactericidal.

III. SPECTRUM

Gram positive pathogens:
  Staphylococci
  Streptococci
  Enterococcus faecium
    note: poor activity against E. faecalis, which is clinically more prevalent
  Listeria monocytogenes

Some degree of susceptibility:
  Neisseria spp.
  Moraxella catarrhalis
  Legionella spp.
  Mycoplasma pneumoniae
  H. Influenza

Anaerobes (Bacteroides fragilis, Clostridium spp., Lactobacillus spp., Antinomyces spp.)

IV. USES

Synercid® should not be a first line agent and should be reserved for the treatment of severe infections caused by multi-resistant gram-positive pathogens:
  Vancomycin-resistant Enterococcus faecium (VRE)
  Vancomycin-intermediate resistant S. aureus (VISA) or
  Vancomycin-allergic patients with MRSA or S. pneumonia (with high level resistant to β-lactams)

It is not indicated for mild gram-positive infections and has no place in the treatment of Pseudomonas aeruginosa or the Enterobacteriaceae.
V. RESISTANCE

Resistance to streptogramin compounds is primarily mediated by the erm gene, which encodes for an enzyme that results in reduced binding of macrolides, lincosamides, and streptogramin B. Antibiotic inactivation may account for some resistant strains. Clinical resistance to quinupristin/dalfopristin has been infrequent in available studies (less than 5% resistant strains). Cross-resistance with macrolides is rare and there are no reports of cross-resistance with β-lactams or aminoglycosides.

VI. ABSORPTION, DISTRIBUTION, METABOLISM, EXCRETION

- Moderately protein-bound
- Vd = 1.5 L/kg (dose-dependent)
- Extensive metabolism with at least one active metabolite.
- Most of the IV dose is excreted in the feces (75%); less than 20% is excreted in the urine; less than 5% excreted unchanged in the urine
- Elimination t½ (total activity) = 1.4 h (although dosed q8-12 h due to postantibiotic effect)
- TBC (total activity) = 74 L/h

VII. ADVERSE EFFECTS

- Infusion-Site Reactions (dose and concentration dependent)
  - (10-68%, 5% had to discontinue - pain, erythema, itching, burning
  - Note: Administering Synercid in at least 250 ml D5W over at least 1 hr can improve venous tolerability
- Nausea (63%)/Vomiting (7%)
- Headache
- Diarrhea (12%)
- Cutaneous reactions (rare)-pruritus, burning, and/or erythema of the neck, face, or upper body
- Hepatotoxicity (0.7%, 1.4% had to discontinue)-reversible elevation of serum transaminases and alkaline phosphatase have occured. Monitoring of liver function is advised during therapy, especially in patients with pre-existent hepatic insufficiency.

VIII. PRODUCT – Synercid® (Aventis)

- Injection, lyophilized: 500 mg (150 mg quinupristin, 350 mg dalfopristin) per 10 mL (in vials)
- Reconstitute by slow adding 5% dextrose in water or sterile water for injection. Do not dilute in saline solutions. Add reconstituted solution to 250 mL of 5% dextrose. Infuse over 60 min.
I. BACKGROUND

Oxazolidinones are a new class of completely synthetic antibiotics. An initial patent in 1978 from DuPont described the synthesis of 5-(halomethyl)-3-aryl-2-oxazolidinones with activity against plant pathogens. Based on these initial findings, several more active analogs with improved pharmacokinetics were developed by DuPont and Upjohn. Linezolid was developed by Pharmacia and Upjohn and was approved in April 2000.

II. MECHANISM OF ACTION

• Oxazolidinones inhibit the initiation of protein synthesis by binding to the 50S ribosomal subunit.
• Binding is inhibited by chloramphenicol and clindamycin, but there does not appear to be cross-resistance with these agents.
• Oxazolidinones do not affect the binding of N-formyl-met tRNA, elongation, or termination, unlike other protein synthesis inhibitors.
• It is hypothesized that these agents bind at the 50S ribosome near the 30S ribosome interface and thus prevent the initiation complex from forming. Bacteriostatic.

