Protein Synthesis Inhibitors II: MISCELLANEOUS ANTIBIOTICS

Suggested Readings:
Mandell, Douglas and Bennett. Principles and Practice of Infectious Diseases, 8th Edition.

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

Prototypical Drugs:

Tetracyclines: Tetracycline, Doxycycline, Minocycline

Glycylcyclines: Tigecycline (Tygacil®)

Sulfonamides: Sulfadiazine, Sulfisoxazole, Trimethoprim-Sulfamethoxazole

Chloramphenicol

Urinary Tract Agents Nitrofurantoin, Methenamine
TETRACYCLINES and GLYCYLCYCLINES

I. INTRODUCTION

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

II. CHEMISTRY

A. The name "tetracycline" refers to antibiotics of either natural or semisynthetic origin that are comprised of a system of four linearly annelated six-membered rings. Tigecycline, a glycylcycline antibiotic, contains a glycyclamido 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, Propionibacterium 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, Propionibacterium, 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 to 100% 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, Chlamydia 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 venerum, and **nongonococcal urethritis** (doxycycline)

4. *Brucellosis, bartonellosis* (doxycycline)

5. Acne (minocycline)


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**

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

I. **INTRODUCTION**

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

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

![Sulfamethoxazole](image)

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

![Folic acid pathway](image)

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

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

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

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

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

V. SPECTRUM OF ACTIVITY

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

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

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

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

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

VI. PHARMACOLOGY

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

B. Absorption

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

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

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

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

D. Elimination

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

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

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

VII. CLINICAL USES

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

B. Acute or chronic bacterial prostatitis

C. Acute bacterial exacerbations of chronic bronchitis (ABECB)

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

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

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

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

H. *Stenotrophomonas maltophilia* infections

I. Listeria meningitis if patient is allergic to penicillins

J. Toxoplasmosis – sulfadiazine (with pyrimethamine)

VIII. ADVERSE EFFECTS

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

B. Hematologic: leukopenia, thrombocytopenia, eosinophilia, megaloblastic anemia, acute hemolytic anemia, aplastic anemia, agranulocytosis
C. **Hypersensitivity reactions:** rash, urticaria, epidermal necrolysis, Steven's Johnson syndrome, erythema multiforme, exfoliative dermatitis, drug fever, malaise, pruritus, serum sickness

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

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

IX. **DRUG INTERACTIONS**

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

X. **DOSING**

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

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

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

<table>
<thead>
<tr>
<th>Indication</th>
<th>Adult Dose</th>
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<tbody>
<tr>
<td>Urinary tract infections</td>
<td>One DS tablet twice daily</td>
</tr>
<tr>
<td>Prostatitis</td>
<td>One DS tablet twice daily</td>
</tr>
<tr>
<td>GI Infections</td>
<td>One DS tablet twice daily</td>
</tr>
<tr>
<td>Skin and soft tissue infections due to CA-MRSA</td>
<td>Two DS tablets twice daily</td>
</tr>
</tbody>
</table>
| *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. Chloramphenicol enters the cell by 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 *Pseudomonas 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, chloramphenicol 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 monoglucuronide. Due to wide variation in the metabolism and excretion in children, dosage requirements vary by age with lower daily doses in newborns.
   
   ii. Monoglucuronide 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 monoglucuronide being excreted by the kidney.

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

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

VI. **Clinical Indications**

A. Not indicated as first line therapy for treatment of infections in the U.S.
B. In developing nations, due to the low cost of this agent, chloramphenicol continues to be used for bacterial meningitis (in areas without high rates of *Hemophilus influenza* resistance), pneumonia, typhoid fever

VII. Adverse Effects
A. Hematologic
   i. Reversible bone marrow depression from inhibition of mitochondrial protein synthesis. This reaction is rare occurring during the course of therapy and is dose related. It is more likely to occur in patients receiving 4 g/day or more and in patients with serum levels >25 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 chloramphenicol 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 a member 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 reductase 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. Organisms 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 renal 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 (1 g 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.