III. SPECTRUM

• Primarily Gram + bacteria are inhibited.
• Active against penicillin-resistant Strep. pneumoniae, methicillin-resistant staphylococci, and vancomycin-resistant enterococci. MIC\textsubscript{90} values are in the 1-4 µg/mL range.
• Activity vs. non-typable H. influenzae is marginal.
• Linezolid has \textit{in vitro} activity vs. Mycobacterium tuberculosis.
• No cross-resistance with chloramphenicol, clindamycin, macrolides, or tetracyclines.
• Note: In 2001, the first clinical report of VRE resistant to linezolid appeared.

IV. USES

1) Methicillin-resistant staphylococcal infections (alternative to vancomycin)
2) Community-acquired pneumonia due to drug-resistant \textit{Strep. pneumoniae}
3) Concurrent bacteremia associated with vancomycin-resistant enterococci
4) Multi-drug resistant tuberculosis (unapproved use)

V. ABSORPTION, DISTRIBUTION, METABOLISM, EXCRETION

Linezolid half-life is 5.5 h. 30% eliminated unchanged in urine. 31% protein bound. After oral dosing of 400 mg or 625 mg TID, mean plasma concentrations were 12.4 and 26.4 µg/ML, respectively, with trough values of 4 µg/mL. Excellent oral bioavailability (>90%).
VI. SIDE EFFECTS

- Good safety profile
- 60% reported some “digestive event”, esp. tongue discoloration
- Headache and diarrhea were most common reported adverse events
- 21% reported folliculitis
- Weak inhibitor of monoamine oxidase

VII. LINEZOLID PRODUCTS

Tablets: 400 mg and 600 mg film-coated tablets (Zyvox®- Pharmacia-Upjohn)
Oral Suspension: 100 mg per 5 mL in 240 mL bottles (orange-flavored)
Injection: 200mg/100 mL

**Bacitracin and Polymyxins**

I. STRUCTURAL CHARACTERISTICS

Bacitracin and polymyxins are peptide antibiotics that are primarily restricted to topical use.

II. MECHANISM OF ACTION

Bacitracin blocks cell wall synthesis by inhibition of the dephosphorylation of lipid pyrophosphate, a reaction that occurs in the second stage of cell wall synthesis.

Polymyxin B and Colistin (Polymyxin E) - bactericidal - appear to act like cationic detergents. Disrupt the integrity of cell membrane by interacting with phospholipids. Increase cell permeability - bactericidal.

III. SPECTRUM

Bacitracin - good gram positive spectrum, *Clostridium difficile*

Polymyxin B and Colistin (Polymyxin E) - good against gram negative bacilli except *Proteus.*

All gram positive bacteria, gram negative cocci e.g. *Neisseria sp.*, and fungi are resistant.

IV. USES

**Bacitracin**

a.) Treatment of minor skin and eye infections (often in combination with neomycin and Polymyxin B - see topical products section of aminoglycosides)

b.) *C. difficile* pseudomembranous colitis - oral. Alternative to oral vancomycin or metronidazole.

c.) *Staph.* infections - Third line alternative (given IM)

**Polymyxin B, Colistin (polymyxin E) & Colistimethate**

a.) Topical gram negative infections esp. due to *Pseudomonas aeruginosa.*

b.) Polymyxins are a third choice alternative for systemic gram negative infections (by intravenous infusion) when less toxic drugs are contraindicated or ineffective. Colistimethate sodium (injectable) has similar indications to Polymyxin B.
c.) Oral colistin used for diarrhea in infants due to *E. coli* and for *Shigella*

V. DISPOSITION and EXCRETION

– not absorbed orally. Does not cross into CNS. Excreted renally

VI. ADVERSE EFFECTS

- Nephrotoxic - systemic therapy with polymyxins and bacitracin

- Neurologic effects - respiratory arrest has occurred with polymyxins

VII. PRODUCTS

Bacitracin - Powder for Injection - 50,000 units
Baciguent® (Upjohn) - Ointment and Ophthalmic ointment - 500 units per gram
Bacitracin oral - Altracin® (A.L. Labs) - orphan drug for *C. difficile* enterocolitis

Colistin - Coly-Mycin S (Parke-Davis) - Powder for Oral Suspension - 25 mg/5ml
Colistmethate - Coly-Mycin M (Parke-Davis) - Injection (lyophilized cake) - 150 mg
Polymyxin B - Aerosporin® (Burroughs-Wellcome) - Injection - 500,000 units
Polymyxin B sulfate (Roerig) – Injection – 500,000 units

see Topical Products section of aminoglycosides for combination products.
Mupirocin

I. STRUCTURAL CHARACTERISTICS

Mupirocin (pseudomonic acid A) is a topical antibacterial agent produced by *Pseudomonas fluorescens*. It is structurally unrelated to other antibacterial agents.

II. MECHANISM OF ACTION

Mupirocin is an inhibitor of bacterial isoleucyl transfer-RNA synthetase and thus blocks protein synthesis. There is no cross-resistance with other protein synthesis inhibitors.

III. SPECTRUM AND USES

Mupirocin has a good gram positive spectrum against virtually all species of *Staphylococcus* and *Streptococcus*. It is indicated for the topical treatment of impetigo (a skin infection), infected eczema, folliculitis due to *Staph.* and other minor skin infections. In nosocomial settings, it is often used to reduce the carriage of resistant staphylococci (especially MRSA) in the nose.

IV. DISPOSITION AND EXCRETION

There is no measurable systemic absorption of mupirocin ointment through the skin. Nasal absorption has not been well studied but is probably negligible.

V. ADVERSE REACTIONS

Local burning, stinging, or pain (1.5%). Incidence of rash or contact dermatitis is low (<1%). Prolonged or repeated therapy may result in bacterial or fungal overgrowth leading to a secondary infection or superinfection. Polyethylene glycol may be absorbed and can cause renal toxicity. Therefore, mupirocin should not be applied to large open wounds such as burns.

VI. PRODUCT

Ointment (2%) in a polyethylene glycol base (Bactroban®-SK-Beecham)
The ointment is usually applied to the affected area 3 times daily. Response should be evaluated in 3-5 days for impetigo.
I. HISTORY & STRUCTURAL CHARACTERISTICS

Clindamycin (7-deoxy,7-chloro-lincomycin) is a derivative of lincomycin, an antibiotic isolated from *Streptomyces lincolnensis*, a soil organism found near Lincoln, Nebraska by workers at Upjohn. Lincomycin is still marketed, but is rarely used. Clindamycin is more potent and has better oral absorption.

II. MECHANISM OF ACTION

Clindamycin binds to the 50S ribosomal subunit at a similar or overlapping site as do the macrolides and chloramphenicol. Inhibits protein synthesis. Bactericidal for *Strep.* and *Staph.*

III. SPECTRUM

a.) Gram positive cocci, especially streptococci. *Enterococcus sp.* are generally resistant. Most staphylococci are susceptible, but resistance is increasing. Cross-resistance in *S. aureus* to erythromycin & clindamycin.

b.) Anaerobes - Clindamycin is often considered the drug of choice for anaerobic infection caused by *Bacteroides fragilis* and other *Bacteroides sp.* Also effective versus clostridia, peptococci and peptostreptococci, *Propionibacterium acnes*, *Fusobacterium*, *Eubacterium*, *Veillonella*.

c.) Parasites - *Toxoplasma gondii* & *Pneumocystis carinii*; others - *Gardnerella vaginalis*,

IV. USES

a) Treatment of susceptible strains of pneumococci, streptococci, and staphylococci in penicillin allergic patients. Should not be considered a first or second line agent due to toxicity. Most common uses would be in chronic otitis media and chronic sinusitis that did not respond to initial therapy (clindamycin + cefixime)

b.) Anaerobic infections especially those due to *Bacteroides fragilis* group. Often useful in cases of bowel perforation or as adjunct to abdominal surgery. Also useful for lung abscess - may be preferable to penicillin. Alternative for *C. perfringens* infections

c.) Topical treatment of acne vulgaris.

d.) Topical (vaginal) treatment of *Gardnerella vaginalis* (fish odor vaginosis).

e.) Toxoplasmosis in AIDS patients – alternative treatment to sulfonamides (in combination with pyrimethamine)
f.) *Pneumocystis carinii* pneumonia - alternative treatment to pentamidine or TMP-SMX (in combination with primaquine)

g.) Pelvic inflammatory disease due to *Chlamydia trachomatis* – in combo with gentamicin

V. DISPOSITION, METABOLISM, AND EXCRETION

Absorption - Clindamycin is well absorbed (~90%) but undergoes extensive first pass metabolism. The esters clindamycin palmitate (oral suspension) and clindamycin phosphate (IM) are absorbed intact and rapidly cleaved to clindamycin.

Distribution - Clindamycin is widely distributed except into the CNS. Inadequate levels are achieved even when meninges are inflamed. Accumulates in PMNs - high concentrations in abscesses.

Metabolism - Extensively metabolized. N-desmethyl-clindamycin is more active than clindamycin, sulfoxide less active. Highly excreted in bile, even after IV administration. Extensive EHC and prolonged fecal elimination

<table>
<thead>
<tr>
<th>Pharmacokinetic parameters of Clindamycin</th>
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<tr>
<td>Oral Bio-Availability</td>
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<td>-------------------------</td>
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<tr>
<td>23-38%</td>
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VI. ADVERSE EFFECTS

a.) Diarrhea - occurs in 20% of patients.

b.) **Pseudomembranous colitis due to *C. difficile***. Clindamycin drastically alters the intestinal flora which is primarily anaerobic. This allows overgrowth of *Clostridium difficile*. Incidence is 0.01-10% and depends upon the institution (may be endemic). May occur during or several weeks after treatment. Symptoms - diarrhea (sometimes blood), fever, cramps, yellow-white plaques on colonic mucosa. Toxin will appear in stools. Syndrome is hard to treat and may be fatal. Treat with oral vancomycin, metronidazole, or oral bacitracin.

c.) Hepatic toxicity - elevation of transaminases - reversible. Rare - jaundice.

d.) Hypersensitivity - rare

VII. PRODUCTS AND DOSES

**Dosing:** Adults: 150-300 mg q 6 h. For more severe infections 300-450 mg q 6 h. Take with a full glass of water or with food to avoid esophageal irritation. Absorption is not affected by food. Serious anaerobic infections - start with parenteral, then switch to oral.

Children: 20-40 mg/kg day in 3 or 4 equal doses or based on body surface area (350-450 mg/m²/day)

Clindamycin HCl (oral) - Cleocin® (Pharmacia-Upjohn) 75, 150, and 300 mg capsules. Clindamycin palmitate - Cleocin Pediatric® (Pharmacia-Upjohn) - granules for oral solution (75 mg/ml)

Clindamycin Phosphate - 150 mg/ml injection solution -infuse over 10-60 min.
Topical products:
Cleocin T® (Pharmacia-Upjohn) – Gel, Lotion, or Topical solution 10 mg/ml - apply as thin film to face for acne.

Cream (Pharmacia-Upjohn) - 2% apply one (5 g containing 100 mg of clindamycin phosphate, preferably at bedtime for 7 consecutive days.

Vaginal cream (Pharmacia-Upjohn) – 2% clindamycin phosphate (20 mg/g). Apply one applicatorful (5 g) for treatment of bacterial vaginosis.

Metronidazole

I. HISTORY AND STRUCTURAL FEATURES

Introduced in 1959 for treatment of Trichomonas vaginalis infections. Also effective against other protozoa as well as anaerobic infections. Metronidazole is a 5-nitroimidazole. The nitro group is essential for activity.

II. MECHANISM OF ACTION

Appears to be suicide substrate for bacteria. After entry into the cell, the nitro group is reduced to reactive metabolites (that may generate free radicals). The reactive metabolites damage DNA and perhaps affect other macromolecules.
III. SPECTRUM

a.) Excellent activity against gram negative anaerobes e.g. *Bacteroides sp.* and some gram positive anaerobes e.g. *Clostridium sp.*

b.) Various protozoa - including *Trichomonas vaginalis*, *Giardia lamblia*, *Entamoeba histolytica* (see Medical Letter on Antiprotozoal drugs).

c.) *Helicobacter pylori* (causative agent of peptic ulcers) often combined with tetracycline or amoxicillin and bismuth subsalicylate. (see Tetracycline monograph)

IV. RESISTANCE

Resistance is rare among anaerobes. Primary resistance in *Helicobacter pylori* occurs in 20-40% of isolates and is associated with prior exposure, esp. in young women treated for vaginal infections. Resistance is due to altered nitroreductase.

V. USES

a.) Treatment of serious anaerobic infections in peritoneum, liver, skin, CNS, bone and joins, and lower respiratory tract., esp. caused by *Bacteroides sp.* >85% of brain abcesses are due to anaerobes - (peptostreptococci > fusobacteria > *Bacteroides*)

b.) Prophylaxis prior to abdominal, gynecologic, or colorectal surgery

c.) *C. difficile* pseudomembranous colitis - cheaper alternative to vancomycin

d.) Bacterial vaginosis –*Trichomonas vaginalis* and *Gardnerella vaginalis* - oral or topical

e.) Hepatic encephalopathy - may be better than neomycin

f.) Crohn's disease - rectal disease only

g.) Recurrent peptic ulcers due to *Helicobacter pylori* (see III c.)

h.) Protozoal disease - alternative to quinacrine for Giardiasis, amebic liver abcess

i.) acne rosacea - topical treatment

VI. DISPOSITION, METABOLISM, AND EXCRETION

– well absorbed

– large apparent volume of distribution, penetrating all tissues well. CSF levels are approximately 50% of serum levels. 20% bound.

– extensively metabolized by oxidation and glucuronidation. 2-hydroxymethyl-MTZ is active. 20% excreted unchanged. MTZ half-life = 8 hrs, 2-hydroxymethyl-MTZ half-life = 15 hr. MTZ and 2-hydroxymethyl-MTZ may accumulate with renal and hepatic dysfunction. Half-life is prolonged in newborns.

\[
\text{MTZ} \xrightarrow{P450} \text{MTZ-2-OH} + \text{MTZ-2-COOH}
\]
VII. ADVERSE EFFECTS

a.) Neurologic effects - seizures at high doses, peripheral neuropathy

b.) Disulfiram-like effect in persons consuming alcohol. Instruct patients to avoid ethanol.

c.) GI upset. Metallic taste. Darkened urine (due to MTZ metabolite).

d.) Carcinogenic at high doses in rats?. Retrospective studies in humans have failed to show increased risk of cancer. Mutagenic *in vitro*. Recommendation is to avoid in pregnancy.

VIII. PRODUCTS AND DOSING

Metronidazole - Flagyl® (Pharmacia) 250 and 500 mg tablets

For trichomoniasis: 2g oral once or 500 mg b.i.d. x 7 days

Metronidazole HCl - Flagyl I.V.® (Sciapparelli Searle) Powder for injection, lyophilized - 500mg & Ready-to-use injection 500 mg/100 ml

For preparation of infusion solution order of mixing is important. 1.) Reconstitute. 2.) Dilution of IV solution in 0.9% NaCl or 5% dextrose. 3.) pH neutralization with Na bicarbonate. Should avoid use of aluminum-containing equipment as solution will interact turning an orange/rust color.

*For anaerobic infections:*

Loading dose is 15 mg/kg infused over 1 hr (~1g), then 7.5 mg/kg infused over 1 hr q 6hrs. do not exceed 4 g in 24 hrs or switch to oral administration (7.5 mg/kg).

Topical products

Metronidazole gel - MetroGel® (Curatek) - 0.75% gel - apply and rub in a thin film twice daily to affected areas for acne. Should see improvement in 3 weeks.

MetroGel-Vaginal® (Curatek) - 0.75% gel. Insert one applicatorful (~5 g containing 37.5 mg MTZ) intravaginally twice daily for 5 days. Indicated for treatment of bacterial vaginosis due to *Trichomonas, Gardnerella, Corynebacterium*, or other anaerobes. Note: some systemic absorption (~2% of serum concentration after a 500 mg oral dose.)